I5Q-MC-CGAH SAP Version 4

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 in Patients with Episodic Migraine – the EVOLVE-2 Study

NCT02614196

Approval Date: 25-Apr-2017

1. Statistical Analysis Plan for Protocols I5Q-MC-CGAG and I5Q-MC-CGAH: Phase 3, Randomized, Double-Blind, Placebo-Controlled Studies of LY2951742 in Patients with Episodic Migraine

LY2951742 (Galcanezumab)

I5Q-MC-CGAG is a Phase 3, multisite, double-blind, randomized, placebo-controlled study of LY2951742 in patients with episodic migraines to evaluate clinical efficacy, safety, and tolerability. 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 will be randomized 2:1:1 to either placebo, 120 mg, or 240 mg LY2951742 administered as a subcutaneous (SC) injection once every month. I5Q-MC-CGAH is identical to I5Q-MC-CGAG.

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I5Q-MC-CGAG
I5Q-MC-CGAH
Phase 3

Statistical Analysis Plan Version 1 was signed and approved: 23 Nov 2015
Statistical Analysis Plan Version 2 was signed and approved: 13 Sep 2016
Statistical Analysis Plan Version 3 was signed and approved: 17 Jan 2017
Statistical Analysis Plan Version 4 electronically signed and approved by Lilly on date provided below.

Approval Date: 25-Apr-2017 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.

Statistical Analysis Plan Version 2 was approved prior to first interim analysis. The SAP version supersedes the statistical plans described in the protocol.

The changes incorporated in SAP Version 2 are as follows:

- With the exception of efficacy analyses on migraine headache days or categorical analysis of response rate (such as 50% response rate) derived from migraine headache days where the continuous value of baseline migraine headache days will be used as covariate, all other efficacy analyses will include baseline number of migraine headache days category (<8 vs >=8) as a covariate in the MMRM, AN(C)OVA, GLIMMIX and logistic regression model. Specifically, 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 migraine headache days category (<8 vs >=8) as one of the covariate.
- Additional exploratory efficacy analyses were added to both Section 5.4.1 (Efficacy Endpoints) and Table 5.6 (Secondary and Exploratory Efficacy Variables and Analysis Methods).
- For MIDAS, the clarification is added to state that "No imputation is needed when calculating the total score, as patients are not allowed to send partial data."
- The calculation of duration of exposure to study drug was updated to use study phase disposition date (instead of derivation using half-life of LY2951742) when applicable.
- Analysis method for PGI-I was updated for clarification.
- Analyses of C-SSRS for SP IV were added.
- For categorical safety measures, analysis method was updated to Fisher's exact method instead of CMH method adjusting for pooled region1 because it is it expected that pooled region1 variable should not have any impact on safety measures.
- "Upper respiratory tract infections" replaces "infections" in Section 5.5.12.1.1.3.
- Updated the subsetting criteria for analysis of elevation in ALT, AST, ALP, and TBIL.
- Response to previous migraine prevention therapy was updated based on eCRF, and a definition of previous migraine prevention therapy was added.
- Definition of concomitant therapy was added.
- Section 5.5.1.3. Definition of geographic regions was updated.
- Section 5.5.10.2. Sensitivity analysis to assess the robustness of primary analysis for missing data assumptions was updated to use the most recent approach recommended by Permutt (2015). Due to this change, the section 7 (appendix) for selection model was removed.
- Section 5.5.10.4. Corrected a typo in the multiple testing algorithm.
- Section 5.5.12.1.6. Immunogenicity was updated to clarify the study phases that will be included for each of the immunogenicity analyses and to provide additional listings.

- Section 5.5.13. Subgroup Analysis was updated.
  - Baseline ADA status was removed, i.e., no subgroup analyses will be conducted by baseline ADA status.
  - Subgroup analyses for safety measures were removed.
- Section 5.5.14 Exploratory Analysis was deleted.
- Section 5.6. Interim Analysis was updated due to faster enrollment and enrollment rate difference between CGAG and CGAH.

Statistical Analysis Plan Version 3 was approved prior to second interim analysis (the interim analysis for primary efficacy endpoint, which is the first unblinding to study team). The SAP version supersedes the statistical plans described in the protocol.

The changes incorporated in SAP Version 3 are as follows:

- In Section 5.4.1, derivation of the number of weekly migraine headache days in Month 1 was added. In Section 5.5.10.3, a detailed analysis approach for the number of weekly migraine headache days in Month 1 was added.
- In Section 5.4.3.1 MSQ Role-Function Restrictive Domain Responder definition was updated and other MSQ Domain Responder definitions were removed . In Section 5.5.11, analysis for MSQ Role-Function Restrictive Domain Responders was updated to refer to the "Statistical Analysis Plan for Psychometric Properties of the MSQ v2.1 Role Function-Restrictive Domain" for response threshold, and other MSQ Domain Responder analyses were removed.
- In Section 5.5.1.1, ANOVA/ANCOVA model was updated with pooled region1 removed from analyses for continuous safety measures.
- In Section 5.5.1.4, safety population and its definition were added.
- In Section 5.5.1.5, postbaseline visits for continuous efficacy and safety analyses (other than LOCF analyses) were clarified to include scheduled visits only. Also baseline and postbaseline definitions were updated for blood pressure, pulse and ECGs with detailed descriptions in each specific section.
- In Section 5.5.10.4, multiple comparison approach was updated to switch the order between 100% response rate and PGI-S.
- In Section 5.5.12.1.1.1, the analyses for potential allergic/hypersensitivity events were updated.

Statistical Analysis Plan Version 4 will be approved prior to second interim analysis (the interim analysis for primary efficacy endpoint, which is the first unblinding to study team). The SAP version supersedes the statistical plans described in the protocol.

The changes incorporated in SAP Version 4 are as follows:

- Section 5.5.3 title was updated to "Important Protocol Deviations". The detailed important protocol deviations table, which includes categories, subcategories, study-specific terms of important protocol deviations, source of identification, and the method to identify each deviation was added to Section 7 (Appendix).

- Section 5.5.8, Previous migraine prevention therapies definition was updated to "Previous migraine prevention therapies are those therapies that started prior to the date of the first injection and stopped prior to or at the date of first injection and indication is "primary study condition" or corresponding medical history event preferred term that includes "migraine".
- Section 5.5.10.2, for sensitivity analysis for missing data assumption, additional text were added to clarify that the multiple imputation method will be done for all missing data regardless of the reasons the data are missing; additional sensitivity analysis for normality assumption was added to examine the residuals from the primary analysis MMRM model and identify outliers.
- The section for primary analysis following design adaptation (previously numbered Section 5.5.10.3) was removed. This is due to the fact that after interim analysis #1 happened on Oct 2016, DMC recommended continuing the trial as is, without dropping any treatment arm. Following deletion of this section, which included Table 5.6, subsequent sections and tables were renumbered.
- Section 5.5.10.3, for the "Analyses for Number of Weekly Migraine Headache Days in Month 1" subsection, the additional term of "baseline number of migraine headache days by week interaction" was added to the model.
- Section 5.5.10.4, clarifying texts were added which did not change multiple comparison procedure.
- Section 5.5.11, the last sentence was updated to state that "The endpoint for comparing LY2951742 with placebo will be estimated using LSMESTIMATE statement in PROC MIXED as the average across Months 4- 6".
- Section 5.5.12.1.6, immunogenicity analyses have been updated based on additional input from the study team.
- Section 5.5.12, additional text was added to state that individual patient listings of data collected from CGAG Protocol Addendum 2 (CGAH Protocol Addendum 7) including concomitant medication, adverse events, and ADA measurements will be created.
- Throughout the document, "allergic / hypersensitivity events" has been changed to "hypersensitivity events"; "injection site reactions" has been changed to adverse events related to injection sites. When it refers to a high level term, it remains as "injection site reactions".
- Section 5.8.2, for the reports to be generated at interim analysis #2, text was updated to add a few additional analyses that included data from Study Period IV. It also clarified that those analyses will serve as an interim review of Study Period IV data and will be rerun again at final database lock.

4. Study Objectives

4.1. Primary Objective

The primary efficacy objective is to test the hypothesis that 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. Superiority is defined as greater improvement for LY2951742 compared with placebo, at an overall one-sided 0.025 significance level, 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 5.1 in Section 5.4.1).

4.2. Secondary Objectives

4.2.1. Key Secondary Objectives

If LY2951742 (120 or 240 mg/month) is statistically significantly superior to placebo on the primary objective, the following key secondary objectives will be tested with adjustment for multiplicity. The specific methodology (including testing order, relationship, and type I error allocation and propagation) for tests of the key secondary measures are specified in Section 5.5.1.4.

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

Table 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 of 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	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 or headache 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 4.2 reflect the comparison of LY2951742 (120 or 240 mg/month) with placebo. No multiplicity adjustment will be implemented for the secondary objectives.

Table 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 proportions of patients demonstrating ≥30% reduction from baseline in the number of 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 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 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
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

List of Other Secondary Objectives and Their Endpoints

Other Secondary Objectives	Endpoints
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 Month 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)
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 LY2951742 with respect to immunogenicity	Throughout the study: • Development and consequences of anti-drug antibodies and neutralizing anti-drug antibodies to LY2951742
To evaluate LY2951742 with respect to pharmacokinetics	Serum concentrations of LY2951742
To evaluate LY2951742 with respect to pharmacodynamics (target engagement)	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 • Time to first loss of response 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

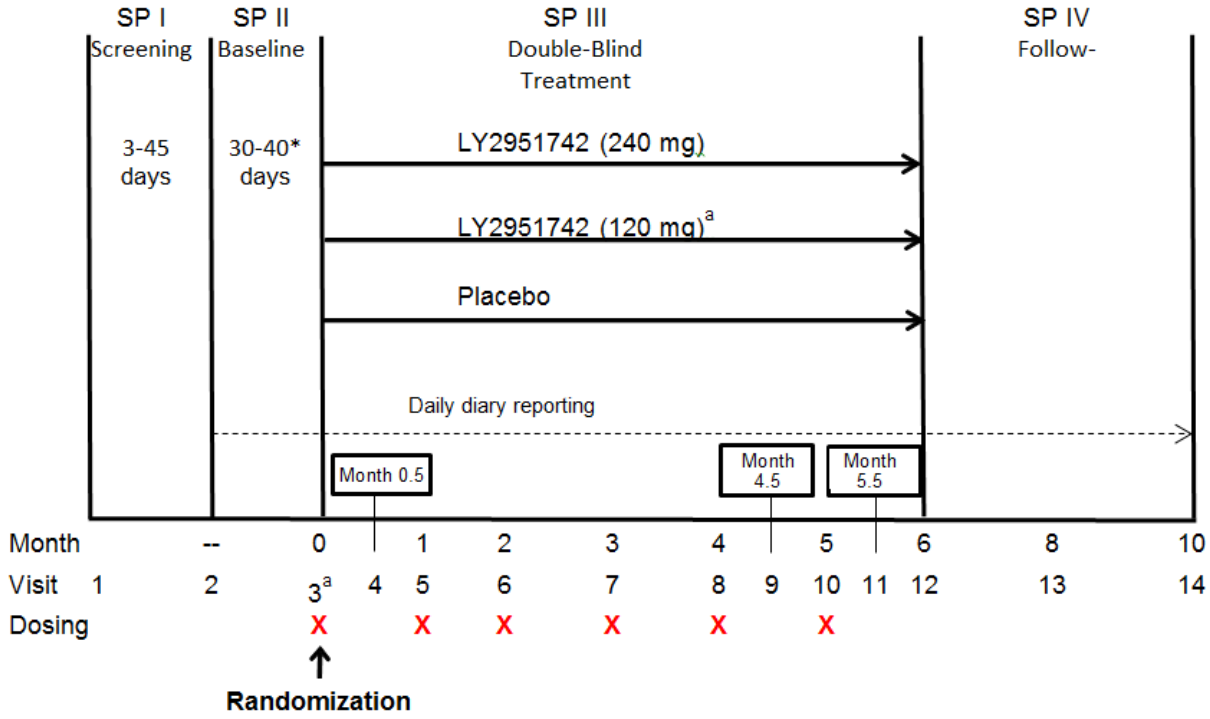
4.3. Exploratory Objectives

Table 4.3. List of Exploratory Objectives and Their Endpoints

Objectives	Endpoints
CCI	
To explore the effect of LY2951742 on non-migraine chronic pain	Mean change from baseline in average pain severity of other chronic pain conditions.
To compare LY2951742 with placebo with respect to categorical changes in quality of life	Percentages of patients with • ≥50% improvement in MIDAS total score • change from baseline in MSQ Role Function-Restrictive ≥10.9 • change from baseline in MSQ Role Function-Preventive ≥8.3 • change from baseline in MSQ Emotional Function ≥12.2
To compare LY2951742 with placebo with respect to the proportion of migraine headache days requiring medication for the acute treatment of migraine or headache	Change from baseline in the proportion of monthly migraine headache days requiring medication for the acute treatment of migraine or 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

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).

Abbreviations: SP = study period.

Figure 5.1. Study I5Q-MC-CGAG and Study I5Q-MC-CGAH protocol design.

5.2. Determination of Sample Size

The study will enroll approximately 825 patients. Eligible patients will be randomized in blinded fashion in a 2:1:1 ratio to placebo (approximately 413 patients), LY2951742 120 mg/month (target of 206 patients), or 240 mg/month (target of 206 patients). With the assumption of a 26% discontinuation rate and an effect size of 0.33 in the last month of the 6-month treatment phase, it is estimated that this sample will provide approximately 95% power that at least 1 dose of LY2951742 will separate from placebo at a one-sided 0.025 significance level based on simulations using Dunnett test. Assumptions were based on data from 2 double-blind, placebo-controlled, Phase 2 studies, with adjustment to reflect the longer treatment duration and greater variability expected in a larger, multi-country, Phase 3 study.

Approximately 1557 patients may be screened to ensure randomization of 825 patients, with an estimated 611 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 413 on placebo, 206 on LY2951742 120 mg, and 206 on LY2951742 240 mg). Randomization will be stratified within each region (as defined in region1 in Table 5.4 in Section 5.5.1.3) and by baseline migraine frequency (<8 migraine headache days per 30-day period, and ≥8 migraine headache days per 30-day period). To ensure an appropriate balance of low- and high-frequency patients, the enrollment of low-frequency patients will be stopped if the number of low-frequency patients exceeds 578.

5.4. Endpoints

5.4.1. Efficacy Endpoints

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

Table 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 one of the following: • Nausea and/or vomiting • Photophobia and phonophobia *(Definition adapted from the Standard International Headache Society [IHS] International Classification of Headache Disorders (ICHD)-3 beta)*
Probable migraine	A headache of ≥30 minutes, with or without aura, but missing 1 of the migraine features in the IHS ICHD-3 beta definition. To be exact, it meets either at least two A criteria and zero B criteria, or one A criterion and at least one B criterion.
Migraine headache day (primary objective)	A calendar day on which a migraine headache or probable migraine headache occurs.
ICHD migraine headache day	A calendar day on which a migraine occurs.
Migraine headache attack	Beginning on any day a migraine headache is recorded and ends when a migraine-free day occurs.

Migraine and Headache Endpoint Definitions

Diagnosis	Definition/Criteria
Non-migraine headache	All headaches of ≥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 occurs.
Headache day	A calendar day on which any type of headache occurs (including migraine, probable migraine, and non-migraine headache).

Headache information will be collected via an 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 5.2.

Table 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 adjusted 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 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 2 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 2 visits is odd, then the days will be split similarly, but the first one-month period will have 1 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 1 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. The same approach will also be applied to secondary and exploratory efficacy measures that are derived from ePRO data.

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, 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. For the rest of months and patients, the compliance rate will be calculated as described in Section 5.5.7.

Other Secondary and Exploratory Efficacy Measures

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 which 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 5JAN and ending on 6JAN will result in a migraine/probable migraine-free day on 7JAN (assuming that there is no migraine/probable migraine on 7JAN). This will count as 1 migraine attack that started on 5JAN and ended on 6JAN. For a migraine attack that begins in one 30-day period but ends in another, only 1 migraine attack will be counted in the first of the 2 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 1 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 of migraine or headache on migraine headache days 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** 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 3 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 criterion in the number of migraine headache days for 3 consecutive months to patient's endpoint in the double-blind treatment phase.
- **50% responders sustained for all 6 months during treatment phase in the number of migraine headache days** is defined as meeting 50% responder criterion in the number of migraine headache days for Months 1-6 in the double-blind treatment phase.
- **Time to first 50% response (in months)** is defined as the first month when 50% response is met during double-blind treatment phase (SP III). If a patient has not met 50% response during SP III, they will be censored at the last month where 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 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 disposition date of previous study period before entering post-treatment follow-up phase minus the date of start of the migraine preventive medication (based on information collected from concomitant medication electronic case report form [eCRF]) in post-treatment follow-up phase (Study Period IV, SP IV). 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 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 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 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 headache days with an answer of "yes" to Question 13 in a 30-day period.
- **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, proportion of aura among migraine attack is calculated as the total number of migraine attacks with aura divided by total number of migraine attacks.
- **Number of days with abortive medication use** is calculated as the number of calendar days in a 30-day period on which 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 $i = 0,1,..,5$.

- **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 $i = 0,1,..,5$.

- **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 is 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 is 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 2 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 2 classes of the following 5 classes on a day: triptans, NSAIDs/aspirin, Acetaminophen/paracetamol, ergots, anti-nausea.
- **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 will be counted as week 4.

Combination medications (such as aspirin/acetaminophen/caffeine) will be counted in each medication category that applies (such as NSAIDs/aspirin and Acetaminophen/paracetamol).

5.4.2. Other Efficacy Measures

5.4.2.1. Patient Global Impression

The Patient Global Impression of Severity (PGI-S) will be collected at baseline and monthly post-baseline visits. 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).

The Patient Global Impression of Improvement (PGI-I) will be collected at monthly post-baseline visits during the treatment phase.

Change from baseline in PGI-S scores will be analyzed. Patient Global Impression of Improvement scores at post-baseline visits will be analyzed by adjusting for PGI-S score at baseline.

5.4.2.2. Non-Migraine Chronic Pain Assessment 

The Lilly-developed non-migraine chronic pain assessment (questions shown below) will provide exploratory information on any changes in non-migraine chronic pain conditions that patients may be experiencing. The following questions are to be collected:

Q1: Does the subject have any non-migraine chronic pain conditions?

- Yes
- No

If Yes, go to Q2 and Q3.

Q2: What is the subject's chronic pain condition?

- AE Number: _____
- Medical History Number: ____

Q3: In the past week, what was the subject's average pain score related to this condition?

- 0 – No Pain
- 1-9 - The patient would enter value of 1–9, and the bigger the number, the worse the pain.
- 10 – Worst pain imaginable

The average pain score of all non-migraine chronic pain conditions will be derived for each subject by averaging the pain scores of all reported non-migraine chronic pain conditions. The mean change from baseline in the average pain score will be used as the analysis value.

If a specific non-migraine chronic pain condition is reported by more than 15% of the study population at baseline, the pain score of that specific condition will also be analyzed.

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 3 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 5.3. All item values range from1 to 6. Final item value will be used as for analysis with higher score reflecting better quality of life.

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

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. In general, no imputation for missing values is necessary because the MSQ was collected using patient direct data entry on an electronic device which did not allow patients to skip items. Patient either completed the scale in its entirety or not at all.

The raw score of each domain will be calculated as the sum of the raw scores of each question in that domain, using imputed scores where applicable. Should it be the case that the number of missing responses was more than half the questions in that domain, meaning that imputation of missing scores will not be done, the raw score for that domain will not be calculated, hence missing.

The total score of all 3 domains will be calculated as the sum of raw scores of 3 domains. If any of the 3 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):

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

If any of the Role Function-Restrictive, Role Function-Preventive or Emotional Function domain is missing, then the total score will be missing, otherwise, the total score will be calculated as the sum of Role Function-Restrictive, Role Function-Preventive, and Emotional Function domain scores.

Responders in Role Function-Restrictive will be derived as outlined in "Statistical Analysis Plan for Psychometric Properties of the MSQ v2.1 Role Function-Restrictive Domain."

5.4.3.2. MIDAS (Migraine Disability Assessment) Questionnaire

The Migraine Disability Assessment questionnaire (MIDAS) consists of 5 questions (Q1-Q5) and 2 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.

5.4.4. 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, 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.

5.5. Statistical Analyses

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

5.5.1. General Considerations

Treatment effects will be evaluated based on an overall one-sided significance level of 0.025 for all efficacy and safety analyses. Ninety-five percent confidence intervals (CIs) for the difference in least-square means (LSMeans) between treatment groups will be provided.

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. Additionally, an analysis of variance (ANOVA) or an analysis of covariance (ANCOVA) model will also be used to analyze the change from baseline to the average monthly measures during 6-month treatment phase (for measures with corresponding objectives evaluated over the 6-month treatment period), or to last observation carried forward (LOCF) endpoint (for measures with corresponding objectives evaluated at Month 6).

For other continuous variables, the change from baseline to LOCF endpoint will be analyzed using an 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 LSMeans will be used for the statistical comparisons.

Binary variables with repeated measures will be analyzed in a generalized linear mixed models (GLIMMIX) as pseudo-likelihood-based mixed effects repeated measures analysis.

For categorical efficacy variables without repeated measures, comparisons between treatment groups will be performed using logistic regressions to adjust for more covariates (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 specified otherwise, Fisher's exact test will be used for comparisons of baseline measures (eg, baseline patient characteristics, previous therapy, etc.) and categorical safety measures; logistic regression will be used for comparisons of post-baseline efficacy measures.

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.

Comparisons between LY2951742 and Placebo refer to comparison of each LY2951742 arm with Placebo.

5.5.1.1. Adjustments for Covariates

The MMRM models will include the fixed, categorical effects of treatment, pooled region1, 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. Pooled region1 is defined in Section 5.5.1.3. Pooled region1 will be excluded from MMRM models for safety measures.

When an ANOVA model is used to analyze a continuous efficacy variable at the LOCF endpoint, the model will contain the main effects of treatment and pooled region1. When an ANCOVA model is used to analyze a continuous efficacy at the LOCF endpoint, the model will contain the main effects of treatment and pooled region1 and appropriate baseline value as a covariate. When an ANOVA or ANCOVA model is used to analyze a continuous safety variable, the pooled region1 will be removed from the model.

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. Pooled region1 and the baseline value-by-month interaction will be excluded from the model in order to increase the likelihood of convergence.

When a logistic regression is used to analyze a binary variable, the model will include the main effect of treatment, pooled region1 (if appropriate), and appropriate baseline value as a covariate. Pooled region1 may be excluded from the model in case of non-convergence.

With the exception of efficacy analyses on migraine headache days or categorical analysis of response rate (such as 50% response rate) derived from migraine headache days where the continuous value of baseline migraine headache days will be used as covariate, all other efficacy analyses will include baseline number of migraine headache days category (<8 vs ≥ 8) as a covariate in the MMRM, AN(C)OVA, GLIMMIX and logistic regression model. Specifically, 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 migraine headache days category (<8 vs ≥ 8) as 1 of the covariates.

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/ANOVA model using change from baseline to the average of observed monthly values during 6 months of treatment phase (for measures with objectives evaluated during the entire 6 months of treatment phase), or change from baseline to LOCF endpoint (for measures with objectives evaluated at Month 6).

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 missing at random.

Please refer to Section 5.4.1 for approach to handling missing diary data for derivation of the number of migraine headache days and other efficacy measures (with the exception of migraine attacks) derived from ePRO data per 30-day period.

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 diary 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 for compliance rate calculation.

5.5.1.3. Definition of Geographic Regions

In CGAG, eligible patients will be randomized within each of the following 4 regions: United States (US) east, US west, Puerto Rico, and Canada. In CGAH (which includes additional countries from European Union (EU) and other regions), eligible patients will be randomized within each country.

In CGAH and integrated efficacy analysis, subgroup analyses for primary measure will be done by a subgroup variable of region defined below:

- North America, including the US;
- Europe, including United Kingdom (UK), Netherlands, Spain, Czech, and Germany;
- Other, including Argentina, Israel, Korea, Taiwan, and Mexico

In order to clarify the different definitions of regions and be consistent for CGAG and CGAH, 2 variables of regions are defined. Region1 is the smallest geographic area within which the randomization is done. Region2 is a larger geographic area which defines the subgroup variable of region. The definitions are summarized in Table 5.4 below.

All regions in region1 (as defined in Table 5.4 below) with fewer than 2 randomized patients per LY-treated group or fewer than 4 randomized patients in placebo group with nonmissing baseline and at least 1 post-baseline values of the number of migraine headache days will be pooled.

All analyses will use pooled region1, unless otherwise specified.

Table 5.4. Definition of Region1 and Region2

Variable Name	Definition in CGAG	Definition in CGAH
Region1 (Randomization Region)	• US east • US west • Canada • Puerto Rico	• Country
Region2 (Subgroup Region)	NA* (all from one region, ie, North America, including the US and Canada)	• North America, including the US; • Europe, including UK, Netherlands, Spain, Czech, and Germany; • Other, including Argentina, Israel, Korea, Taiwan, and Mexico

*No subgroup analysis by region2 for CGAG since all patients will be from North America.

5.5.1.4. Analysis Populations

There were 3 analysis populations defined:

- **Intent-to-Treat (ITT) Population**: All patients who are randomized and received at least one dose of study drug.
- **Safety Population**: This population is the same as the ITT population defined above.
- **Post-treatment Population**: All patients who entered the post-treatment phase (Study Period IV) as indicated by entering any post-treatment visit (telephone or office visit). Analyses of Study Period IV only (that is, excluding Study Period III) will be based on the post-treatment population.

Unless otherwise specified, all analyses will be conducted according to the ITT principle on the ITT population. That is, patients will be analyzed according to the treatment they were randomized to, regardless of whether they actually received a different treatment.

Safety analyses (in Section 5.5.12), as well as analyses for disposition and exposure, will be conducted based on the modal treatment the patient received during the double-blind treatment period. 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.

5.5.1.5. Baseline and Post-Baseline Definition

Table 5.5 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 5.5. 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 or average of observed monthly values)	ITT population with a baseline and at least one post-baseline observation	Visit 3	All scheduled visits 3<Visits<=12
Primary/secondary/exploratory efficacy analyses at LOCF endpoint	ITT population with a baseline and at least one post-baseline observation	Visit 3	Last of 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 scheduled visits 3<Visits<=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	Last of Visit 3.01-12
TEAEs	Safety population	All Visits 1-3	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	Low: Minimum value from Visits 1-3 High: Maximum value from Visits 1-3	Low: Minimum value from Visits 3.01-12 High: Maximum value from Visits 3.01-12
Treatment emergent immunogenicity	Safety population	Visit 3	All Visits 3.01-12
Treatment emergent changes in temperature and weight	Safety population with a baseline and at least one post-baseline observation	Low: Minimum value from Visits 1-3 High: Maximum value from Visits 1-3	Low: Minimum value from Visits 3.01-12 High: Maximum value from Visits 3.01-12

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			
Treatment emergent changes in blood pressure, pulse, and ECGs	Safety population with a baseline and at least one post-baseline observation	Low: Last non-missing from Visits 1-3 High: Last non-missing from Visits 1-3	Low: 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	All 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 of Visits 3.01-12
Study Period III and IV combined			
Primary/secondary/exploratory efficacy analyses	ITT population with a baseline and at least one post-baseline observation	Visit 3	All scheduled visits 3<Visits≤14
Quality of Life analyses	ITT population with a baseline and at least one post-baseline observation	Visit 3	All scheduled visits 3<Visits≤14
Continuous safety analyses (repeated measures)	Safety population with a baseline and at least one post-baseline observation	Visit 3	All scheduled visits 3<Visits≤14
Treatment-emergent immunogenicity	Safety population	Visit 3	All Visits 3.01-14
Study Period IV			
Post-treatment–emergent adverse events	Post-treatment population	All Visits 1-12	All Visits 12.01-14
Serious adverse events, discontinuations due to adverse events	Post-treatment population	NA	All Visits 12.01-14
Post-treatment–emergent abnormal laboratory values	Post-treatment 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	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
Treatment-emergent immunogenicity	Post-treatment population	Visit 3	All Visits 12.01-14

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 IV			
Treatment-emergent changes in temperature and weight	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
Treatment-emergent changes in blood pressure, pulse and ECGs	Post-treatment population with a baseline and at least one post-baseline observation	Low: Last non-missing from Visits 1-12 High: Last non-missing from Visits 1-12	Low: Minimum value from Visits 12.01-14 High: Maximum value from Visits 12.01-14

Abbreviations: ANCOVA = analysis of covariance; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; ITT = intent-to-treat; LOCF = last observation carried forward; NA = not applicable; 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.

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

5.5.2. Patient Disposition

The number and percentage 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 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.

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

Patient allocation by investigator will also be listed for all study periods.

5.5.3. Important Protocol Deviations

Important protocol deviations that potentially compromise the data integrity and patients' safety will be summarized by treatment group for all intent-to-treat population.

Section 7 (Appendix) contains a table that lists the categories, subcategories, and study-specific terms of important protocol deviations, source of identification, and the method to identify each deviation. Per study team's discretion, for non-programmable protocol deviations, additional categories and subcategories other than the ones in Appendix Table 1 can always be added into the final non-programmable protocol deviations list, as deemed necessary.

A table and listing of important protocol deviations for Intent-to-Treat patients during baseline, double-blind treatment phase, or post-treatment phase, will be provided by each randomized treatment arm and overall.

5.5.4. Patient Characteristics

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

- Demographic (age, gender, ethnic origin, height, weight, body mass index)
- Migraine and/or headache measures per 30-day baseline period.
    - number of migraine headache days
    - number of migraine headache days with abortive (acute) medication use
    - number of migraine headache hours
    - number of migraine attacks
    - number of headache days
    - number of moderate-severe headache days
    - number of headache hours
    - number of ICHD migraine headache days

- mean severity of migraine headaches
- number of migraine headache days with aura
- number of migraine headache days with nausea and/or vomiting
- number of migraine headache days with photophobia and phonophobia
- number of migraine headache days with prodromal symptoms other than aura
- Had migraine with Aura at baseline
- Prior migraine preventive treatment:
  - Without prior migraine preventive treatment
  - With prior migraine preventive treatment and did not fail
  - With prior migraine preventive treatment and failed at least 1 medication
  - With prior migraine preventive treatment and failed at least 2 medications.
  - Number of prior migraine treatment failed: 1, 2, 3, …
- Baseline number of migraine headache day category (<8 versus ≥8)

- PGI-S
- Alcohol, tobacco, caffeine and nicotine consumption
- Medical history and Pre-existing condition

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.

Medical history and pre-existing conditions will be summarized by preferred term (PT) within system organ class (SOC), and comparison between treatment groups will be performed using Fisher's exact test. Medical history is defined as illness(es) that ended prior to the signing of informed consent. Pre-existing conditions and AEs at baseline are those AEs occurring during the baseline/screening visits for the study period, that is, Visit 1, 2, and 3.

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 information will be recorded on the eCRF for each dose:

- Confirmation that the patient received the IMP (including reason if the IMP was not given)
- Date and time of administration

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 disposition date – first date IMP administered +1.
- For treatment phase (SP III), number and percentage of patients with 1, 2 and 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 Fisher's exact test.

In addition, injections not administered will be listed.

5.5.6. Treatment Compliance

Treatment compliance will be calculated for Study Period III as:

$$\frac{\text{number of doses received} * 100}{\text{number of intended doses}}$$

Comparisons between treatments for treatment compliance will be performed using an ANOVA with treatment in the model. For this analysis, partial dose (for example, a patient only got 1 injection instead of 2) will be considered as no dose received.

5.5.7. Electronic Patient Reported Outcomes Diary Compliance

Electronic patient reported outcomes diary compliance at each 1-month period (including baseline, Month 1, 2, 3, … till Month 10) as well as for SP III overall (Month 1 through Month 6) will be calculated. 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 is calculated as date of injection (date of visit for post-treatment follow-up phase) at the end of interval minus date of injection (date of visit for post-treatment follow-up phase) at the beginning of the interval +1.

Treatment comparisons for diary compliance for each period will be performed separately using an ANOVA with treatment and pooled region1 in the model.

5.5.8. Previous Migraine Prevention Therapy

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 all ITT patients. Treatment group comparisons will be done using Fisher's exact test. Previous migraine prevention therapies are those therapies that started prior to the date of the first injection and stopped prior to or at the date of first injection and indication is "primary study condition" or corresponding medical history event preferred term that includes "migraine".

5.5.9. Concomitant Therapy

The proportion of patients who received concomitant medication collected from eCRF as well as abortive medications collected through ePRO will be summarized for all ITT patients for Study Period III and Study Period IV separately. Concomitant therapies for Study Period III are those which 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 a 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.

Treatment group comparisons will be done using 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 post-treatment population.

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 restricted maximum likelihood (REML)-based mixed models repeated measures (MMRM) technique. The analysis will include the fixed categorical effects of treatment, pooled region1, 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 with both the Hessian and the G matrix being positive definite under the default fitting algorithm used by PROC MIXED, the Fisher scoring algorithm will be implemented by specifying the SCORING option 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
- Heterogeneous First-order autoregressive
- Toeplitz
- First-order autoregressive

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 option in SAS®. SAS® PROC MIXED will be used to perform the analysis.

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). Specific details of the testing procedure for the primary outcome and the secondary gatekeeper objectives are provided in Section 5.5.10.4.

The results of the statistical tests 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, then the earliest month when statistical significance is observed and maintained for all the subsequent months during double-blinded treatment phase will be considered as the onset of effect.

5.5.10.2. Sensitivity Analysis for Primary Outcome

Two types of sensitivity analyses are planned to assess the robustness of deviations from the assumptions of primary analysis including normality assumption and missing data assumption. Another sensitivity analysis is planned to explore the influence of slight change in the definition of episodic migraine prevention.

Missing Data Assumption

Sensitivity analyses will be performed to assess the robustness of the primary analysis conclusions to deviations from missing at random (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 ($\Delta_{120},\Delta_{240},\Delta_P$) to the predictions in the LY2951742 120 mg/month, LY2951742 240 mg/month, and placebo treatment groups respectively, regardless of the reason the data are missing. This approach is consistent with the sensitivity approach suggested in Permutt (2015). This procedure will be repeated multiple times for different values of ($\Delta_{120},\Delta_{240},\Delta_P$) 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. $\Delta_{120},\Delta_{240,\text{ or }}\Delta_P$) 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 ($\Delta_{120},\Delta_{240},\Delta_P$) 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, pooled region1, 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, pooled region1 and/or baseline-by-month interaction may be excluded from the model. Directional consistency of treatment effects from this model and the primary analysis MMRM model as specified in Section 5.5.10.1 will be examined.

In addition, as another form of sensitivity analysis, residuals from the primary analysis MMRM model will be examined and outliers identified. Consistency of results before and after removing patients with outlier residuals will be examined.

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 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 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 one of the following:
   - Nausea and/or vomiting
   - Photophobia and phonophobia

OR

C. Patient takes a triptan or ergot derivative.

5.5.10.3. Secondary and Exploratory Efficacy Analyses

Table 5.6 summarizes all the planned secondary and exploratory efficacy analyses for Study Period III and Study Period III/IV. All response rates are derived from migraine headache days.

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.

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.

In addition to the repeated measures analyses, the mean change from baseline to the average monthly measures during 6-month treatment phase or LOCF endpoint in study period III will be estimated for the continuous efficacy measures using ANCOVA models with covariates adjustment described in Section 5.5.1.1.

Binary Efficacy Measures

For the repeated binary efficacy measures such as responder indicators based on the number of migraine headache days, the visit wise 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). 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.

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

- Heterogeneous Toeplitz,
- Heterogeneous autoregressive,
- Toeplitz, and
- Autoregressive.

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 visit wise indicators of 50% responders, the results of the statistical tests at each month in the double-blinded treatment phase from categorical MMRM analysis 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, baseline and pooled region1 will be conducted.

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

The following measures are conditional on the number of migraine headache days >0:

- Mean severity of remaining migraine on migraine headache days
- Proportion of migraine headache days with abortive (acute) medication use

They will be modelled individually using 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. 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, pooled region1, week, and treatment-by-week interaction, as well as the continuous, fixed covariate of baseline number of migraine headache days 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 pooled region1 and 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
- Time to initiation of preventative treatment for migraine or probable migraine in post-treatment phase

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-I

The PGI-I raw value will be analyzed with a mixed model repeated measures analysis where the covariates are the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline PGI-S score and baseline PGI-S score-by-visit interaction.

Table 5.6. Secondary and Exploratory Efficacy Variables and Analysis Methods

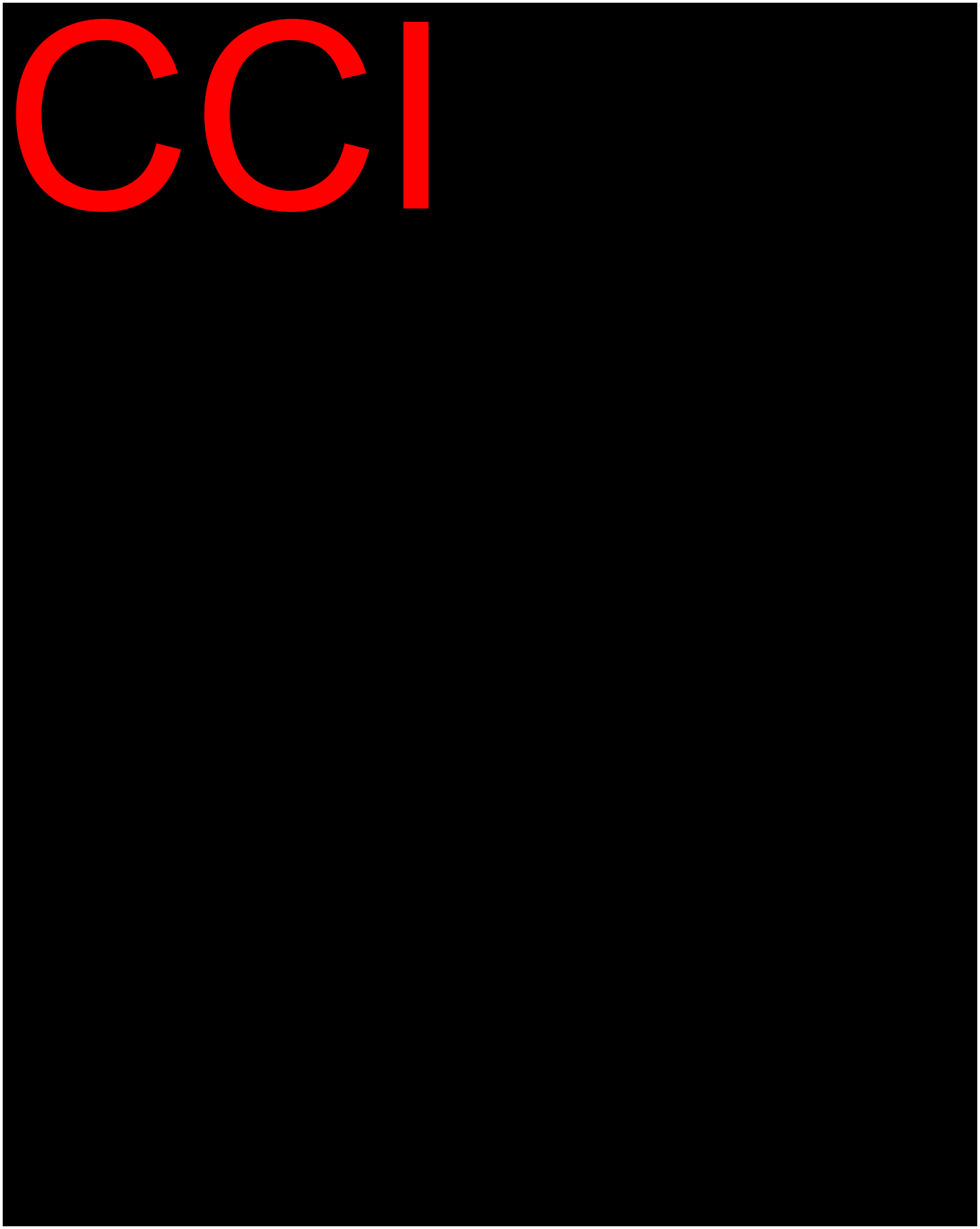
Efficacy Variables	Analysis in SP III	Analysis in SP III/IV
Number of migraine headache hours	MMRM, ANCOVA[a]	MMRM for SP III/IV
Number of migraine attacks		
Number of migraine headache days with abortive (acute) medication use		
Proportion of migraine headache days with abortive (acute) medication use		
Number of headache days		
Number of moderate-severity headache days		
Number of headache hours		
Number of ICHD migraine headache days		
PGI-S		
PGI-I (adjusting for PGI-S)		
Average Pain Score for non-migraine chronic pain		
Mean severity of migraine headache		
Number of migraine headache days with nausea and/or vomiting	MMRM	
Number of migraine headache days with photophobia and phonophobia		
Number of migraine headache days with aura		
Number of migraine headache days prodrome symptoms other than aura		
Number of non-migraine headache days with aura		
Proportion of aura among migraine attacks		
Number of days with abortive medication use		
Number of classes of abortive medication use		
Number of classes of abortive medication use on migraine headache days		
Average number of classes of abortive medications use		
Average number of classes of abortive medications use on migraine headache days		
Number of days with triptans use		
Number of migraine headache days with triptan use		
Number of days with NSAIDs/aspirin use		
Number of migraine headache days with NSAIDs/aspirin use		

Secondary and Exploratory Efficacy Variables and Analysis Methods (cont)

Efficacy Variables	Analysis in SP III	Analysis in SP III/IV
Number of days with NSAIDs/aspirin use		
Number of migraine headache days with NSAIDs/aspirin use		
Number of days with acetaminophen/paracetamol use		
Number of migraine headache days with acetaminophen/paracetamol use		
Number of days with ergots use		
Number of migraine headache days with ergots use		
Number of days with anti-nausea medication use		
Number of migraine headache days with anti-nausea medication use		
Number of days with Multi-Class abortive medication use		
Number of migraine headache days with multi-class abortive medication use		
Average number of abortive medication classes		
Average number of abortive medication classes on migraine headache days		
X% response rate (X=30, 50, 75, or 100) (visit wise)	GLIMMIX	GLIMMIX
50% response sustained for 3 consecutive months until patient's endpoint in 6-month treatment phase	Logistic regression	NA
50% response sustained from month 1 to month 6		
Distribution of response rate in SP III	GLIMMIX (to get estimated response rates)	N/A
Time to first 50% response in SP III	Kaplan-Meier curve and stratified log-rank test	N/A
Time from the end of SP III to no longer meeting 50% response criterion	N/A	Kaplan-Meier curve and stratified log-rank test for SP V
Time from the end of SP IV to start use of preventative treatment for migraine		
Number of weekly migraine headache days in month 1	Ordinal repeated measures model implemented with GLIMMIX	NA

Abbreviations: ANCOVA = analysis of covariance; GLIMMIX = Generalized linear mixed model (for binary variables); MMRM = Mixed models repeated measures; SP = Study Period; NA = not applicable.

a ANCOVA for change from baseline in the average of monthly values for measures with corresponding objectives evaluated during 6-month treatment phase, or change from LOCF endpoint at Month 6 for measures with corresponding objectives evaluated at Month 6.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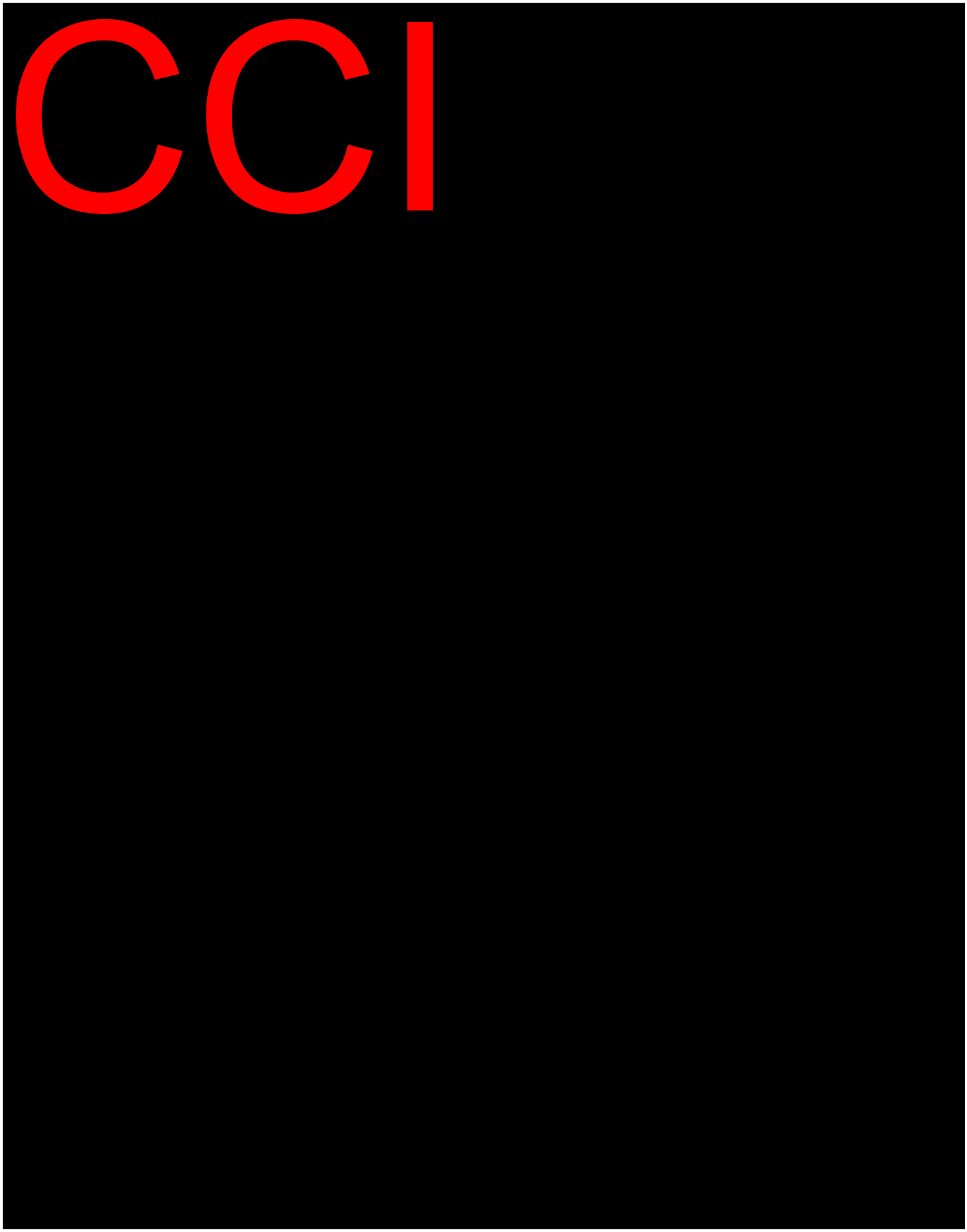
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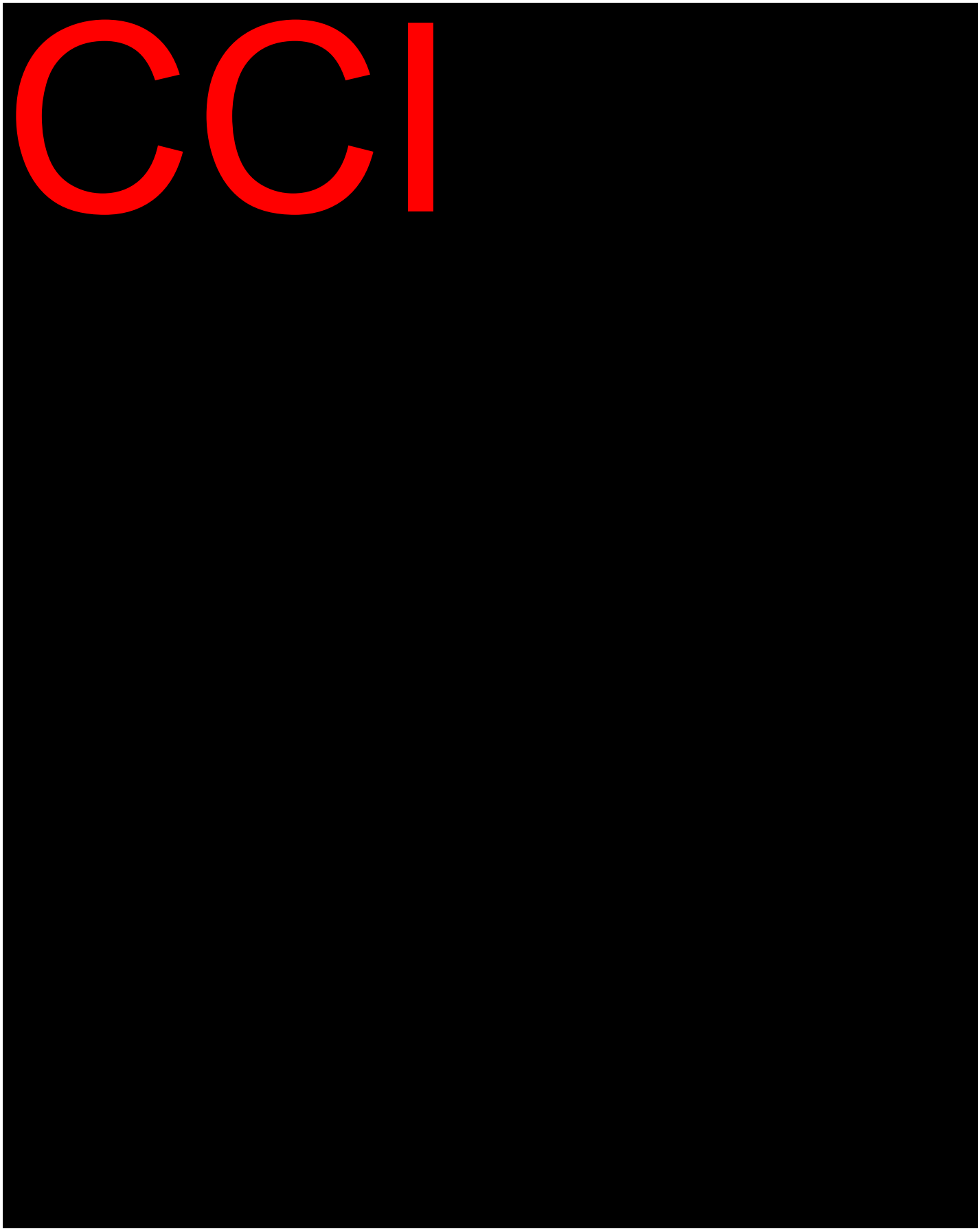
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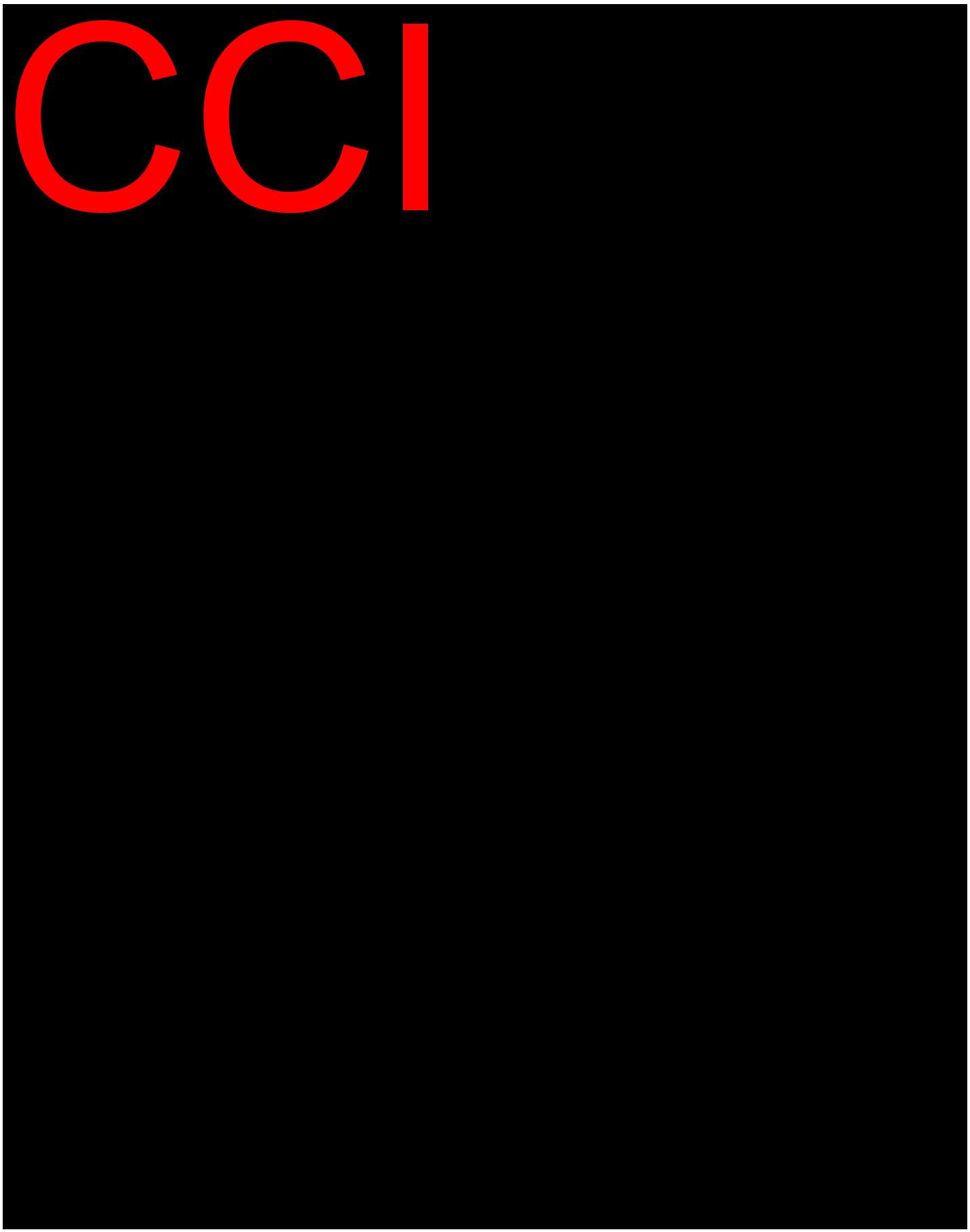
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5.5.11. Quality-of-Life (QoL) Analyses

The mean change from baseline to each post-baseline visit for Study Period III and Study Period III/IV for MIDAS (item scores and total score), I as defined in Section 5.4.3 will be evaluated using MMRM as described in Section 5.5.10.1.

The mean change from baseline to each post-baseline visit for Study Period III and Study Period III/IV for MSQ total score and domain scores averaged across Months 4-6 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 LSMESTIMATE statement in PROC MIXED as the average across Months 4-6.

Mean change from baseline to LOCF endpoint in the 6-month treatment phase for above quality of life measures will be evaluated using the ANCOVA model as described in Section 5.5.10.1.

The MSQ Role Function Restrictive domain responders and MIDAS responders will be analyzed using GLIMMIX. The threshold for MSQ Role-Function Restrictive Domain Response will be derived as outlined in "Statistical Analysis Plan for Psychometric Properties of the MSQ v2.1 Role Function-Restrictive Domain." The threshold for MIDAS response will be a 50% improvement from baseline in MIDAS total score.

5.5.12. Safety Analyses

The safety analyses will be conducted for Study Period III, Study Period IV, as well as Study Periods III and IV combined.

For Study Period III and Study Period IV separately, the safety analyses outlined in the following sub-sections will be conducted.

For Study Period III and IV combined, only the change from baseline with MMRM analysis (Section 5.5.10.1) will be conducted.

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

- TEAEs
  - By PT by decreasing frequency
  - By SOC

  - By maximum severity
  - By High Level term
  - By considered to be related to investigational produce by investigator
- SAEs
- AEs leading to discontinuation
- 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 5.5 unless specified otherwise.

As summarized in CGAG protocol addendum 2 (CGAH Protocol Addendum 7), to characterize the time course of treatment-emergent ADA, additional data will be collected after patients completed or discontinued from study. Individual patient listings of those data including concomitant medication, adverse events and ADA measurements will be created.

5.5.12.1. Categorical Safety Variables

Unless specified otherwise, the categorical safety analyses will include both scheduled and unscheduled visits. 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 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.

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 baseline phase. 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.

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

Adverse event leading to discontinuation will also be summarized.

5.5.12.1.1.1. Potential Hypersensitivity Events

Potential hypersensitivity events (immediate and nonimmediate) will be identified from a review of preferred terms generated from the following queries:

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

A listing of patients having an event identified from these analyses will be medically reviewed to determine if the terms identified represent actual hypersensitivity events. Listings should include information on timing of event relative to last administered dose of study drug, the event term from this query, other AEs for the patient and timing, any abnormal laboratory findings, medical history, and anti-drug antibody test results including titer. Only those that are judged medically to be hypersensitivity events will be included in the final tables.

The number and percentage of patients with TEAEs, SAEs, and AEs resulting in study drug discontinuation 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 will be summarized by treatment groups using MedDRA PT.

The number and percentage of patients with TEAEs hypersensitivity events by timing 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 four categories:

- 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

The relationship between the development of TEAE of hypersensitivity events and treatment-emergent ADA within LY2951742 dose groups will be examined.

5.5.12.1.1.2. Adverse Events Related to Injection Sites

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, SAEs related to injection sites, and AEs related to injection sites resulting in study drug discontinuation will be summarized using MedDRA PT nested within the High Level Term. 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 will be summarized by treatment groups using MedDRA PT nested within the High Level Term. 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 related to injection sites by timing will be summarized using MedDRA preferred terms ordered by decreasing frequency. Note the timing of AEs related to injection sites is collected through eCRF and categorized into the same categories as for hypersensitivity events.

The relationship between the development of TEAEs related to injection sites and TEAEs of hypersensitivity events will be explored for all treatment groups. Additionally, the relationship between the development of TEAEs related to injection sites and treatment emergent ADA will be explored for LY2951742 group.

5.5.12.1.1.3. Upper Respiratory Tract Infections

Upper respiratory tract infections will be defined using all the PTs from the 2 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 will be summarized by treatment group using MedDRA PTs. Events will be ordered by decreasing frequency in the pooled LY2951742 group.

The number and percentage of patients with TEAEs of upper respiratory tract infections by maximum severity 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.

By-subject listings of treatment-emergent upper respiratory tract infections, and upper respiratory tract infections leading to study drug discontinuation will be provided.

5.5.12.1.2. Suicide-Related Thoughts and Behaviors

Suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent occurring during treatment, based on the Columbia-Suicide Severity Rating Scale (C-SSRS), will be summarized by treatment. 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 1 of various composite measures during Study Period III and Study Period IV separately will be presented and compared. Composite measures include suicidal behavior (completed suicide, non-fatal suicidal attempts, interrupted attempts, aborted attempts, and preparatory acts or behavior), suicidal ideation [active suicidal ideation with specific plan and intent, active suicidal ideation with some intent to act without specific plan, active suicidal ideation with any methods (no plan) without intent to act, non-specific active suicidal thoughts, and wish to be dead], and suicidal ideation or behavior.

The number and percent of patients who experienced at least 1 of various comparative measures during treatment will be presented and compared for Study Period III and summarized for SP IV. Comparative measures include treatment emergent suicidal ideation compared to recent history, treatment emergent serious suicidal ideation compared to recent history, emergence of serious suicidal ideation compared to recent history, improvement in suicidal ideation at endpoint compared to baseline, and emergence of suicidal behavior 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 Study Period 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 12.02 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 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.
- 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 1 treatment group.

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 measurements will be taken when the patient is in a sitting position. Three measurements of sitting blood pressure and pulse will be collected at approximately 30-60 second intervals at every visit and the 3 sitting blood pressure measurements and 3 pulse values will be averaged and used as the value for that visit.

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. Treatment group comparisons will be performed using Fisher's exact test. Table 5.7 displays the criteria used to define treatment emergent changes in vital signs and weight. The last column of the table displays the patient populations defined by baseline categories, the treatment-emergent categorical changes will be analyzed for each of those patient populations. The criteria generally consist of 2 parts, an absolute threshold and a change from baseline amount. The baseline and post-baseline definitions for vital signs analyses are in Table 5.5.

Table 5.7 displays the criteria for categorical changes of interest in vital signs and weight, The last column of the table displays the patient populations defined by baseline categories.

The criteria generally consist of 2 parts, an absolute threshold and a change from baseline amount.

- The absolute threshold in the criteria is based on 1) minimum post baseline when the direction is low; 2) maximum post baseline when the direction is high.
- The change from baseline amount in the criteria is 1) decrease from baseline (defined below and in Table 5.5) to minimum post baseline when the direction is low; 2) increase from baseline (defined below and in Table 5.5) to maximum post baseline when the direction is high.

The baseline for SBP, DBP, and pulse is defined as the last non-missing baseline value during the baseline period (see Table 5.5). To be exact,

- For analyses including double-blind treatment phase, the baseline for SBP, DBP, and pulse is defined as the last non-missing value before randomization. The rationale for using the last available value in the baseline period is to minimize the potential

confound of discontinuing or dose stabilization of medications that modulate BP and pulse during the screening phase (which early in the baseline period).

- Similarly, for other study phases, the baseline is defined as the last non-missing value before patients enter the study phases of interest. The baseline definition was chosen to be consistent with the analysis approach for the double blind treatment phase as described above.

This baseline definition for SBP, DBP, and pulse applies to all analyses (both continuous and categorical) for SBP, DBP, and pulse.

The baseline and postbaseline values for temperature and weight are defined below (also in Table 5.5):

- For continuous analyses of temperature and weight, last nonmissing baseline during the baseline period will be used as the baseline.
- For the analyses of categorical changes of interest in temperature and weight,
    - the baseline is defined as the minimum value during baseline period when the direction of change is low.
    - the baseline is defined as the maximum value during baseline period when the direction of change is high.

Table 5.7. Criteria for Categorical Changes of interest in Vital Signs and Weight

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 (° F)	Low	<96° F and decrease ≥2° F	≥96°F
	High	≥101° F and increase ≥2° F	<101°F

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

5.5.12.1.4. Electrocardiogram Intervals and Heart Rate

Analyses of corrected QT (QTc) interval will be calculated using 2 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, the QT and QTc interval will be excluded from the analyses. A listing of ECG data for patients with QRS ≥120 milliseconds at any time during the study will be provided.

The baseline for ECG is defined as the last non-missing baseline value during the baseline period (see Table 5.5). To be exact,

- For analyses including double-blind treatment phase, the baseline for ECG is defined as the last non-missing value before randomization. The rationale for using the last available value in the baseline period is to minimize the potential confound of discontinuing or dose stabilization of medications that modulate ECG during the screening phase (which is early in the baseline period).
- Similarly, for other study phases, the baseline is defined as the last non-missing value before patients enter the study phases of interest. This baseline definition was chosen to be consistent with the analysis approach for the double-blind treatment phase as described above.

This baseline definition for ECG applies to all analyses (both continuous and categorical, quantitative and qualitative) for ECG.

The baseline and postbaseline values are summarized in Table 5.5.

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. Treatment group comparisons will be performed using Fisher's exact test. Table 5.8 displays the criteria for treatment emergent changes in ECG intervals, 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. The absolute threshold in the criteria is based on 1) minimum post baseline when the direction is low; 2) maximum post baseline when the direction is high.

- For Treatment emergent low analyses: Patients with all normal or high values at baseline (no low values) will be included.
- For Treatment emergent high analyses: Patients with all normal or low values at baseline (no high values) will be included.
- For Treatment emergent increase analyses: Patients with a baseline and at least 1 postbaseline result will be included.

The baseline and post-baseline values are summarized in Table 5.5.

Table 5.8. 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
		>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
		>500 msec	
	Increase	Increase >30 msec	
		Increase >60 msec	
		Increase >75 msec	

In addition, descriptive summary of qualitative ECG abnormalities 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. 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 one of the possible specific descriptions (for example, Sinus Bradycardia, Acute Septal Infarction) within a category.

The summaries of the 11 ECG categories will exclude ECGs with any of the following: overall ECG could not be evaluated by the cardiologist, lead reversals or <9 leads, nonmatching demographic data, and those suggesting patient identification errors.

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 Fisher's exact test for each laboratory test.

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 Fisher's exact test..

- The percentages of patients with an alanine aminotransferase (ALT) or 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 the treatment 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 the treatment 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 the treatment period will be summarized for all patients with a post-baseline value.

Hy's law is defined as the combination of drug related elevation of ALT ≥3× ULN and TBIL ≥2× ULN, in the absence of significant cholestasis (ie, ALP < 2× ULN), and in the absence of other causes of liver injury

The analysis of elevation in ALT, AST , ALP and TBIL will contain 3 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× 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× ULN for ALP and TBIL.
- patients whose nonmissing maximum baseline value is greater than 2× ULN for ALT and AST, 1.5× ULN for ALP and TBIL.

5.5.12.1.6. Immunogenicity

To evaluate the changes in immunogenicity data (Anti-LY2951742 Antibody (hereafter "Anti-Drug Antibody (ADA)," Neutralizing ADA (hereafter "Neutralizing Antibody (NAb)") after treatment, the following statistical analyses are planned for comparison between treatment groups.

- The incidence of ADA positive and NAb Positive during baseline.
- The incidence of treatment-emergent ADA (TE ADA) between treatment groups will be summarized for Study Period III. The incidence of TE ADA during Study Periods III and IV combined will be summarized. The baseline and post-baseline definitions for each study period is shown in Table 5.5. 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 between treatment groups will be summarized for the same time periods as planned for the incidence of TE ADA. .
- The following will also be created:
  - Listing of subjects with TE ADA at any time during study, NAb Status will also be displayed.
  - Listing of subjects with ADA detected at any time during study, excluding subjects with TE ADA.
  - Line plot of ADA titers over time for each subject with TE ADA at any time.
  - Listing of subjects with TEAEs for hypersensitivity events or TEAEs related to injection sites for subjects with ADA present at any time.

5.5.12.2. Continuous Safety Measures

Analyses of continuous safety data will be conducted on patients who have a baseline and at least one post-baseline observation for Study Period III and Study Period III/IV. In those analyses, values from unscheduled visits will be ignored and only value collected at scheduled visit will be used.

For all the continuous safety measures (including laboratory measures, vital signs and weight, ECG intervals and heart rate), changes from last baseline value to LOCF endpoint during Study

Period III, will be assessed using an ANCOVA model as described in Section 5.5.1.1 with treatment , baseline value as the covariate. If repeat laboratory values exist at the same scheduled visit, only the last nonmissing laboratory value at a visit (selected by using the variable with highest lab sequence ID) will be used in the ANCOVA analysis for mean change from last baseline value to LOCF endpoint.

For vital signs of blood pressure and pulse, as well as weight (when applicable) , the mean change from baseline will be analyzed for both Study Period III and Study Period III/IV using a MMRM 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.

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. Table 5.9 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 variables (sex, racial origin, ethnicity, and region2) are not prognostic nor predictive. But they are standard subgroup variables needed for regulatory submission. The rest of subgroup variables 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 5.9. Definition of Subgroup Variables

Subgroup Variable	Categories
Sex	Male, female
Racial Origin (combine those with less than 10%)	American Indian / Alaskan Native Asian Black / African American Native Hawaiian / Pacific Islander White Multiple
Ethnicity	Hispanic or Latino Not Hispanic or Latino
Region2 (for CGAH only)	North America, including United States; Europe, including UK, Netherlands, Spain, Czech, and Germany; Other, including Argentina, Israel, Korea, Taiwan, and Mexico
Baseline category of MHD	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	Treatment resistant status about whether a patient has failed two or more prophylactic treatments: Yes vs No
Having aura or not (during baseline 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)

For the subgroup variables of race, all the categories that have less than 10% of the patients in the study will be combined as one category. For the subgroup variables of region2, if sample size in "other " region is less than 10% of total sample size, we will pull them into "Europe" region for subgroup analysis.

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 each category of the subgroup variable, comparisons between each treatment group with placebo will be assessed during the 6-month treatment period.

For the analysis within a subgroup using MMRM, the LSMeans and LSMeans 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.

5.6. Interim Analyses

Two interim analyses may be conducted for Studies CGAG and CGAH, which are summarized in the following Table 5.10.

For the first interim analysis, the unblinded review of efficacy and safety data will be conducted with external data monitoring committee (DMC). Details of this unblinded efficacy and safety review are provided in migraine prevention DMC charter.

Table 5.10. List of Unblinded Analyses and Their Purposes

Unblinded Analysis	Approximate Timing	Purpose
Interim Analysis #1	Due to faster enrollment as well as enrollment rate difference between CGAG and CGAH, the interim analysis #1 will happen when CGAG have approximately 390 and CGAH have approximately 210 randomized patients with the opportunity to complete 3 months of treatment.	Safety / Futility
Interim Analysis #2	All randomized patients with the opportunity to complete 6 months of treatment	Final analysis of the primary efficacy endpoints; Efficacy and safety analysis of double blind phase

Interim Analysis #1

Due to faster enrollment, as well as enrollment rate difference between CGAG and CGAH, the interim analysis #1 will happen when CGAG has approximately 390 randomized patients and CGAH has 210 randomized patients with the opportunity to complete 3 months of treatment. Safety and futility analyses will be performed at interim analysis #1. Details will be documented in DMC charter and SAC SAP.

Study sites will receive information about interim results ONLY if they need to know for the safety of their patients.

If the study stops early for safety or futility, investigators will be informed that the study is stopping and that patients who are ongoing in the treatment period (Study Period III) of the study must discontinue from study drug but complete the follow-up phase (Study Period IV). The reason for stopping will not be provided to the investigators until after the final data are locked and reported.

Interim analysis #1 will be conducted by an independent DMC with members external to Lilly. Additional details in regard to the data, frequency and procedure of the DMC review, as well as

the criteria for evaluation and recommendations are provided in DMC Charter for CGAG, CGAH, CGAI, and CGAJ.

Interim Analysis #2

Interim analysis #2 is planned when all randomized patients have had the chance to complete 6 months of treatment and, thus, will be the final analysis of the primary efficacy endpoint. Interim analysis #2 will be conducted using internal unblinded study team members who do not have direct interaction with sites.

5.7. Unblinding Plan

The unblinding plan for interim analyses #1 is documented in the SAC SAP.

Interim analysis #2 will be conducted by unblinded study team members who do not have direct interaction with sites. All study personnel with direct interaction with sites are kept blinded to the interim #2 analysis results.

The study unblinded statistician will maintain a list of personnel involved in an internal data review (if applicable), the date and level of their unblinding, and a description of what subset of data, if not all the data, was shared.

A designated study team member in collaboration with the project statistician will be responsible for keeping a running log of individuals given access to any unblinded study data. This log will include the person's name, title, date of unblinding, level of unblinding (ie, group or patient), and purpose of unblinding.

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

5.8.1. Reports to be Generated at Interim Analysis #1

Please refer to CGAG/H interim statistical analysis plan for the list of reports to be generated at Interim Analysis #1.

5.8.2. Reports to be Generated at Interim Analysis #2

At the time of interim analysis #2, all randomized patients will have had the chance to complete 6 months of treatment. The following analyses including tables, figures and listings will be conducted for all randomized patients who have had a chance to complete 6 months of treatment:

- Patient disposition as specified in Section 5.5.2, but for Study Periods III and IV.
- Patient Characteristics as specified in Section 5.5.4.
- Exposure to Investigational Product as specified in Section 5.5.5.
- ePRO Diary Compliance as specified in Section 5.5.7, but for Study Period III only.
- Previous Migraine Prevention Therapy as specified in Section 5.5.8.

- Concomitant Therapy as specified in Section 5.5.9, but for Study Periods III and IV.
- 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 with the exception of immunogenicity related analyses and main analyses for AEs. For immunogenicity related analyses, all analyses as specified in Section 5.5.12.1.6 will be conducted. In addition, post treatment-emergent AEs for Study Period IV will also be analyzed.
- Listing of abnormal safety findings will include data from both Study Periods III and IV.

As specified above, most analyses conducted at interim analysis #2 do not include any data from Study Period IV, and will be considered as the final Study Period III analyses. However, for the analyses conducted at interim analysis #2 that included data from Study Period IV, those analyses will be served as an interim review of SP IV data and will be rerun at final database lock.

5.8.3. Report to be Generated at Final Database Lock

For final database lock, the following analyses including tables, figures and listings will be conducted for all randomized patients who have had a chance to complete 6 months of treatment and 4 months of post-treatment period:

- Patient disposition as specified in Section 5.5.2, but for Study Period IV only.
- ePRO Diary Compliance as specified in Section 5.5.7, but for Study Period IV only.
- Concomitant Therapy as specified in Section 5.5.9, but for Study Period IV only.
- All the efficacy, quality-of-life and safety analyses as specified in Section 5.5.10, Section 5.5.11 and Section 5.5.12, but only for Study Period IV, as well as Study Period III/IV.

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 Preferred Term.

- 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.

6. References

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7. Appendix: Description of Important Protocol Deviations

Appendix Table 1. Description of Important Protocol Deviations

Category	Subcategory	Study-specific	Source	Methods of Identification
Informed Consent	**Informed consent not obtained**	Initial ICF date is missing or is after (Visit 1 Date or Visit 1 lab date)	Programmable – Stats	For all patients, if Initial ICF date is missing or after (Visit 1 date or Visit 1 lab date).
	Improper Consent	ICF not signed prior to initiation of protocol procedures	Non-Programmable-Monitor identified	Or determined by study team
Eligibility	**Inclusion/ Exclusion**	Age <18 or >65 years old at study entry	Non-Programmable-Monitor identified	
		BMI ≥40 at baseline	Programmable - Stats	
		Number of migraine headache days <4 or >14 at baseline	Programmable - Stats	Number of Normalized migraine headache days <4 or >14 at baseline
		Number of migraine attack <2 at baseline	Programmable - Stats	Number of Normalized migraine headache attack <2 at baseline
		Baseline ePRO compliance <80%	Programmable - Stats	
		Female patients who have a positive serum pregnancy test prior to randomization visit	Programmable – Stats	For randomized female patients, if serum pregnancy test is positive any time prior to Visit 3
		Female patients who have a positive or no serum pregnancy test prior to randomization visit	Non-Programmable-Monitor identified	

Description of Important Protocol Deviations

Category	Subcategory	Study-specific	Source	Methods of Identification
Eligibility	**Inclusion/ Exclusion**	Insufficient Washout of prohibited migraine preventive medication for at least 30 days prior to Visit 2	Programmable - Stats	Patients must have discontinued such treatment at least 30 days prior to Visit 2.
		Insufficient Washout of Botulinum toxin A and B at least 4 months prior to Visit 2	Non-Programmable-Study Team identified	1) Stats will create the list of patients meet this IPD criteria. 2) Among those, the true IPDs will be manually added into non-programmable excel sheet.
		With suicidal ideation (Q4 or Q5) within past month of visit 1.	Programmable - Stats	Randomized patients with answer "yes" for C-SSRS suicidal ideation Q4 or Q5 occurred within past 1 month of Visit 1.
		Positive or No urine drug screen prior to randomization	Programmable - Stats	For randomized patients if prior to Visit 3, a patient has a positive UDS result and a repeated UDS not done or last repeat UDS is positive or UDS never collected.
		ECGs abnormalities compatible with acute cardiovascular events and/or serious cardiovascular risk	Non-Programmable-Monitor identified	
		Corrected QT (QTcB) interval >470 msec for women and >450 msec for men at Visit 1 or Visit 3	Non-Programmable-Study Team identified	1) Stats will program the list of all patients with corrected QT (QTcB [Bazett's]) interval >470 msec for women and >450 msec for men at Visit 1 or Visit 3; 2) Among those, the true IPDs will be manually added into non-programmable excel sheet.
		Liver enzyme elevation of >2X ULN for ALT, or >1.5X ULN for TBL or >2X ULN for ALP at Visit 1	Non-Programmable-Study Team identified	1) Stats will program the list of all patients with Liver enzyme elevation of >2X ULN for ALT, or >1.5X ULN for TBL or >2X ULN for ALP at Visit 1 2) Among those, the true IPDs will be manually added into non-programmable excel sheet.
		Randomized pts had prior exposure to CGRP antibody	Non-Programmable-Monitor identified	

Description of Important Protocol Deviations

Category	Subcategory	Study-specific	Source	Methods of Identification
Data Quality	**Treatment Assignment/ Randomization Error**	IWRS data entry errors that impact patient stratification	Programmable – Stats	If migraine headache day categories (<8 vs ≥8) from IWRS was not the same as derived from ePRO.
	Other	ePRO compliance <=50% for half or more months of double blind treatment phase	Programmable – Stats	With≤50% ePRO compliance rate for half or more months of double blind treatment phase, where "month" refers to a dosing interval. For example, • if patient remained in the study for 5 or 6 months (ie, dose intervals), and ≥3 months have ePRO compliance ≤50%. • if patient remained in the study for 3 or 4 months (ie, dose intervals), and ≥2 months have ePRO compliance ≤50%. • if patient remained in the study for 1 or 2 months (ie, dose intervals), and >=1 month have ePRO compliance ≤50%. Lost to follow-up patients' last month interval should not be included in the consideration above. If a patient discontinued at V3 or V4, the patient should not be counted here.
		Missing safety measurement: *CSSRS at baseline or double-blind treatment phase*	Programmable – Stats	For randomized patients with non-missing Visit 5 date, if C-SSRS (suicidal ideation question 1 to 2, suicidal behavior question 5 to 10, as well as non-suicidal self-injurious behavior) , are missing all baseline or missing all post-baseline measures during treatment phase. For patients who discontinued due to "lost to follow up", if all post-baseline measures are missing, it is not protocol deviation.

Description of Important Protocol Deviations

Category	Subcategory	Study-specific	Source	Methods of Identification
Data Quality	**Other**	Missing safety measurement: *CSSRS at post-treatment Phase*	Programmable – Stats	For patients who completed or discontinued (due to reasons other than "lost to follow up") post-treatment phase , if C-SSRS (suicidal ideation question 1 to 2, suicidal behavior question 5 to 10, as well as non-suicidal self-injurious behavior) , are missing all post-baseline measures during post-treatment phase. For patients who discontinued due to "lost to follow up" at post treatment phase, if all post-baseline measures are missing, it is not protocol deviation.
		Missing safety measurement: Vital Signs (*Blood Pressure,* body temperature, *Pulse) at Baseline or double blind treatment Phase*	Programmable – Stats	For randomized patients with non-missing visit 5 date, if blood pressure, body temperature, or pulse, are missing all baseline or missing all post-baseline measures or missing two consecutive measures during double blind treatment Phase. For patients who discontinued early, as long as they have one post-baseline Vital sign measures, it is not an important protocol deviation. For patients who discontinued due to "lost to follow up", if all post-baseline measures are missing, it is not protocol deviation.

Description of Important Protocol Deviations

Category	Subcategory	Study-specific	Source	Methods of Identification
Data Quality	**Other**	Missing safety measurement: Vital Signs (*Blood Pressure,* body temperature, *Pulse) at post-treatment Phase*	Programmable – Stats	For patients who completed or discontinued (due to reasons other than "lost to follow up") post-treatment phase, if blood pressure, body temperature, or pulse, are missing all post-baseline measures during post-treatment Phase. For patients who discontinued due to "lost to follow up" at post treatment phase, if all post-baseline measures are missing, it is not protocol deviation.
		Missing safety measurement: Chemistry or Hematology at baseline or double-blind treatment phase	Programmable – Stats	For randomized patients with non-missing Visit 7 date , if calcium and hemoglobin are missing all baseline or missing all post-baseline measures during double blind treatment phase. For patients who discontinued early, as long as they have one post-baseline lab measures, it is not an important protocol deviation. For patients who discontinued due to "lost to follow up" , if all post-baseline measures are missing, it is not protocol deviation.
		Missing safety measurement: Chemistry or Hematology at post-treatment phase	Programmable – Stats	For patients who completed or discontinued (due to reasons other than "lost to follow up") post-treatment phase, if calcium and hemoglobin is missing all postbaseline measures during the post-treatment phase. For patients who discontinued due to "lost to follow up" at post treatment phase, if all post-baseline measures are missing, it is not protocol deviation.

Description of Important Protocol Deviations

Category	Subcategory	Study-specific	Source	Methods of Identification
Data Quality	**Other**	Missing safety measurement: ECGs at baseline or double-blind treatment phase.	Programmable – Stats	For randomized patients, if ECGs are missing all baseline, or if there is non-missing Visit 12 date and missing all post-baseline measures during the double blind treatment phase.
Study Procedures	**Excluded Conmeds**	Taking prohibited migraine preventive medication for primary indication only for >7 consecutive days during Study Period II or III	Programmable - Stats	Prior therapy should be excluded in the consideration.
		Taking prohibited medication for any indication for >7 consecutive days during Study Period II or III	Programmable - Stats	Prior therapy should be excluded in the consideration.
		Taking Botulinum toxin A and B for any indication during Study Period II or III	Non-Programmable- Study Team identified	1) Stats will create the list of patients meet this IPD criteria. 2) Among those, the true IPDs will be manually added into non-programmable excel sheet
		Opioids, barbiturates use >7 consecutive days during Study Period II or III	Programmable – Stats	Prior therapy should be excluded in the consideration.
	Visit schedule criteria	Dosing interval outside specified limits	Programmable – Stats	For randomized patients, compare dosing interval to allowable visit intervals between doses. Allowable dosing intervals: 21 to 37 days

Description of Important Protocol Deviations

Category	Subcategory	Study-specific	Source	Methods of Identification
Investigational Product	**Patient took medication not fit for use**	Patient received drug that was declared "Not Fit for Use"	Non-Programmable-Monitor identified	
	Dosing Error	Dose was not observed for 30 minutes at randomization visit	Programmable – Stats	Answers to CRF question 'Was the subject observed at the study site for 30 minutes post dose?" was "No".
		Other Significant violations of study drug dosing	Non-Programmable-Monitor identified	
	Other	IP lost or stolen	Non-Programmable-Monitor identified	
	Unblinding	Unjustified un-blinding of patient treatment assignment	Non-Programmable-Monitor identified	
Administrative/Oversight	**Suspected misconduct**	Suspected Fraud	Non-Programmable-Monitor identified	
	Patient privacy violation	Privacy Breach	Non-Programmable-Monitor identified	
	Other	Administrative oversight	Non-Programmable-Monitor identified	CSSR scale administered by unqualified rater
Safety	**Other**	Site did not appropriately report SAE	Non-Programmable-Monitor identified	Failure to report an SAE within 24 hours of the investigator being made aware of the SAE Failure to respond to SAE queries

Description of Important Protocol Deviations

Category	Subcategory	Study-specific	Source	Methods of Identification
Safety	**Other**	Dosed female with positive pregnancy test at treatment phase, but not discontinued from treatment	Non-Programmable-Monitor identified	

Abbreviations: AE = adverse event, BMI = body mass index; Con-Meds = concomitant medications; CRF = case report form; ICF = informed consent form; IP = investigational product; ePRO= electronic patient reported outcome; C-SSRS= Columbia-Suicide Severity Rating Scale ;SAE = serious adverse event.