I5Q-MC-CGAI Statistical Analysis Plan Version 4

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 in Patients with Chronic Migraine – the REGAIN Study

NCT02614261

Approval Date: 25-Apr-2017

1. Statistical Analysis Plan for Protocol I5Q-MC-CGAI: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 in Patients with Chronic Migraine – the REGAIN Study

LY2951742 (Galcanezumab)

I5Q-MC-CGAI is a Phase 3, multisite, double-blind, randomized, placebo-controlled 3-month study to compare the efficacy and safety of 2 doses of LY2951742 in preventing migraine headaches in patients suffering from chronic migraine. Patients may continue into a 9-month open-label extension following the double-blind treatment period.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Statistical Analysis Plan Version 1 was signed and approved on 23-Nov-2015 GMT
Statistical Analysis Plan Version 2 was signed and approved on 13-Sep-2016 GMT
Statistical Analysis Plan Version 3 was signed and approved on 16-Jan-2017 GMT
Statistical Analysis Plan Version 4 electronically signed and approved by Lilly on date provided below

Approval Date: 25-Apr-2017 GMT

2. Table of Contents

Section **Page**

Table of Contents

Table **Page**

Table of Contents

Figure **Page**

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 the first interim analysis. The SAP Version 2 supersedes the statistical plans described in the protocol.

The changes made in SAP Version 2 are listed below:

- Criterion C for determination of migraine headache days was added to Table CGAI.5.2
- Section 5.2 was updated. Specifically, the sample size was set to the originally planned maximum sample size (1140). Sample size re-estimation will no longer apply.
- Any text related to sample size re-estimation was removed, and surrounding text was modified to maintain fluency. Sample size re-estimation will no longer be conducted because of faster than expected enrollment removes the ability to adapt the sample size following interim analysis.
- Additional exploratory efficacy analyses were added to both Section 5.4.1 (Efficacy Endpoints) and Table CGAI.5.5 (Secondary and Exploratory Efficacy Variables and Analysis Methods).
- For MIDAS, added "No imputation is needed when calculating the total score, as patients are not allowed to send partial data."
- Explained why CMH test is stratified by baseline medication overuse and concurrent prophylaxis use.
- 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 and SP V were added.
- "Treatment emergent" was changed to "treatment-emergent."
- Pooled country was removed from the list of controlling factors for analyses for categorical safety measures.
- 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, Appendix 1 for selection model was removed.
- Section 5.5.10.4. Corrected a typo in the multiple testing algorithm.
- "Upper respiratory tract infections" replace "infections" in Section 5.5.12.1.1.3.
- Response to previous migraine prevention therapy was updated based on eCRF, and a definition of previous migraine prevention therapy was added.
- A typo was corrected in Table CGAI.5.6.
- An increase category for QTcF, >75 msec, was added in Table CGAI.5.7.
- 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, that is, no subgroup analyses will be conducted by baseline ADA status.
  - Subgroup analyses for safety measures were removed except for analyses by the following 2 subgroup variables - baseline medication overuse and concurrent prophylaxis use.
- Section 5.6 (Interim Analysis) was updated to reflect the removal of sample size re-estimation and to indicate the change of the timing of interim analyses due to fast enrollment rate.

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). This SAP version supersedes the statistical plans described in the protocol and previous versions of the SAP.
The changes incorporated in SAP Version 3 are as follows:

- In Section 5.4.1, number of weekly migraine headache days in Month 1 was added. The statistical method used for this measure was added to Section 5.5.10.3.
- In Section 5.5.1.1, ANOVA / ANCOVA model was updated with pooled country removed from analyses for continuous safety measures.
- In Section 5.5.1.4, safety population and its definition were added. Safety analyses and analyses for disposition and exposure will be conducted using modal treatment group that patients have actually received. The algorithm for determining the modal treatment group was 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.
- In Section 5.5.11, analysis for MSQ Role-function Restrictive domain responders was updated, referring to the Statistical Analysis Plan for Psychometric Properties of the MSQv2.1 Role Function-Restrictive Domain, for response threshold. Responder analyses for other MSQ domains were removed. Section 5.4.3.1 was updated to reflect these changes.
- In Section 5.5.12.1.1.1, the analyses for potential hypersensitivity events were updated. The list of SMQs for search was updated and the medical review algorithm was added.
- In Section 5.5.12.1.3 and Section 5.5.12.1.4, the baseline definition for analyses for blood pressures, pulse, and ECG was updated. For all analyses for blood pressures, pulse, and ECG, the baseline is defined as the last non-missing value during the baseline period. See the specific sections for the rationales. Table CGAI.5.4 was updated to reflect the changes.

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). This SAP version supersedes the statistical plans described in the protocol and previous versions of the SAP.
The changes incorporated in SAP Version 4 are as follows:

- Section 5.5.1.4: Open-label treatment population was updated to patients receiving any injections starting from Visit 7.

- Section 5.5.3: The 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".
- The section for primary analysis following design adaptation was removed due to DMC recommendations for futility analyses for Interim Analysis #1 to continue the trial as is without dropping any treatment arm. Following removal of this section, subsequent sections were renumbered.
- Section 5.5.10.2: For sensitivity analysis for missing data assumption, additional texts 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.
- Section 5.5.10.3: For the "Analysis 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 text was added to the overview of the procedure for multiple testings.
- Section 5.5.12.1.6: Immunogenicity analyses have been updated based on additional inputs from study team. In addition, individual patient listing of data collected from protocol addendum 2 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".

4. Study Objectives

Table CGAI.4.1 shows the key objectives and endpoints of the study. Table CGAI.5.1 provides definitions for the terms referenced below.

Table CGAI.4.1. Objectives and Endpoints

Objectives	Endpoints
Primary 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 chronic migraine.	The overall mean change from baseline in the number of monthly migraine headache days during the 3-month double-blind treatment phase.
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 the tests of the following key secondary endpoints will be specified in Section 5.5.10.4.
• 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 3-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 3-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 3-month double-blind treatment phase
• To compare LY2951742 with placebo with respect to change in functioning	• The mean change from baseline in the Role Function-Restrictive domain score of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) at Month 3
• To compare LY2951742 with placebo with respect to change in use of acute (abortive) migraine treatment	• The overall mean change in the number of monthly migraine headache days requiring medication for the acute treatment of migraine or headache during the 3-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 at Month 3

Objectives and Endpoints

Objectives (cont.)	Endpoints (cont.)
Other Secondary Objectives	
• 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 3-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 3-month double-blind treatment phase
• To compare LY2951742 with placebo with respect to 30% response rates	• The proportions of patients demonstrating ≥30% reduction from baseline in the number of monthly migraine headache days during the 3-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 3-month double-blind treatment phase
• To compare LY2951742 with placebo with respect to time to 50% response	• Time to first occurrence of a ≥50% reduction from baseline in the number of monthly migraine headache days (Kaplan-Meier analysis)
• To compare LY2951742 with placebo with respect to onset of effect	• The initial month at which statistical separation in mean change from baseline in the number of monthly migraine headache days is demonstrated and maintained through Month 3
• 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 maintained at all subsequent months through Month 3
• To compare LY2951742 with placebo with respect to maintenance of 50% response	• The proportion of patients who maintain 50% response criteria for all 3 months of double-blind treatment
• To compare LY2951742 with placebo with respect to changes in other efficacy parameters, specifically: o International Classification of Headache Disorders (ICHD) migraine headache days o migraine attacks o migraine headache hours o headache hours o severity of remaining migraines	• The overall mean change from baseline (during the 3-month double-blind treatment phase) on the following monthly measures: o International Classification of Headache Disorders (ICHD) migraine headache days o migraine attacks o migraine headache hours o headache hours o severity of remaining migraines
• To compare LY2951742 with placebo with respect to global assessment of illness	• Overall mean Patient Global Impression-Improvement (PGI-I) rating during the 3-month double-blind treatment phase

Objectives and Endpoints

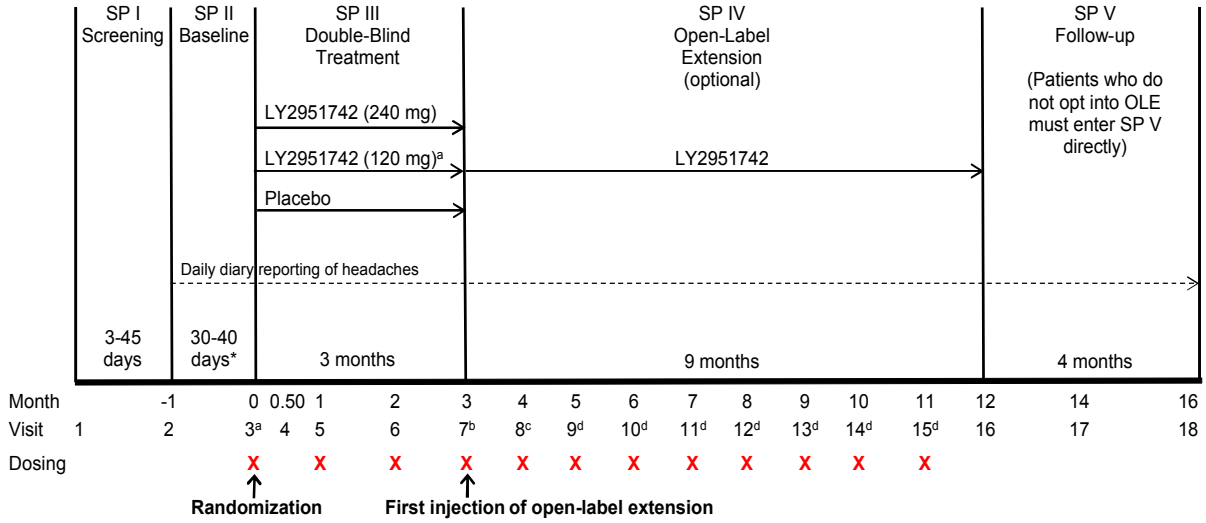
Objectives (cont.)	Endpoints (cont.)
Other Secondary Objectives (cont.)	
• To compare LY2951742 with placebo with respect to changes in disability and quality of life	• Changes from baseline to Month 3 on the following measures: o Migraine Disability Assessment test (MIDAS) total score and individual items o MSQ v2.1 total score, and Role Function-Preventive and Emotional Function domain scores o Health Care Resource Utilization and Employment Status
• To compare LY2951742 with placebo with respect to safety and tolerability	• Analysis of: o treatment-emergent adverse events (TEAEs) o discontinuation rates o vital signs and weight o electrocardiograms (ECGs) o laboratory measures o other safety parameters, including suicidality using the Columbia-Suicide Severity Rating Scale (C-SSRS)
• To evaluate LY2951742 with respect to immunogenicity	• Throughout the study: o 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, safety, and functional outcomes during Study Period IV (open-label treatment)	• In Study Period IV: o Mean changes in all continuous measures of efficacy, safety, and functional outcomes that are also assessed in the double-blind period o Among patients previously treated with LY2951742 who met 50% response criteria at Month 3 in the double-blind treatment period, the proportion of patients who demonstrate response for at least 6 of the 9 months in the open-label treatment period

Objectives and Endpoints

Objectives (cont.)	Endpoints (cont.)
Other Secondary Objectives (cont.) • To assess changes in efficacy outcomes during Study Period V as collected by electronic patient-reported outcomes (ePRO) diary data	• In Study Period V: o Changes in the number of monthly migraine and headache days from the baseline to the end of the post-treatment follow-up phase o Time to first loss of response among patients who met 50% response criteria at their last injection interval o Time to initiation of treatment with a migraine prevention medication
Tertiary Objectives	
[redacted]	
• 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: o ≥50% improvement in MIDAS total score o change from baseline in MSQ Role Function-Restrictive domain ≥10.9 o change from baseline in MSQ Role Function-Preventive domain ≥8.3 o change from baseline in MSQ Emotional Function domain ≥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: o nausea and/or vomiting o photophobia and phonophobia o aura o 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).
[b] At Visit 7, all patients who enter the open-label extension will receive LY2951742 at a dose of 240 mg.
[c] At Visit 8, all patients will receive LY2951742 at a dose of 120 mg.
[d] Starting at Visit 9, patients will have the option to receive either LY2951742 dose of 120 mg or 240 mg (flexible dosing).

Abbreviations: OLE = open-label extension; SP = study period.

Figure CGAI.5.1. Illustration of study design for Clinical Protocol I5Q-MC-CGAI.

5.2. Determination of Sample Size

The study will enroll approximately 1140 patients. Eligible patients will be randomized in blinded fashion in a 2:1:1 ratio to placebo (approximately 570 patients), LY2951742 120 mg/month (approximately 285 patients), or 240 mg/month (approximately 285 patients). With the assumption of a 15% discontinuation rate and an effect size of 0.30 in the last month of the 3-month treatment phase, it is estimated that this sample size will provide approximately 95% power that at least 1 dose of LY2951742 will separate from placebo at a 1-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 greater variability expected in a larger, multi-country Phase 3 study.

5.3. Randomization and Treatment Assignment

Patients will be randomized in a 2:1:1 ratio to placebo, LY2951742 120 mg/month, or 240 mg/month. Randomization will be stratified within country and by acute headache medication overuse (yes versus no), and use of concurrent migraine prophylactic medication (yes versus no).

The acute headache medication overuse will be based on the frequency of acute headache medication intake during the 30-day baseline, and will be adapted from Section 8.2 of the ICHD-3 beta guidelines (ICHD-3 2013).

To ensure an appropriate balance of patients with concurrent prophylaxis use, the sponsor will stop enrollment of patients with concurrent prophylaxis use if the number of patients exceeds approximately 1/3.

5.4. Endpoints

5.4.1. Efficacy Endpoints

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

Table CGAI.5.1. Migraine and Headache Endpoint Definitions

Diagnosis	Definition/Criteria
Migraine headache	A headache, with or without aura, of ≥30 minutes duration with both of the following required features (A and B): A. At least 2 of the following headache characteristics: • Unilateral location • Pulsatile quality • Moderate or severe pain intensity • Aggravation by or causing avoidance of routine physical activity AND B. During headache at least 1 of the following: • Nausea and/or vomiting • Photophobia and phonophobia OR C. The headache is believed by the patient to be migraine at onset and is relieved by a triptan or ergot derivative. *(Definition adapted from the Standard International Headache Society [IHS] International Classification of Headache Disorders (ICHD)-3 beta)*
Probable migraine	A headache of ≥30 minutes, but missing 1 of the migraine features in the IHS ICHD-3 beta definition. To be exact, it meets either at least 2 A criteria and 0 B criteria, or 1 A criteria and at least 1 B criteria. It must not meet criterion C.
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.
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 electronic patient-reported outcomes (ePRO) diary. Patients will need to enter ePRO diary data daily beginning from Visit 2, continuing until Visit 18.

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

Table CGAI.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 2 migraine Criteria As and at least 1 migraine Criterion B are met; or Migraine Criterion C is met.
	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 medicine for pain other than headache?	Yes	
	No	
Q12. Yesterday, did you experience aura?	Yes	
	No	
Q13. Yesterday, did you experience any warning symptoms (prodrome symptoms) that a migraine was coming other than aura?	Yes	
	No	
Q14. Yesterday, do you believe you experienced a migraine AND it was relieved by a triptan or ergot derivative?	Yes	Migraine Criterion C
	No	

[a] If "No" is answered for Q1, then the patients will skip Q2 - Q6, and Q14, only answer questions Q7 - Q13 by removing reference to headache.

Primary Measure: Migraine Headache Days

The primary measure is the number of monthly migraine headache days (per 30-day period). 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 in each 30-day period will be summarized from daily data for each patient in that period (including approximately 30 days of daily data from the baseline period prior to randomization, 3 months of daily data during double-blind treatment phase, 9 months of daily data during open-label treatment phase, and 4 months of daily data during post-treatment phase).

The daily data will reflect whether the patients meet the migraine / probable migraine criteria; those 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 post-treatment period, the monthly intervals will be derived as below:

- Firstly, the 2-month visit interval will be split into two 1-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 1-month period and the second half will be in the second 1-month period. If the number of days between 2 visits is odd, then the days will be split similarly, but the first 1-month period will have 1 day more than the second 1-month period.
- Secondly, after the 2-month visit intervals are split into two 1-month periods, the monthly data will be derived in the same way for each 1-month period as for treatment phase. For patients who discontinued early during post-treatment phase (Study Period V [SP V]), if the date of discontinuation is within 30 days of the 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 assumed that the rate of migraine headache per day is the same for days with missing and nonmissing ePRO diary days. 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 a monthly interval is $\leq$50%, then all endpoints to be derived from the ePRO diary data for that 1-month period will be considered missing.

For the post-treatment phase, the derived 1-month periods (resulting from splitting the 2-month visit interval) will be treated similarly.

For a patient who discontinues early in the double-blind (Study Period III [SP III]) or open-label treatment phase (Study Period IV [SP IV]) or post-treatment phase (SP V), compliance rate for the last month of that study period will be calculated with a denominator of 30 days (or the actual number of days in the interval if greater than 30).

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 for 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-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 medication use** is calculated as the number of calendar days in a 30-day period on which migraine or probable migraine occurs and abortive medication is used.
- **Number of migraine attacks** is calculated as the number of sets of consecutive migraine headache days separated by at least 1 migraine **headache-free** day in a 30-day period. For example, a migraine headache day starting on 5JAN and ending on 6JAN will result in a migraine headache free day on 7JAN (assuming that it is not a migraine headache day on 7JAN). This will count as 1 migraine attack that started on 5JAN and ended on 6JAN. For migraine attack that begins in 1 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 headache days with 3 days in baseline period and 4 days in Month 1, only 1 migraine attack will be counted in the baseline period; the 4 days of migraine headache days in Month 1 will not be counted as migraine attack in Month 1.

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

- **Mean severity of remaining migraine headaches** will be calculated at each period (including baseline and any postbaseline 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 treatment of migraine or probable migraine headache will be calculated at each period as:

$$\frac{\text{number of migraine headache days with medication use}}{\text{number of migraine headache days in the Period}}$$

  For periods with 0 migraine headache days, the proportion would be missing.

- **Percent change from baseline in the number of migraine headache days** will be calculated for any postbaseline 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 (X=0, 5, 10, …, 95, and 100).

- **50% responders sustained for all 3 months during double-blind treatment phase in the number of migraine headache days** is defined as meeting 50% responder criterion in migraine headache days for Month 1 to Month 3 in the double-blind treatment phase.

- P**roportion of patients who continue to demonstrate 50% response for at least 6 (not necessarily consecutive) of the 9 months in the open-label treatment period**. This analysis will include patients previously treated with LY2951742 who met 50% response criteria at Month 3 in the double-blind treatment phase (SP III) and entered the open-label treatment phase (SP IV). If a patient discontinued early during SP IV and met 50% response for 6 months, the patient will be defined as a responder, any patient who discontinued before Month 6 of the open-label phase will be counted as a non-responder.

- **Time to first 50% response (in months)** is defined as the first month when 50% response is met. If a patient has not met 50% response during SP III, the patient will be censored at the last month where 50% response status is not missing.
- **Time to first loss of 50% response in post-treatment phase (in months)** is defined as the time from the beginning of the post-treatment phase to the first month when 50% response is no longer met during the post-treatment phase (SP V). If a patient has met 50% response during all the months of SP V, the patient will be censored at the last month where 50% response status is not missing. This analysis will be conducted only for patients who met 50% response criteria at their last injection interval and are also entered into SP V.
- **Time to initiation of treatment with a migraine preventive medication (in days) in the post-treatment phase** is defined as the disposition date of the previous study period before entering SP V minus the date of start of the migraine preventive medication (based on information collected from concomitant medication electronic case report form [eCRF]) in the post-treatment phase. If a patient did not initiate preventive treatment during SP V, they will be censored at the disposition date of SP V. This analysis will be conducted only for patients who entered SP V and those who are not in concurrent preventive treatment group.
- **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 prodrome 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 attacks 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 used** is calculated as the total number of classes of abortive medications taken during a 30-day period.

Abortive medication use will be classified into the following 5 classes: triptans, nonsteroidal anti-inflammatory drugs (NSAIDs)/aspirin, acetaminophen/paracetamol, ergots, anti-nausea. If Question 10 in patient diary questionnaire has an answer of "No", any abortive medication entered for that date will not be included in the analyses.

- **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 medications used per day** is calculated as follows for each 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 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 triptan use** is calculated as the number of days with triptan use during a 30-day period.
- **Number of migraine headache days with triptan use** is calculated as the number of migraine headache days with triptan use during a 30-day period.
- **Number of days with NSAIDs/aspirin use** is calculated as the number of calendar days with NSAIDs/aspirin use during a 30-day period.
- **Number of migraine headache days with NSAIDs/aspirin use** is calculated as the number of migraine headache days with NSAIDs/aspirin use during a 30-day period.
- **Number of days with acetaminophen/paracetamol use** is calculated as the number of days with acetaminophen/paracetamol use during a 30-day period.
- **Number of migraine headache days with acetaminophen/paracetamol use** is calculated as the number of migraine headache days with acetaminophen/paracetamol use during a 30-day period.
- **Number of days with ergot use** is calculated as the number of days with ergot use during a 30-day period.
- **Number of migraine headache days with ergot use** is calculated as the number of migraine headache days with ergot use during a 30-day period.

- **Number of days with anti-nausea medication use** is calculated as the number of days with anti-nausea medication use during a 30-day period.
- **Number of migraine headache days with anti-nausea medication use** is calculated as the number of migraine headache days with anti-nausea medication use during a 30-day period.
- **Number of days with multiple class medication use** is calculated as the number of days with multiple class medication use during a 30-day period.
  Multiple class medication use is defined as using at least 2 of the 5 classes (defined above) on a day.
- **Number of migraine headache days with multiple class medication use** is calculated as the number of migraine headache days with multiple class medication use during a 30-day period.
- **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, and the rest of 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 (Visit 3) and monthly postbaseline visits during the double-blind treatment, open-label treatment, and post-treatment phase. 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 postbaseline visits during the treatment phase.

Change from baseline in PGI-S scores will be analyzed. Patient Global Impression of Improvement scores at postbaseline 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 where the patient would enter value of 1, 2, 3,…, up to 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 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 and Other 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 MSQ item responses are shown in Table CGAI.5.3. All item values range from 1 to 6. Final item values will be used for analysis with higher scores reflecting better quality of life.

Table CGAI.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.

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. Patients 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 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 MSQv2.1 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 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 for missing values is necessary because the MIDAS was collected using patient direct data entry on an electronic device which did not allow patients to skip items. Patients either completed the scale in its entirety or not at all.

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

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

5.4.3.3. Health Care Resource Utilization (HCRU) and Employment Status

Health Care Resource Utilization (HCRU) will be solicited by study personnel while documenting patient responses. Data to be collected include whether patients have hospital emergency room (ER) visits, overnight hospital stays, and other visits with healthcare professional, and, if yes, the numbers of above visits, as well as the numbers of above visits that are related to migraine headaches. Visits associated with their participation in the clinical trial should not be included in the responses. A question on employment status is also solicited, given the correlation and potential confounding with health outcomes measures.

At the baseline visit, these questions will be asked for the time frame of past 6 months. At postbaseline visits, the questions will be asked for the time from last visit to current visit.

Health Care Resource Utilization data will be analyzed at every 3-month interval. Baseline 3 months value will be derived as the baseline number divided by 2. Data from monthly Visit 5 to Visit 16 will be added for every 3 months. If missing data occur in more than 2 monthly visits, the 3-month period will have a missing data point.

If there is at least 1 non-missing data for HCRU for the patient, then all the other missing HCRU data for the same patients will be imputed as 0.

Data from the 3-month double-blind period will be analyzed relative to 3-month baseline data. Data from the entire 12-month treatment period (double-blind plus open-label periods) will also be analyzed in 3-month increments relative to the 3-month baseline data.

5.4.4. Safety Endpoints

Safety endpoints consist of the incidences of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs) and discontinuations due to adverse events (AEs), 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), laboratory measures (chemistry, hematology and urinalysis).

5.4.5. Immunogenicity Endpoints

Immunogenicity endpoints consist of the incidences of Anti-LY2951742 Antibody (hereafter Anti-Drug Antibody [ADA]) in all trial participants at baseline, including placebos (pre-existing ADAs), and in all trial participants at postbaseline (treatment-emergent ADAs). An additional endpoint is the incidence of Neutralizing ADA (NAb) present in those trial participants with ADAs.

CCI [redacted]

5.4.7. Pharmacokinetic Assessment

Pharmacokinetic assessment will be summarized in the pharmacokinetic/pharmacodynamic (PK/PD) SAP.

5.5. Statistical Analyses

5.5.1. General Considerations

Treatment effects will be evaluated based on an overall 1-sided significance level of 0.025 for all efficacy and safety analyses. The 95% 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 postbaseline 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 average monthly measures during 3-month treatment phase (for measures with corresponding objectives evaluated over the 3-month treatment period) or to last-observation-carry-forward (LOCF) endpoint (for measures with corresponding objectives evaluated at Month 3). For other continuous variables, the change from baseline to LOCF endpoint will be analyzed using an ANOVA or ANCOVA model.

Unless otherwise specified, when 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 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. For other categorical variables without

repeated measures, comparisons between treatment groups will be performed using Cochran-Mantel-Haenszel (CMH) or Fisher's exact tests. Unless otherwise stated, CMH test will be controlled for baseline medication overuse (yes versus no) and concurrent prophylaxis use (yes versus no). Unless specified otherwise, Fisher's exact test will be used for comparisons of baseline measures (that is, baseline patient characteristics, previous therapy, etc.). The CMH test will be used for comparisons of postbaseline efficacy or safety measures when needed. The CMH test for postbaseline safety measures will be stratified by both baseline medication overuse and concurrent prophylaxis use, as baseline medication overuse and concomitant prophylaxis may have an impact on safety profiles.

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 SAP and/or in the clinical study report (CSR).

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.

5.5.1.1. Adjustments for Covariates

The MMRM models will include the fixed, categorical effects of treatment, pooled country, month, baseline medication overuse (yes versus no), concurrent prophylaxis (yes versus no), and treatment-by-month interaction, as well as the continuous, fixed covariates of baseline value and baseline value-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 postbaseline values. Rules for pooling countries are defined in Section 5.5.1.3. Pooled country will be excluded in MMRM models for safety measures.

When an ANOVA model is used to analyze a continuous efficacy variable, the model will contain the main effects of treatment, baseline medication overuse (yes versus no), concurrent prophylaxis use (yes versus no) and pooled country. When an ANCOVA model is used to analyze a continuous efficacy variable, the model will contain the main effects of treatment, baseline medication overuse (yes versus no), concurrent prophylaxis use (yes versus no) and pooled country, and appropriate baseline value as a covariate. When an ANOVA or ANCOVA model is used to analyze a continuous safety variable, pooled country will be removed from the model.

The GLIMMIX models for the repeated binary outcomes will include the fixed, categorical effects of treatment, month, baseline medication overuse (yes versus no), concurrent prophylaxis (yes versus no), and treatment-by-month interaction, as well as the continuous, fixed covariate of baseline value. Pooled country 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, baseline medication overuse (yes versus no), concurrent prophylaxis use (yes versus no) and pooled country, and appropriate baseline value as a covariate. Pooled country may be excluded from the model in case of non-convergence.

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 measures during the 3-month treatment phase (for measures with objectives evaluated during the entire 3 months of treatment phase) or LOCF endpoint (for measures with objectives evaluated at Month 3).

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 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 ePRO 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 monthly migraine attacks during that month will be considered missing. Please refer to Section 5.5.7 for compliance rate calculation.

5.5.1.3. Rules for Pooling Countries

All countries with fewer than 4 randomized patients for placebo arm or fewer than 2 patients for any LY2951742 arm with baseline and at least 1 postbaseline migraine headache day's value will be pooled together within region and considered a single country for analyses.

All analyses will use pooled country when applicable. The investigative site numbers will be included in the listings.

5.5.1.4. Analysis Populations

There were 4 analysis populations defined:

Intent-to-Treat (ITT) Population: All patients who are randomized and receive at least 1 dose of study drug.

Safety Population: This population is the same as the ITT population defined above.

Open-label treatment population: All patients who enter the open-label treatment phase (Study Period IV) as indicated by receiving any injections starting from Visit 7. Patients in the open-label treatment population will be analyzed as a single group as they start with the same dose in the study period. Analyses for open-label phase only will be based on open-label treatment population.

Post-treatment Population: All patients who enter the post-treatment phase (Study Period V) as indicated by entering any post-treatment visit (telephone or office visit). Analyses for post-treatment phase only (that is, excluding earlier study periods) will be based on post-treatment population.

Unless otherwise stated, all analyses will be analyzed 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 (Section 5.5.1.2) and analyses for disposition and exposure will be conducted based on the modal treatment group patients have received (Placebo, LY120mg, or LY240mg) during the double-blind Study Period from the first to last injections at Visit 3 through Visit 6. For determining modal dose, do not consider the loading dose visit for subjects assigned to an LY120mg treatment group; do consider it for subjects assigned to the Placebo and LY240mg treatment groups. If there are 2 or more modes, then add the loading dose visit and recalculate the mode, if any. If a tie still remains, the highest LY dose of the modes will be used.

5.5.1.5. Baseline and Postbaseline Definition

Table CGAI.5.4 describes the rules for determining the patient population and baseline and postbaseline 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 CGAI.5.4. Patient Population with Baseline and Postbaseline Definitions by Study Period and Type of Analysis

Study Period / Analysis	Patient Population	Baseline Observation	Postbaseline Observation(s)
Study Period III			
Efficacy analyses (Repeated Measures) or average of observed monthly values	ITT Population with a baseline and at least 1 postbaseline observation	Visit 3	All scheduled visits 3 < Visits ≤7
Efficacy analyses at LOCF endpoint		Visit 3	Last of Visit 3.01-7
Quality of Life analyses (Repeated Measures)		Visit 3	All scheduled visits 3 < Visits ≤7
Quality of Life analyses at LOCF endpoint or for average of observed monthly values		Visit 3	Last of Visit 3.01-7
TEAEs	Safety Population	All Visits 1–3	All Visits 3.01–7
Serious Adverse Events, Discontinuations due to Adverse Events	Safety Population	NA	All Visits 3.01–7
C-SSRS categorical analyses	Patients with a baseline and at least 1 postbaseline C-SSRS assessment	Recent History: Visits 1–3 excluding lifetime[a] All Prior History: Visits 1 – 3 including lifetime[a]	All Visits 3.01–7
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 1 postbaseline observation	Low: Minimum from Visits 1–3 High: Maximum from Visits 1–3 Abnormal: All Visits 1–3	Low: Minimum from Visits 3.01–7 High: Maximum from Visits 3.01–7 Abnormal: All Visits 1–3
Treatment-emergent immunogenicity	Safety Population	Visit 3	All Visits 3.01–7
Treatment-emergent changes in temperature and weight	Safety Population with a baseline and at least 1 postbaseline observation	Low: Minimum from Visits 1–3 High: Maximum from Visits 1–3	Low: Minimum from Visits 3.01–7 High: Maximum from Visits 3.01–7
Treatment-emergent changes in blood pressures, pulse, and ECGs	Safety Population with a baseline and at least 1 postbaseline observation	Low: Last non-missing from Visits 1–3 High: Last non-missing from Visits 1–3	Low: Minimum from Visits 3.01–7 High: Maximum from Visits 3.01–7

Patient Population with Baseline and Postbaseline Definitions by Study Period and Type of Analysis

Study Period / Analysis	Patient Population	Baseline Observation	Postbaseline Observation(s)
Study Period III			
Continuous safety analyses (Repeated Measures)	Safety Population with a baseline and at least 1 postbaseline observation	Last of Visits 1–3	All scheduled visits 3 < Visits ≤7
Continuous safety analyses – change from baseline to LOCF endpoint (ANCOVA)	Safety Population with a baseline and at least 1 postbaseline observation	Last of Visits 1–3	Last of Visits 3.01–7
Study Period IV			
TEAEs	Open Label treatment Population	All Visits 1- 7	All Visits 7.01–16
Serious Adverse Events, Discontinuations due to Adverse Events	Open Label treatment Population	NA	All Visits 7.01–16
Treatment-emergent abnormal laboratory values	Open Label treatment Population and Patients with normal laboratory values at all nonmissing baseline visits (with respect to direction being analyzed) and who have at least 1 postbaseline observation	Low: Minimum from Visits 1–7 High: Maximum from Visits 1–7 Abnormal: All Visits 1–7	Low: Minimum from Visits 7.01-16 High: Maximum from Visits 7.01-16 Abnormal: All Visits 7.01-16
C-SSRS categorical analyses	Open Label treatment Population and Patients with a baseline and at least 1 postbaseline C-SSRS assessment	Recent History: All Visits 1–7 excluding lifetime[a] All Prior History: Visits 1 – 7 including lifetime[a]	All Visits 7.01–16
Treatment-emergent immunogenicity	Open Label treatment Population	Visit 3	All Visits 7.01–16
Treatment-emergent changes in temperature and weight	Open Label treatment Population and Patients with a baseline and at least 1 postbaseline observation	Low: Minimum from Visits 1–7 High: Maximum from Visits 1–7	Low: Minimum from Visits 7.01–16 High: Maximum from Visits 7.01–16
Treatment-emergent changes in blood pressures, pulse, and ECGs	Open Label treatment Population and Patients with a baseline and at least 1 postbaseline observation	Low: last non-missing from Visits 1–7 High: last non-missing value from Visits 1–7	Low: Minimum from Visits 7.01–16 High: Maximum from Visits 7.01–16

Patient Population with Baseline and Post-baseline Definitions by Study Period and Type of Analysis

Study Period / Analysis	Patient Population	Baseline Observation	Postbaseline Observation(s)
Study Period V			
TEAEs	Post-treatment Population	All Visits 1- 16	All Visits 16.01–18
Serious Adverse Events, Discontinuations due to Adverse Events	Post-treatment Population	NA	All Visits 16.01–18
Post-treatment-emergent abnormal laboratory values	Post-treatment Population and Patients with normal laboratory values at all nonmissing baseline visits (with respect to direction being analyzed) and who have at least 1 postbaseline observation	All Visits 1- 16	All Visits 16.01–18
C-SSRS categorical analyses	Post-treatment Population and Patients with a baseline and at least 1 postbaseline C-SSRS assessment	Recent History: All Visits 1–16 excluding lifetime[a] All Prior History: Visits 1 – 16 including lifetime[a]	All Visits 16.01–18
Treatment-emergent immunogenicity	Post-treatment Population	Visit 3	All Visits 16.01–18
Post-treatment-emergent changes in temperature and weight	Post-treatment Population and Patients with a baseline and at least 1 postbaseline observation	Low: Minimum from Visits 1–16 High: Maximum from Visits 1–16	Low: minimum from Visits 16.01–18 High: maximum from Visits 16.01–18
Post-treatment-emergent changes in blood pressures, pulse, and ECGs	Post-treatment Population and Patients with a baseline and at least 1 postbaseline observation	Low: last non-missing from Visits 1–16 High: last non-missing from Visits 1–16	Low: minimum from Visits 16.01–18 High: maximum from Visits 16.01–18

Patient Population with Baseline and Post-baseline Definitions by Study Period and Type of Analysis

Study Periods III / IV Combined			
Efficacy analyses	ITT Population with a baseline and at least 1 postbaseline observation	Visit 3	All scheduled visits 3 < Visits ≤16
Quality of Life analyses	ITT Population with a baseline and at least 1 postbaseline observation	Visit 3	All scheduled visits 3 < Visits ≤16
Treatment-emergent immunogenicity	Safety Population	Visit 3	All Visits 3.01–16
Continuous safety analyses (Repeated Measures)	Safety Population with a baseline and at least 1 postbaseline observation	Visit 3	All scheduled visits 3 < Visits ≤16
Study Periods III/ IV/V Combined			
Efficacy analyses	ITT Population with a baseline and at least 1 postbaseline observation	Visit 3	All scheduled visits 3 < Visits ≤18
Quality of Life analyses	ITT Population with a baseline and at least 1 postbaseline observation	Visit 3	All scheduled visits 3 < Visits ≤18
Continuous safety analyses (Repeated Measures)	Safety Population with a baseline and at least 1 postbaseline observation	Visit 3	All scheduled visits 3 < Visits ≤18
Treatment-emergent immunogenicity	Safety Population	Visit 3	All Visits 3.01–18

Abbreviations: ANCOVA = analysis of covariance; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; eCRF = electronic case report form; ITT = intent-to-treat; LOCF = last observation carried forward; TEAE = treatment-emergent adverse event.

Note: Visit 3.01 indicates the first unscheduled visit occurring after Visit 3 and prior to Visit 4. Visit 7.01 indicates the first unscheduled visit occurring after Visit 7 and prior to Visit 8. Visit 16.01 indicates the first unscheduled visit occurring after Visit 16 and prior to Visit 17.

[a] Lifetime is captured in the C-SSRS Visit 1 eCRF.

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 SP III, SP IV, and SP V, separately, both overall and by visit. Reasons for discontinuation will be compared between treatment groups using CMH test for SP III with the ITT population. Descriptive statistics only will be presented for the treatment groups in SP IV and SP V. In addition, subcategories of discontinuation due to subject decision will be summarized.

Patient allocation by investigator will be summarized for SP 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) 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 on Section 7 (appendix) can always be added into the final non-programmable protocol deviations list as deemed necessary.

Tables and listings of important protocol deviations for intent-to-treat patients during baseline, double blind treatment phase, open-label 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, BMI)
- Migraine and/or headache measures per 30-day baseline period.
  - number of migraine headache days
  - number of migraine headache days with acute (abortive) 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 headache

  - 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 aura
  - 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, and so on
- Baseline medication overuse
- Concurrent prophylaxis use
- Patient global impression - severity
- Alcohol, tobacco, caffeine and nicotine consumption
- Medical history and pre-existing conditions

Comparisons between treatment groups will be performed using Fisher's exact test for categorical data and ANOVA with treatment and pooled country 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, Visit 2, and Visit 3.

5.5.5. Exposure to Investigational Medicinal Product

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

- Beginning of Month 1 (Visit 3)
- Beginning of each month from Month 2 to Month 11 (Visit 5 to Visit 15)

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 double-blind treatment phase (SP III), duration of exposure in days is calculated as treatment phase disposition date – first date IMP administered +1.
- For open label phase (SP IV), duration of exposure in days is calculated as open label disposition date - first date IMP administered during SP IV +1.
- For double-blind treatment phase (SP III), number and percentage of patients with 1 dose, 2 doses, and 3 doses injected.
- For open label phase (SP IV), number and percentage of patients with 1 dose, 2 doses, 3 doses, …., 8 doses, and 9 doses injected.

Comparisons between treatments for duration of IMP exposure will be performed using an ANOVA with treatment, baseline medication overuse (yes versus no) and concurrent prophylaxis (yes versus no) in the model. The number of patients with 1 dose, 2 doses, 3 doses, 4 doses, 5 doses, 6 doses, 7 doses, 8 doses, …, 12 doses injected will be summarized. The number of patients with 1 dose, 2 doses, and 3 doses will be compared between treatment groups with CMH test. In addition, injections not administered with the corresponding reasons will be listed.

5.5.6. Treatment Compliance

Treatment compliance will be calculated for SP 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, baseline medication overuse (yes versus no) and concurrent prophylaxis (yes versus no) in the model. For this analysis, partial dose (for example, a patient only received 1 injection instead of 2 in the double-blind treatment phase) 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, Month 2, Month 3, … to Month 12) as well as for SP III overall (Month 1 through Month 3) will be calculated. Diary compliance at each 1-month 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 ePRO diary days is calculated as date of injection (date of visit for SP V) at the end of the interval minus date of injection (date of visit for SP V) at the beginning of the interval +1.

Treatment comparisons for ePRO diary compliance for each period will be performed separately using an ANOVA with treatment, pooled country, baseline medication overuse (yes versus no) and concurrent prophylaxis (yes versus no) in the model.

5.5.8. Previous Migraine Prevention Therapy

The proportion of patients who received previous migraine prevention therapy, 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 the 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 eCRFs as well as abortive medications collected through ePROs will be summarized for all ITT patients for SP III, SP IV, and SP V separately. Concomitant therapies for SP III are those which stopped during SP III or continued in SP 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 SP IV are those which either started, stopped or continued in SP IV.

Treatment group comparisons will be done using CMH test for Study Period III with ITT population. Descriptive statistics only will be presented for the treatment groups in Study Periods IV and V.

5.5.10. Efficacy Analyses

5.5.10.1. Primary Outcome and Methodology

The primary objective of this study 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 chronic 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 3-month double-blind treatment phase.

The primary analyses will be performed using a REML-based MMRM technique. The analysis will include the fixed categorical effects of treatment, pooled country, month, baseline

medication overuse (yes versus no), concurrent prophylaxis use (yes versus no) 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 the 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 treatment main effect from the MMRM analysis model. This provides the average treatment effect across Month 1, Month 2, and Month 3. 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, 1-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 will be used to assess the onset of effect for LY2951742 120 mg compared with placebo. In particular, if the primary efficacy analysis is statistically significant, then the earliest month where the statistically significant improvement is observed and maintained for all the subsequent months during the double-blinded treatment phase will be considered as the period that demonstrated the onset of effect. Identical logic will be used for the LY2951742 240 mg and placebo comparison.

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.

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 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 (that is, $\Delta_{120},\Delta_{240,\text{ or }}\Delta_P$) 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 raw number of migraine headache days (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 model fitted with SAS PROC GLIMMIX. The model will include treatment, pooled country, month, baseline medication overuse (yes versus no), concurrent prophylaxis use (yes versus no) 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 days within each month/30) as the offset in the model. In case of non-convergence, pooled country 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.

5.5.10.3. Secondary and Exploratory Efficacy Analyses

Key secondary efficacy measures will be tested with adjustment for multiple testing as specified in Section 5.5.10.4.

Other planned secondary and exploratory efficacy analyses will be conducted without multiplicity adjustment. Table CGAI.5.5 summarizes all the planned (unadjusted) secondary and exploratory efficacy analyses for SP III, SP III/IV, and SP III/IV/V, additional statistical analysis details are also provided below.

Continuous Secondary Efficacy Measures

For the continuous secondary efficacy measures, the change from baseline to each postbaseline 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 3 month double-blind treatment phase, the endpoint for each LY2951742 dose arm compared with placebo will be estimated as the treatment main effect from the MMRM analysis assessing the average treatment effect across Months 1, 2, and 3.

In addition to the repeated measures analyses, the mean change from baseline to average monthly measures during the 3-month treatment phase or LOCF endpoint in SP 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 outcomes indicating whether patients meet X% response criteria 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, baseline medication overuse (yes versus no), concurrent prophylaxis (yes versus no), 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's 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 binary secondary efficacy measures where the objective is to assess proportion of patients with X% response during the 3-month double-blind treatment phase, the endpoint for each LY2951742 dose arm compared with placebo will be estimated as the treatment main effect from the categorical MMRM analysis assessing the average response rate across Month 1, Month 2, and Month 3.

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 120 mg compared with placebo. In particular, if the gated secondary measure of 50% response rate is statistically significant, then the earliest month where the statistically significant improvement is observed and maintained for all the subsequent months during double-blinded treatment phase will be considered as the period that demonstrated the onset of 50% sustained response. Identical logic will be used for the LY2951742 240 mg and placebo comparison.

For binary secondary efficacy measures such as the proportion of patients who maintain 50% response criteria for all 3 months of double-blind treatment, as well as the proportion of patients who demonstrate 50% response for at least 6 of the 9 months in the open-label treatment period among patients previously treated with LY2951742 who met 50% response criteria at Month 3 in the double-blind treatment period. Treatment differences will be determined using logistic regression with covariate of treatment, pooled country, baseline medication overuse (yes versus no), concurrent prophylaxis (yes versus no) and continuous baseline value.

Measures Conditional on the Postbaseline Number of Migraine Headache Days >0

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

- Mean severity of remaining migraine headaches
- Proportion of migraine headache days with medication use

Those measures will be analyzed using MMRM model, assuming that data are missing for months without migraine headache.

Analyses for the 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, and etc. and 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 country, baseline medication overuse, concurrent prophylaxis use, 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 included 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 stratified log-rank test stratifying for pooled country, baseline medication overuse and concurrent prophylaxis use will be provided.

- Time to first 50% response in SP III for ITT population.
- Time to first loss of 50% response in SP V for patients who met 50% response criteria at their last injection interval and also entered SP V.
- Time to initiation of preventative treatment for migraine or probable migraine in SP V for patients who entered SP V and those who are not on concurrent preventive treatment group.

Distribution of Response Rate

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

When analyzing PGI-I, baseline PGI-S score will be included as a covariate. Specifically, it will be analyzed with an MMRM analysis while the covariates include the fixed categorical effects of treatment, month, pooled country, baseline medication overuse (yes versus no), concurrent prophylaxis use (yes versus no) and treatment-by-month interaction, as well as the continuous fixed covariates of baseline PGI-S score and baseline PGI-S score-by-month interaction.

Table CGAI.5.5. Secondary and Exploratory Efficacy Variables and Analysis Methods

Efficacy Variables	SP III	SP III/IV, SP III/IV/V, SP V
Number of migraine headache hours	MMRM, ANCOVA*a	MMRM for SP III/IV and SP III/IV/V
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		
Mean severity of migraine headache		
Patient Global Impression of Severity*a		
Patient Global Impression of Improvement		
Number of migraine headache days with nausea and/or vomiting	MMRM	MMRM for SP III/IV
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		
Average number of classes of abortive medications used		
Average number of classes of abortive medications used on migraine headache days		
Number of classes of abortive medications used		
Number of classes of abortive medications used on migraine headache days		
Number of days with triptan 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		

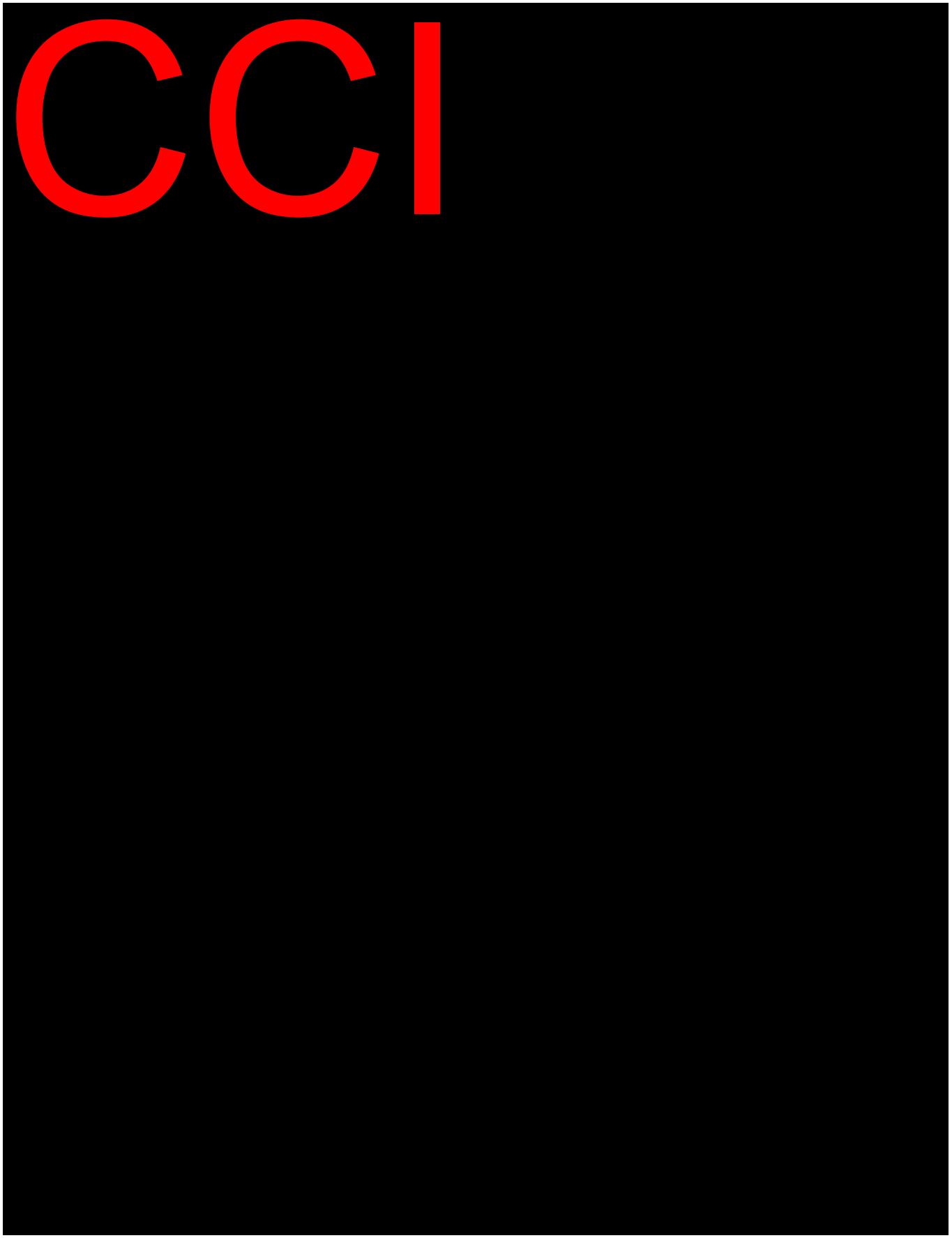
Secondary and Exploratory Efficacy Variables and Analysis Methods (cont)

Efficacy Variables	SP III	SP III/IV, SP III/IV/V, SP V
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		
Efficacy Variables	**SP III**	**SP III/IV, SP III/IV/V, SP V**
Number of migraine headache days with anti-nausea medication use		
Number of days with Multi-Class abortive medication use*b		
Number of migraine headache days with multi-class abortive medication use*b		
Number of weekly migraine headache days in Month 1	GLIMMIX for ordinal outcome	N/A
Average pain score for non-migraine chronic pain assessment	ANCOVA*a	MMRM for SP III/IV
Among patients previously treated with LY2951742 who met 50% response criteria at Month 3 in the double-blind treatment period, the proportion of patients who demonstrate 50% response for at least 6 of the 9 months in the open-label treatment period	N/A	Logistic regression for SP IV
X% response rate (X=30, 50, 75, or 100) (visit wise)	GLIMMIX	GLIMMIX for SP III/IV and SP III/IV/V
Distribution of response rate in SP III	GLIMMIX (to get estimated response rates)	N/A
50% response sustained from month 1 to month 3	Logistic Regression	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 IV 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		

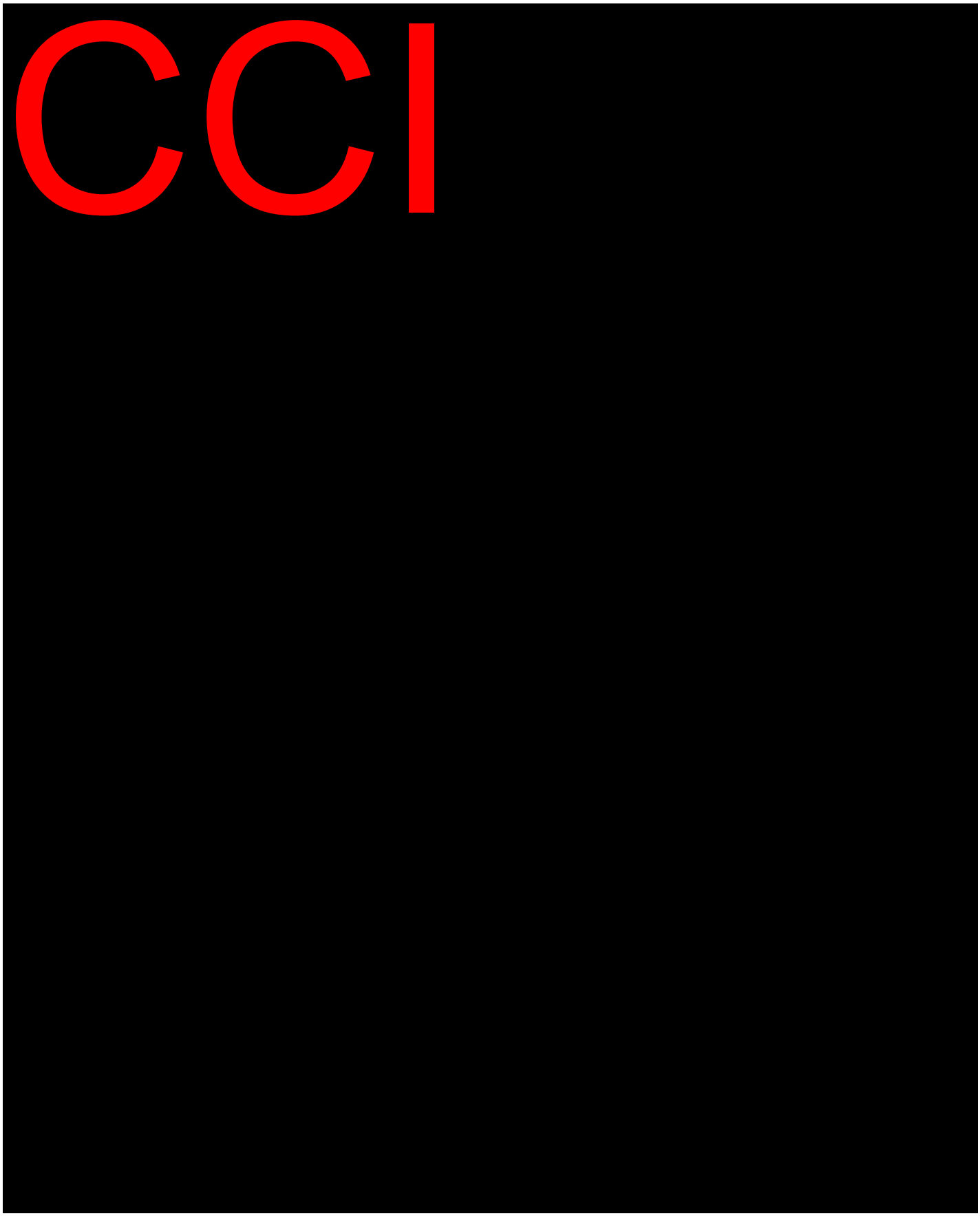
Abbreviations: ANCOVA = analysis of covariance; GLIMMIX = Generalized linear mixed model (for binary variables); MMRM = Mixed models repeated measures; N/A= Not applicable.

*a For PGI-S, ANCOVA with LOCF endpoint will be conducted; for all the other measures, ANCOVA with average monthly measures during 3 month treatment phase will be conducted.


CCI


CCI


CCI


CCI

5.5.11. Quality-of-Life (QoL) Analyses

The mean change from baseline to each postbaseline visit for SP III and SP III/IV/V for MSQ (including Role Function-Restrictive, Role Function-Preventive, Emotional Function, and total score), as defined in Section 5.4.3 will be evaluated using MMRM as described in Section 5.5.10.1.

Mean change from baseline to LOCF endpoint in the 3-month treatment phase for above quality of life measures will be evaluated using the ANCOVA model as described in Section 5.5.1.1.

The change from baseline to Month 3 score in MIDAS (item scores and total score) will be evaluated using the ANCOVA model as described in Section 5.5.1.1. The mean change from baseline to each postbaseline visit for SP III/IV and for SP III/IV/V for MIDAS (item scores and total score) will be evaluated using MMRM as described in Section 5.5.10.1.

Indicators of the MSQ Role Function Restrictive domain responders and MIDAS responders will be analyzed using GLIMMIX (as described in Section 5.5.10.3). Threshold for MSQ Role Function Restrictive domain response will be derived as outlined in "Statistical Analysis Plan for Psychometric Properties of the MSQv2.1 Role Function-Restrictive Domain". The threshold for MIDAS response will be a 50% improvement from baseline in MIDAS total score.

For the HCRU, the following measures will be analyzed:

- number of hospital emergency room (ER) visits
- number of overnight hospital stays
- number of other visits with healthcare professional
- number of hospital ER visits related to migraine headache
- number of overnight hospital stays related to migraine headache
- number of other visits with healthcare professional related to migraine headache

All of the above measures for the HCRU will be analyzed with a repeated measures negative binomial regression analysis fitted with SAS PROC GLIMMIX. The model includes pooled country, month, baseline medication overuse (yes versus no), concurrent prophylaxis use (yes versus no) and treatment-by-month interaction, as well as the continuous fixed covariates of

baseline and baseline-by-month interaction, log (number of actual number of days within every 3 month/90) as the offset in the model. In case of non-convergence, pooled country and/or baseline-by-month interaction may not be included in the model.

Employment status at each visit will be summarized separately for each treatment groups.

5.5.12. Safety Analyses

The safety analyses will be conducted for SP III, SP IV, SP V, SP III/IV, and SP III/IV/V.

Unless specified otherwise, for SP III, SP IV, SP V, and SP III/IV separately, the safety analyses outlined in the following sub-sections will be conducted; for SP III/IV/V, only the change from baseline with MMRM analysis and time to event analysis will be conducted.

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

- TEAEs
  - By PT
  - By SOC
  - By maximum severity
  - By considered to be related to investigational produce by investigator
- SAEs
- AE leading to discontinuation
- Suicide-Related Thoughts and Behaviors
- Vital signs and weight
- Laboratory measurements
- ECGs
- Antibodies (ADA and NAb)

The baseline and postbaseline for all safety measures are described in Table CGAI.5.4 unless specified otherwise.

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 SP III, SP IV, SP V, and SP III/IV separately.

Comparisons between treatment groups for all categorical safety measures will be made using CMH test for SP III, and SP III/IV with the ITT population.

Descriptive statistics only will be presented for the treatment groups in SP IV and SP V.

5.5.12.1.1. Adverse Events

Treatment-emergent AEs are defined as the reported AEs that first occurred or worsened during the postbaseline 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 postbaseline is greater than the maximum baseline severity, the event is considered to be treatment-emergent for the specific postbaseline period. For each patient and TEAE, the maximum severity for the MedDRA level being displayed (PT, High Level Term, or SOC) is the maximum postbaseline 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.

5.5.12.1.1.1. Potential Hypersensitivity Events

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

- Anaphylactic reaction (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 latest dose of study drug administration, 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 TE hypersensitivity events by timing will be summarized using MedDRA PT. Events will be ordered by decreasing frequency. Note the timing of the hypersensitivity events is collected through eCRF and categorized into the following 4 categories:

- Immediate - occurs within minutes (<60 minutes) from study drug administration.
- Acute Reaction - occurs from 1 up to 6 hours from study drug administration.

- Delayed Reaction - occurs from >6 hours through 14 days from study drug administration, which will be split into 2 categories: on the same day of injection and after the day of injection.
- Reaction >14 days from 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 AE related to injection sites, the maximum severity for the MedDRA level being displayed (PT) is the maximum postbaseline 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 TE hypersensitivity events will be examined for all treatment groups. Additionally, the relationship between the development of TEAEs related to injection sites and treatment-emergent ADA will be examined 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 postbaseline 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 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 will be presented and compared. These 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 summarized and compared for SP III, and summarized for SP IV and SP V. These 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 1 of the 5 suicidal ideation questions (Categories 1-5) on the C-SSRS.
- Suicidal behavior: A "yes" answer at any time during treatment to any 1 of the 5 suicidal behavior questions (Categories 6-10) on the C-SSRS.
- Suicidal ideation or behavior: A "yes" answer at any time during treatment to any 1 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. A score of 0 is assigned if no ideation is present.

For SP III, SP IV and SP V, 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 (Visit 3.01 to Visit 7 for SP III; Visit 7.01 to Visit 16 for SP IV; Visit 16.01 to Visit 18 for SP V) 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 Visit 1 to Visit 7 excluding "lifetime" for SP IV; C-SSRS scales taken at Visit 1 to Visit 16 excluding "lifetime" for SP V).
- 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 (Visit 3.01 to Visit 7 for SP III; Visit 7.01 to Visit 16 for SP IV; Visit 16.01 to Visit 18 for SP V) from not having serious suicidal ideation (scores of 0-3) during the screening and lead-in periods (C-SSRS scales taken at Visit 1 to Visit 3 excluding "lifetime" for SP III; C-SSRS scales taken at Visit 1 to Visit 7 excluding "lifetime" for SP IV; C-SSRS scales taken at Visit 1 to Visit 16 excluding "lifetime" for SP V).

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 (Visit 3.01 to Visit 7 for SP III; Visit 7.01 to Visit 16 for SP IV; Visit 16.01 to Visit 18 for SP V) from no suicidal ideation (scores of 0) during the screening and lead-in periods (C-SSRS scales taken at Visit 1 to Visit 3 excluding "lifetime" for SP III; C-SSRS scales taken at Visit 1 to Visit 7 excluding "lifetime" for SP IV; C-SSRS scales taken at Visit 1 to Visit 16 excluding "lifetime" for SP V). 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 Visit 3.01 to Visit 7 for SP III; the last measurement during Visit 7.01 to Visit 16 for SP IV; the last measurement during Visit 16.01 to Visit 18 for SP V) from the baseline measurement (the measurement taken just prior to treatment (Visit 3 for SP III; the last non-missing measure during Visit 3.01 to Visit 7 for SP IV; the last non-missing measure during Visit 7.01 to Visit 16 for SP V).

Emergence of suicidal behavior compared to all prior history:

- The occurrence of suicidal behavior (Categories 6-10) during treatment (Visit 3.01 to Visit 7 for SP III; Visit 7.01 to Visit 16 for SP IV; Visit 16.01 to Visit 18 for SP V) from not having suicidal behavior (Categories 6-10) prior to treatment (Visit 1 to Visit 3 including "lifetime" for SP III; C-SSRS scales taken at Visit 1 to Visit 7 including "lifetime" for SP IV; C-SSRS scales taken at Visit 1 to Visit 16 including "lifetime" for SP V).

The same comparative endpoints of interest will also be analyzed for SP IV and SP V (refer to Table CGAI.5.4 for a definition of baseline and postbaseline visits).

Patients who discontinued from the study with no postbaseline C-SSRS value will be considered unevaluable for analyses of suicide-related events. Only evaluable patients will be considered in the analyses. The CMH 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 CMH test.

Table CGAI.5.6 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 two parts, an absolute threshold and a change from baseline amount.

- The absolute threshold in the criteria is based on 1) minimum postbaseline when the direction is low; 2) maximum postbaseline when the direction is high.
- The change from baseline amount in the criteria is 1) decrease from baseline (defined below and in Table CGAI.5.4) to minimum postbaseline when the direction is low; 2) increase from baseline (defined below and in Table CGAI.5.4) to maximum postbaseline 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 CGAI.5.4). 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 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 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 (Table CGAI.5.4):

- 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 is low.
  - the baseline is defined as the maximum value during the baseline period when the direction is high.

Table CGAI.5.6. 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 msecs 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 msecs 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 CGAI.5.4). 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 CGAI.5.4.

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 CMH test.

Table CGAI.5.7 displays the criteria for treatment-emergent changes in ECG intervals, heart rate, and QTcLCTPB. The absolute threshold in the criteria is based on 1) minimum postbaseline when the direction is low; 2) maximum postbaseline when the direction is high.

For QTcLCTPB, the treatment-emergent low and high criteria are listed by gender and age range, based on Lilly reference ranges.

- For treatment-emergent low analyses: Patients with all normal or high values at baseline (no low values) 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.

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

Parameter	Direction	Criteria	
Heart Rate (bpm)	Low	<50 and decrease ≥15	
	High	>100 and increase ≥15	
PR Interval (msec)	Low	<120	
	High	≥220	
QRS Interval (msec)	Low	<60	
	High	≥120	
QTcF (msec)	Low	Males: <330	Females: <340
	High	Males: >450	Females: >470
		>500 msec	
	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	

Abbreviations: bpm = beats per minute; msec = milliseconds.

In addition, a 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 postbaseline. A category is a collection of possible descriptions (findings) of 1 qualitative aspect of an ECG. A category name is the name of the qualitative aspect of the ECG (for example, Rhythm, Conduction, Morphology, Ischemia, and so forth). A finding is 1 of the possible specific descriptions (for example, Sinus Bradycardia, Acute Septal Infarction) within a category.

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

For analytes simply classified as normal or abnormal, patients will be defined as having a treatment-emergent abnormal value if they have all normal values at baseline, followed by an abnormal value at any postbaseline 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 postbaseline will also be summarized and compared between treatment groups using CMH 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 postbaseline 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 postbaseline 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 postbaseline 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 (that is 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 , 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 [ADA and NAb]) after treatment, the following statistical analyses are planned for comparison between treatment groups:

- The incidence of ADA positive during baseline will be summarized.
- The incidence of treatment-emergent ADA (TE ADA) between treatment groups will be summarized and compared for SP III. The incidence of TE ADA for LY-treated patients during LY treatment and the incidence of TE ADA for LY-treated patients during LY treatment and post-treatment phase combined will be summarized. This analysis will be done for each immunogenicity analyte (ADA and NAb). The baseline and postbaseline definitions for each Study Period is shown in Table CGAI.5.4. Treatment-emergent ADA will be defined as any of the following:
  - a negative baseline result and a positive postbaseline ADA result with a titer ≥20. This is also called treatment-induced ADA.
  - a positive baseline result and a positive postbaseline ADA result with a ≥4-fold increase in titers (for example, baseline titer of 10 increasing to ≥40 postbaseline). 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 provided:

- 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 TE hypersensitivity reactions or TEAEs related to injection sites for subjects with ADA present at any time.

In addition, as summarized in the immunogenicity addendum to Study CGAI protocol (Addendum 7), additional data will be collected after patients completed or discontinued from study, to characterize the time course of treatment-emergent anti-drug antibodies (ADA).

Individual patient listing of those data will be created, including concomitant medication, adverse events and ADA measurements.

5.5.12.2. Continuous Safety Measures

Analyses of continuous safety data will be conducted for SP III, SP III/IV, and SP III/IV/V on patients who have a baseline and at least 1 postbaseline observation. In those analyses, values from unscheduled visits will not be included, and only values collected at scheduled visits will be used.

For continuous safety measures (including laboratory measures, vital signs and weight, ECG intervals and heart rate), changes from last baseline value to LOCF endpoint during SP III, will be assessed using an ANCOVA model with treatment, baseline medication overuse, concurrent prophylaxis use, and baseline value as covariates. 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 pressures and pulse rate, as well as weight (when applicable), the mean change from baseline will be analyzed for SP III, SP III/IV, and SP III/IV/V using an MMRM analysis. The analysis will include the fixed categorical effects of treatment, month, baseline medication overuse, concurrent prophylaxis use 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 the primary efficacy measure (overall mean change from baseline on number of monthly migraine headache days) only for the ITT patients in SP III. Table CGAI.5.8 provides definitions for each subgroup variable. Subgroup variables are usually selected if they are potentially prognostic or predictive. A subgroup variable is prognostic if values of the subgroup variable predict the change in efficacy measures regardless of the treatment group assignment. A subgroup variable is predictive if values of the subgroup variable predict heterogeneous treatment effect. Current understanding is that demographic subgroup variables (sex, racial origin, ethnicity, and region) are neither prognostic nor predictive, but they are standard subgroup variables needed for regulatory submission. The rest of the 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.

Subgroup analyses by concurrent prophylaxis use and baseline medication overuse will be performed for TEAEs and vital signs and weight to detect potential differences in these safety measures.

Table CGAI.5.9 summarizes the subgroup analyses to be conducted, using those subgroup variables presented in Table CGAI.5.8.

Table CGAI.5.8. 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
Region	North America, including the United States and Canada; Europe, including UK, Netherlands, Spain, Italy, Czech Republic, Germany, and other European countries; Other, including Argentina, Israel, Korea, and Taiwan
Treatment resistant status	Treatment resistant status about whether a patient has failed 2 or more prophylactic treatments: Yes vs. No
Having aura or not (during baseline period)	Yes vs. No (A patient with aura is defined as patient with answer of "yes" for at least 1 day to ePRO Question 12 "Yesterday, did you experience aura?" during prospective baseline period)
Baseline Medication Over Use	Yes vs. No
Concurrent prophylaxis use	Yes vs. No

Table CGAI.5.9. Subgroup Analyses

Outcome Variable	Subgroup Variables	Analysis
EFFICACY VARIABLES		
1. Change from baseline to each postbaseline visit in the SP III for: • The number of migraine headache days	• Sex • Racial origin • Ethnicity • Region • Baseline Medication Over Use • Treatment resistant status • Having aura or not (during baseline period) • Concurrent prophylaxis use	MMRM using the model described in Section 5.5.1.1 with additional terms for subgroup, subgroup-by-treatment, subgroup-by-month, and subgroup-by-treatment-by-month interactions added as covariates.
SAFETY VARIABLES		
2. Incidence of patients with treatment-emergent adverse events (TEAEs) at any time in SP III.	• Concurrent prophylaxis use • Baseline Medication Over Use	Number and percentage of patients meeting criteria within each subgroup level will be summarized. Breslow-Day test for homogeneity of odds ratios will be used to test the subgroup-by-treatment interaction. Treatment comparisons within each subgroup level use CMH test.
3. Change from baseline to each postbaseline visit in SP III: Blood pressure, body temperature and pulse	• Concurrent prophylaxis use • Baseline Medication Over Use	Repeated measures analysis using the model described in Section 5.5.1.1 with terms for subgroup, subgroup-by-treatment, subgroup-by-month, and subgroup-by-treatment-by-month interactions added to the base model.
4. Change from baseline to LOCF endpoint in the SP III: Weight	• Concurrent prophylaxis use • Baseline Medication Over Use	ANCOVA model with terms for treatment, baseline weight, subgroup, and subgroup-by-treatment interaction.

For the subgroup variables of race, all the categories that have less than 10% of the patients in the study will be combined as 1 category. For the subgroup variables of region, if sample size in "other" region is less than 10% of total sample size, we will pull them into "Europe" region for subgroup analysis.

The subgroup-by-treatment interactions will be tested at a 2-sided 0.10 significance level. Treatment group differences will be evaluated within each category of the subgroup variable.

For all the subgroup variables, the subgroup analysis for change from baseline to each period in the number of migraine headache days will be conducted with MMRM. The same MMRM model as described in Section 5.5.1.1 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, subgroup-by-treatment-by-month and subgroup-by-treatment interactions at last 30-day period of 3-month treatment (Month 3) will be reported.

For subgroup analysis with both MMRM and ANCOVA method, the LSMeans and LSMeans change estimate as well as the treatment comparisons within each subgroup will be analyzed with the data within that specific subgroup only. The MMRM model will be the same as described in Section 5.5.1.1. The ANCOVA model will be the same as described in Section 5.5.1.1.

5.6. Interim Analyses

Two interim analyses are anticipated for Study CGAI, which are summarized in Table CGAI.5.10.

Table CGAI.5.10. List of Unblinded Analyses and Purposes

Unblinded Analysis	Approximate Timing	Purpose
Interim Analysis #1	About 300 randomized patients have had the chance to complete 3 months of double-blind treatment	Safety / Futility
Interim Analysis #2	All randomized patients have had the chance to complete double blind treatment phase	Final analysis of the primary efficacy endpoints; Efficacy and safety analysis of double blind phase

Interim Analysis #1

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

This interim analysis is planned when approximately 300 randomized patients have had the chance to complete 3 months of double-blind treatment phase. Safety and futility assessments will be performed at interim analysis #1.

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 periods (SP III or SP IV) of the study must discontinue from study drug but complete the follow-up phase. The patient should continue in the trial, completing all SP V study procedures as outlined in the protocol. The reason for stopping will not be provided to the investigators until after the final data are locked and reported.

Sample size could be increased as a result of the interim analysis #1. If the sample size is increased or if the sample size remains at the planned sample size, the investigators will not be informed and will remain blinded to the final sample size. The only communication to the investigator will be when enrollment is complete for their site.

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 the DMC Charter for studies CGAI, CGAH, CGAI, and CGAJ.

Interim Analysis #2

Interim analysis #2 is planned when all randomized patients have had the chance to complete 3 months of double-blind treatment phase 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 analysis #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 will be 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 (that is, group or patient), and purpose of unblinding.

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

5.8.1.1. Reports to be Generated at Interim Analysis #1 Database Lock

Reports to be generated at interim analysis #1 are summarized in the SAC SAP.

5.8.1.2. 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 3 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 3 months of double-blind treatment phase (SP III):

- Patient disposition as specified in Section 5.5.2, for SP III and SP IV separately.
- Patient characteristics as specified in Section 5.5.4.
- Exposure to IMP as specified in Section 5.5.5, for SP III and SP IV separately.
- ePRO diary compliance as specified in Section 5.5.7, for SP III and SP IV separately.
- Previous migraine prevention therapy as specified in Section 5.5.8.
- Concomitant therapy as specified in Section 5.5.9, for SP III and SP IV separately.
- Efficacy analyses for the number of monthly migraine headache days, 50% response rate in the number of monthly migraine headache days, MSQ Role Function-Restrictive domain score, and PGI-S for SP III, and up to Month 9 in SPIV, as well as the proportion of patients who continue to demonstrate 50% response for at least 3 (not necessarily consecutive) of the first 6 months in the open-label treatment period.
- Safety analyses for TEAEs, and treatment-emergent changes in laboratory measures, vital signs, and ECG parameters for SP III and SP IV separately.
- ADA-related analyses for all data available, including SP III, SP IV, and SP V.
- All other efficacy, quality-of-life, and safety analyses as specified in Section 5.5.10, Section 5.5.11 and Section 5.5.12 for SP III only.

Analyses conducted at interim analysis #2 will be considered as the final analyses for double-blind treatment phase and will be used in the final CSR.

5.8.1.3. Report to be Generated at Final Database Lock

All reports that have not been generated in interim analyses will be generated at final database lock. Some reports that have been generated in interim analyses and including open-label treatment phase and/or post-treatment phase will be re-run to include all available data.

5.9. Clinical Trial Registry Analyses

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

Analyses provided for the CTR requirements include the following:

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

- 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

Bauer P, Kohne K. Evaluation of experiments with adaptive interim analyses. *Biometrics.* 1994;50:1029-1041.

CCI [redacted]

CCI [redacted]

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

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

CCI [redacted]

CCI [redacted]

[redacted]

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

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

CCI [redacted]

Lipton RB, Varon SF, Grosberg B, McAllister PJ, Freitag F, Aurora SK, Dodick DW, Silberstein SD, Diener HC, DeGryse RE, Nolan ME, Turkel CC. OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine. *Neurology*. 2011;77(15):1465-1472

CCI [redacted]

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

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 Form (ICF)	ICF 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 ICF	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	
		Do not meet criteria of at least 15 normalized headache days of which 8 must have features of migraine	Programmable - Stats	Number of normalized headache days <15, or number of normalized migraine headache days < 8
		At least one headache free day	Programmable - Stats	Number of normalized headache days > 29
		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	
		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.

Description of Important Protocol Deviations

Category	Subcategory	Study-specific	Source	Methods of Identification
Eligibility	Inclusion/ Exclusion	Insufficient washout of Botulinum toxin A and B at least 4 months prior to Visit 2	Non-programmable- Study team identified	Stats will create the list of patients meet this IPD criteria. 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.
		Having ECGs showing abnormalities compatible with acute cardiovascular events and/or serious cardiovascular risk.	Non-programmable- Monitor identified	
		Corrected QT (QTcB [Bazett's]) interval > 470 msec for women and >450 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 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 enzymes-have an elevation of >2X upper limit of normal (ULN) for alanine transaminase (ALT), or >1.5X ULN total bilirubin (TBL) or alkaline phosphatase (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 concurrent prophylaxis category in IWRS was not the same as derived based on eCRF data; or if medication overuse category was not the same as derived from ePRO.
	Other	ePRO pro compliance <=50% for half or more months during 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, based on how long the patient stayed in double-blind treatment phase. 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 in double-blind treatment phase;*	Programmable – Stats	For randomized patients with non-missing visit 5 date, if C-SSRS (questions 1 to 2, questions 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.
		Missing safety measurement: *CSSRS in open-label phase*	Programmable – Stats	For randomized patients with non-missing visit 8 date, if C-SSRS (questions 1 to 2, questions 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 in post-treatment phase*	Programmable – Stats	For randomized patients with non-missing visit 17 date, if C-SSRS (questions 1 to 2, questions 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.
		Missing safety measurement: Vital signs (Blood pressure, body temperature, pulse) at baseline or in 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.
		Missing safety measurement: Vital signs (Blood pressure, body temperature, pulse) in open-label treatment phase	Programmable – Stats	For patients entered open-label treatment phase with non-missing visit 8 date, if blood pressure, body temperature, or pulse, are missing all baseline or missing all post-baseline measures or missing two consecutive measures during open-label 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) in 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 and hematology at baseline	Programmable – Stats	If calcium and hemoglobin is missing all baseline measures.
		Missing safety measurement: Chemistry and hematology in open-label treatment phase	Programmable – Stats	For randomized patients with non-missing visit 10 date , if calcium and hemoglobin is missing all baseline or missing all post-baseline measures in open-label 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 and hematology in 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 post-baseline 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.
		Missing safety measurement: ECGs at baseline	Programmable – Stats	Same rule as for "Missing safety measurement: Chemistry or hematology at baseline"
		Missing safety measurement: ECGs in open-label treatment phase	Programmable – Stats	Same rule as for "Missing safety measurement: Chemistry or hematology in open-label treatment phase
		Missing safety measurement: ECGs in post-treatment phase	Programmable – Stats	Same rule as for "Missing safety measurement: Chemistry or hematology in post-treatment phase

Description of Important Protocol Deviations

Category	Subcategory	Study-specific	Source	Methods of Identification
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 migraine preventive medication for primary indication only for >7 consecutive days during IV.	Programmable - Stats	
		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	Programmable - Stats	Prior therapy should be excluded in the consideration.
		Corticosteroids, oral or injected, or opioids, barbiturates use >7 consecutive days during study period II or III	Programmable – Stats	Prior therapy should be excluded in the consideration.
		Start, stopping or switching dose of topirmate or propranolol during double blind phase.	Non-programmable - Monitor identified	

Description of Important Protocol Deviations

Category	Subcategory	Study-specific	Source	Methods of Identification
Study Procedures	Visit schedule criteria	Dosing interval outside specified limits in double-blind treatment phase	Programmable – Stats	For randomized patients, compare dosing interval to allowable visit intervals between doses. Allowable dosing intervals: 21 to 37 days
		Dosing interval outside specified limits in open-label treatment phase	Programmable – Stats	For randomized patients, compare dosing interval to allowable visit intervals between doses. Allowable dosing intervals: 21 to 37 days
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	
Administrative/ Oversight	Other	Administrative oversight	Non-programmable - Monitor identified	CSSR scale administered by unqualified rater

Description of Important Protocol Deviations

Category	Subcategory	Study-specific	Source	Methods of Identification
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
		Female patients who are dosed and have a positive urine or serum pregnancy test during the treatment phase, and who has not been discontinued from treatment.	Non-programmable - Monitor identified	

Abbreviations: AE = adverse event, BMI = body mass index; Con-Meds = concomitant medications; CRF = case report form; CRP = clinical research physician; EDC = electronic data capture; ICD = informed consent document; IP = investigational product; IVRS = interactive Voice Response System; PK = pharmacokinetics; SAE = serious adverse event.