I5Q-MC-CGAJ Statistical Analysis Plan Version 1

A Phase 3, Long-Term, Open-Label Safety Study of LY2951742 in Patients with Migraine

NCT02614287

Approval Date: 23-Nov-2015

1. Statistical Analysis Plan for Protocol I5Q-MC-CGAJ: A Phase 3, Multisite, 12-month, Open-label Study of LY2951742 in Patients with Episodic or Chronic Migraine

Confidential Information

Anti-CGRP monoclonal antibody (LY2951742)

I5Q-MC-CGAJ is a Phase 3, multisite, 12-month, open-label study to assess the safety of LY2951742 (120 mg/month and 240 mg/month) in patients suffering from migraine headaches (with or without aura). Eligible patients are to be those with episodic or chronic migraine.

Eli Lilly and Company
Indianapolis, Indiana USA 46285
Protocol I5Q-MC-CGAJ
Phase 3

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

Approval Date: 23-Nov-2015 GMT

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 will be approved prior to first patient visit.

4. Study Objectives

4.1. Primary Objective

The primary objective of this study is to evaluate the long-term safety and tolerability of LY2951742 (120 or 240 mg/month) in patients suffering from migraine, for up to 1 year of treatment, by monitoring and assessing the following safety endpoints:

- Treatment-emergent adverse events (TEAEs)
- Discontinuation rates
- Vital signs and weight
- Electrocardiograms (ECGs)
- Laboratory measures
- Other safety parameters, including Suicidality using the Columbia Suicide Severity Rating Scale (C-SSRS)

4.2. Secondary Objectives

Secondary Objectives are summarized in Table CGAJ.4.1.

Table CGAJ.4.1. List of Secondary Objectives and Endpoints

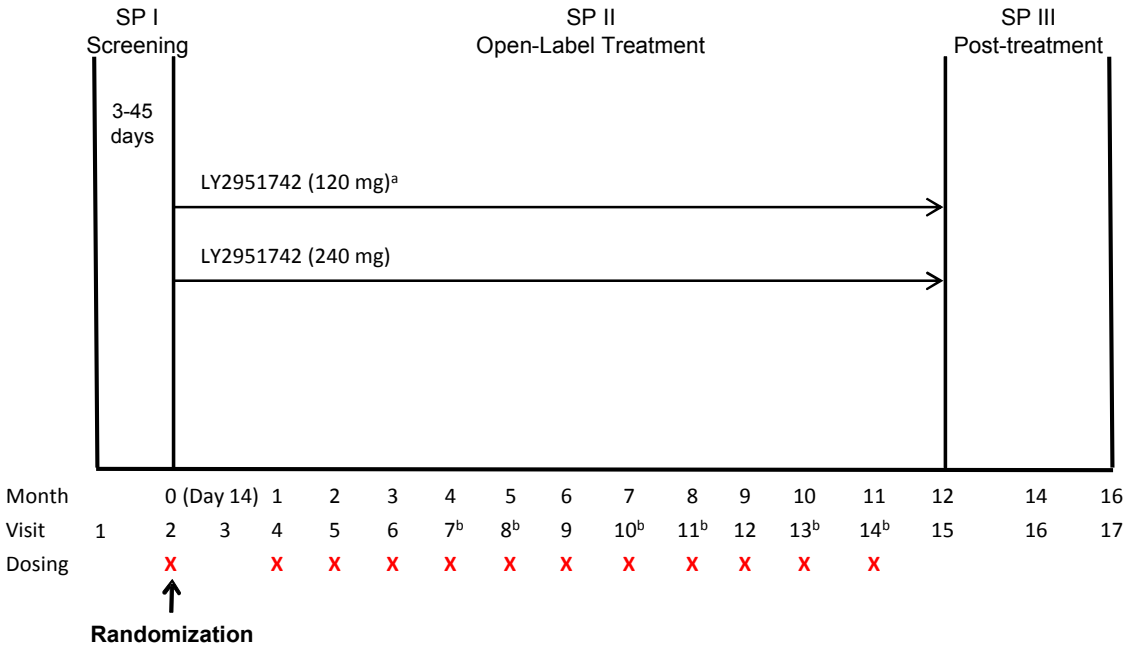
Secondary Objectives	Endpoints
To characterize the long-term pharmacokinetics and pharmacodynamics of LY2951742.	• Assessment of serum concentrations of LY2951742 to enable a pharmacokinetic evaluation. • Assessment of plasma concentrations of CGRP to enable a pharmacodynamic evaluation of target engagement of LY2951742.
To characterize the long-term immunogenicity of LY2951742	• Development and consequences of anti-drug antibodies and neutralizing antibodies to LY2951742
To evaluate the long-term efficacy of LY2951742 in the prevention of migraine.	• Mean change from baseline in o the number of migraine headache days; o the number of headache days; o the frequency of medication use for the acute treatment of migraines or headaches • Proportion of patients meeting 50% response criteria (reduction of at least 50% in the number of migraine headache days) • Patient's global impression of improvement as measured by PGI-Improvement

Secondary Objectives (cont.)	Endpoints (cont.)
To evaluate the long-term effect of LY2951742 on health outcomes and quality of life measures.	• Mean change from baseline in o the Migraine Disability Assessment test (MIDAS) total score and individual items; o the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) total score and individual domains; • Change from baseline in healthcare resource utilization and employment status
To evaluate safety and residual effectiveness during the post-treatment follow-up period.	• Analysis of safety parameters; • Time to first loss of response (when patient no longer meets response criteria and/or starts treatment using migraine prevention medication) during the post-treatment follow-up phase
To evaluate patient satisfaction with medication and device	• Satisfaction with medication using the Patient Satisfaction with Medication Questionnaire-Modified (PSMQ-M). • Satisfaction (and ease of use) with the device for injection using the Subcutaneous Administration Assessment Questionnaire (SQAAQ).
To evaluate results with respect to use of the autoinjector	• Injection-related safety/tolerability and device performance upon use of the autoinjector

5. A Priori Statistical Methods

5.1. Study Design

Study CGAJ is a Phase 3, multisite, long-term, open-label study to assess the safety of LY2951742 (120 mg/month with a 240-mg loading dose, and 240 mg/month) in patients suffering from migraine, with or without aura. Patients will not be permitted to enroll in Study CGAJ if they were previously treated with LY2951742.



a Patients randomized to the 120 mg dose will receive a loading dose of 240 mg at the first injection only (Visit 2).

b Telephone visit.

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

5.2. Determination of Sample Size

Approximately 250 patients will be enrolled in Study CGAJ. This sample size will ensure at least 100 patients with at least 1 year of exposure to fulfill regulatory requirements for registration.

5.3. Randomization and Treatment Assignment

All eligible patients will be randomized to either 120 mg/month or 240 mg/month monthly with 1:1 randomization ratio.

5.4. Endpoints

5.4.1. Safety Endpoints

Safety endpoints consist of

- the incidences of TEAEs, serious adverse events (SAEs), and discontinuations due to adverse events (AEs)
- vital signs (blood pressure, pulse and body temperature), and weight
- ECGs
- laboratory measures (chemistry, hematology and urinalysis)
- C-SSRS

5.4.2. Efficacy Endpoints

In Study CGAJ, no patient diary data will be collected. Migraine and headache frequency as well as abortive medication use will be collected by direct questioning by the investigator at an office/phone visit for the past month retrospectively.

- Migraine headache days - the number of migraine headache days per month
- Number of headache days – the number of headache days per month
- Number of headache days with medication use – number of headache days that patients take any pain medication for headache per month.
- 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 drived for X=30, 50, 75, and 100.

  For all 30%, 50%, 75%, and 100% responder definition, percent change from baseline in migraine headache days in month Y will be calculated as:

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

- Patient Global Impression of Severity (PGI-S)
- Patient Global Impression of Improvement (PGI-I)

The Patient Global Impression of Severity (PGI-S) will be collected at baseline (Visit 3). In this single-item scale, patients rate the severity of their migraine condition on a s cale ranging from "not at all ill" (coded as 1) to "extremely ill" (coded as 7).

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

The PGI-I scores will be used as analysis value, adjusting for PGI-S score at baseline.

5.4.3. Health Outcome/Economics and Device Evaluation

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

Migraine Specific Quality of Life (MSQL) v2.1 consists of 14 questions. The questions measure the impact of migraine on health-related quality of life across three dimensions: 1) Role Function-Restrictive (seven questions), examines the degree to which performance of daily activities is limited by migraine; 2) Role Function-Preventive (four questions), examines the degree to which performance of daily activities is prevented by migraine; 3) Emotional Function (three questions), examines feelings of frustration and helplessness due to migraine. The questionnaire results will be recorded in the electronic case (clinical) report form (eCRF).

Item values for each MSQ item response are shown in Table CGAJ.5.1. All item values range from 1 to 6. Item value will be used as the raw value for analysis.

Table CGAJ.5.1. 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 dimension, questions 8 to 11 as Role Function-Preventive dimension and questions 12 to 14 as the Emotional Function dimension.

In the event that responses on one or more items within a dimension are missing, a missing item value will be estimated using the average of the other items within the same dimension. This will only be done if at least half of the items within a dimension have been answered. Therefore, when the number of missing items is fewer than or equal to 3 for the Role Function-Restrictive, fewer than or equal to 2 for the Role Function-Preventive, and fewer than or equal to 1 for the Emotional Function dimension, the value of missing item(s) can be estimated using the average of the other completed items within the same dimension. For example, if a respondent leaves one item (that is, item 4) within the 7-item Role Function-Restrictive dimension blank, substitute the respondent's average score across the six completed Role Function-Restrictive items (that is, item 1, 2, 3, 5, 6,7) for that one item.

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

The total score of all three domains will be calculated as the sum of raw scores of three domains.

The raw scores of each domain and the total score will be transformed to a 0 to 100 scale using the follow 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):

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

Responders in Role Function-Restrictive, Role Function-Preventive, and Emotional Function will be defined as follows:

- Responders in Role Function-Restrictive: Change from baseline in Role Function-Restrictive ≥ 10.9
- Responders in Role Function-Preventive: Change from baseline in Role Function-Preventive ≥ 8.3
- Responders in Emotional Function: Change from baseline in Emotional Function ≥ 12.2

The MSQ total score, the domain scores, and the indicators of domain responders will be analyzed.

5.4.3.2. MIDAS (Migraine Disability Assessment) Questionnaire

The Migraine Disability Assessment questionnaire (MIDAS) consists of 5 questions (Q1-Q5) and two additional questions (A and B). The questionnaire help measure the impact that migraine headaches have on migraineurs' life, including days of work or school missed, days with productivity at work or school reduced to half or more, days with household work missed, days with productivity in household work reduced to half or more, and days missed family/social/leisure activities.

Each question is answered as a numeric number of days during the past 3 months of assessment, ranging from 0 to 90. The answers to all five questions will be added up to a total MIDAS score. The total MIDAS score and the raw score of each question will be used as values for analysis.

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 count.

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

Data from Visits 3-9 will be added to provide a single number for that 6-month period. If missing data occur in more than 3 months, the six-month period will have a missing data point; otherwise, the month(s) with missing data will be imputed using the mean of the rest of months during the 6-month period. Data from Visits 10-15 will be calculated similarly.

Change from baseline in the following HCRU scores 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 emergency room (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

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

A question on employment status is also solicited, given the correlation and potential confounding with health outcomes measures.

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

The PSMQ-M is a self-rated scale which measures patients' level of satisfaction with study medication. The scale has been modified for use in this study, assessing 3 items related to the clinical trial treatment over the past 4 weeks: satisfaction, preference, and side effects. Satisfaction responses range from "very dissatisfied" to "very satisfied" with the current treatment. Preference compares the current study medication to previous medications, with responses from "much prefer previous medication" to "much prefer study medication."

The PSMQ-M will be collected at Month 1, Month 6, and Month 12. Change over time will be examined using the raw scores as descriptive statistics.

5.4.3.5. Subcutaneous Administration Assessment Questionnaire (SQAAQ)

The SQAAQ is a self-administered questionnaire that provides an assessment of ease of use and confidence with using a device to administer a subcutaneous injection of drug. Patients will respond to questionnaire items using a 7-point Likert scale (from "Strongly Disagree" to "Strongly Agree") shortly after the injection. If a caregiver administers the injection, caregiver's ratings of the questions will be collected.

The 7-point score will be used as analysis value.

5.4.4. Immunogenicity Endpoints

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

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5.4.6. Pharmacokinetic Assessment

Pharmacokinetic assessments will be summarized in the pharmacokinetic/pharmacodynamic (PK/PD) analysis plan.

5.5. Statistical Analyses

The SAP Version 1 will be approved prior to first patient visit. The SAP Version 1 supersedes the statistical plans described in the protocol.

5.5.1. General Considerations

Two treatment arms will be evaluated based on a two-sided significance level of 0.05 for all safety and efficacy analyses. 95% confidence intervals (CIs) for the difference in least-square means (LSMeans) between treatment groups will be provided.

For continuous variables with repeated measures, change from baseline 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.

For continuous variables without repeated measures, the change from baseline to last-observation-carry-forward (LOCF) endpoint will be analyzed using analysis of variance (ANOVA) or analysis of covariance (ANCOVA) model. Unless otherwise specified, when ANOVA model or ANCOVA model is used, 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 variables without repeated measures, categorical comparisons between two treatment arms will be performed using Cochran-Mantel-Haenszel (CMH) test, or Fisher's exact test. Unless otherwise stated, CMH test will be controlled for pooled investigative site. In addition, unless otherwise specified, Fisher's exact test will be used for comparisons of baseline measures (e.g., baseline patient characteristics, previous therapy, etc.); and CMH test will be used for comparisons of post-baseline efficacy or safety measures.

Unless otherwise stated, whenever descriptive statistics of each arm are provided, descriptive statistics of both treatment arms combined will also be provided in the same table.

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

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

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

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

5.5.1.1. Adjustments for Covariates

The MMRM models will include the fixed, categorical effect of pooled investigative site, treatment, and month, as well as the continuous, fixed covariates of baseline value and baseline value-by-month and month by treatment interactions. The baseline value and baseline-by-month interaction are included to account for the differential influence over time that the baseline value has on the post-baseline values. Rules of pooling investigative site are described in Section 5.5.1.3.

When an ANOVA model is used to analyze a continuous efficacy or safety variable, the model will contain the main effects of pooled investigative site, and treatment. When an ANCOVA model is used to analyze a continuous efficacy or safety variable, the model will contain the main effects of pooled investigative site and treatment, and appropriate baseline value as a covariate.

The GLIMMIX models for the repeated binary outcomes will include the fixed, categorical effect of month, as well as the continuous, fixed covariate of baseline value. Pooled investigative site and the baseline value-by-month interaction will not be included in the model in order to increase the likelihood of 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 using change from baseline to LOCF endpoint.

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 and when there is ignorable non-random missing data.

5.5.1.3. Rules for Pooling Investigative Site

All investigative sites with fewer than 2 randomized patients per each LY2951742 treatment group with nonmissing Migraine Headache value at baseline and at least one postbaseline value will be pooled together within a country and considered a single site for analyses. If this results in a pooled site still having fewer than 2 randomized patients per each LY2951742 treatment group, the pooled site will also be pooled with the next smallest site in a country, determined to be the site with the smallest number of randomized patients, or if more than one site meets that criterion, the smallest site with the lowest investigator number. If there are no other sites in the country, no further pooling will be performed. All analyses will use pooled investigative sites. The actual investigative site numbers will be included in the listings.

5.5.1.4. Multiple Comparisons/Multiplicity

No multiplicity adjustment will be conducted for Study CGAJ.

5.5.1.5. Analysis Populations

There were two analysis populations defined:

Intent-to-Treat (ITT) Population: All patients who are randomized and received at least one dose of LY2951742. Patients in the ITT population will be analyzed according to the treatment group to which they were randomized. Unless otherwise specified, the ITT population will be the primary population on which statistical analysis will be performed.

Post-treatment Population: All patients who entered the post-treatment phase (Study Period III) as indicated by entering any post-treatment visit. Patients in the post-treatment population will be analyzed according to the treatment group to which they were previously randomized during Study Period II.

Statistical analysis will be carried out for 12 months treatment phase (Study Period II), 4 months post-treatment phase (Study Period III) as well as 12 months treatment and 4 months post-treatment phase combined (Study Period II /III).

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

5.5.1.6. Baseline and Postbaseline Definition

Table CGAJ.5.2 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 CGAJ.5.2. 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 II			
TEAEs	ITT Population	All Visits 1–2	All Visits 2.01–15
Serious Adverse Events, Discontinuations due to Adverse Events	ITT Population	NA	All Visits 2.01–15
C-SSRS Categorical Analyses	Patients with a baseline and at least one postbaseline C-SSRS assessment	Recent History: All Visits 1–2 excluding lifetime[a] All Prior History: Visits 1 – 2 including lifetime[a]	All Visits 2.01–15
Treatment-emergent abnormal laboratory values	ITT Population and Patients with normal laboratory values at all nonmissing baseline visits (with respect to direction being analyzed) and who have at least one postbaseline observation	All Visits 1–2	All Visits 2.01–15
Treatment-emergent Immunogenicity	ITT Population	Visit 2	All Visits 2.01–15
Treatment-emergent Changes in Vital Signs and Weight	ITT Population and patients with a baseline and at least one postbaseline observation	Low: Minimum value from Visits 1–2 High: Maximum value from Visits 1–2	Low: Minimum value from Visits 2.01–15 High: Maximum value from Visits 2.01–15
Continuous Safety Analyses (Repeated Measures)	ITT Population and patients with a baseline and at least one postbaseline observation	Last of Visits 1–2	All Visits 2.01–15
Continuous Safety Analyses – Change From Baseline to LOCF Endpoint (ANCOVA)	ITT Population and patients with a baseline and at least one postbaseline observation	Last of Visits 1–2	All Visits 2.01–15
Efficacy Analyses (Repeated Measures)	ITT Population and patients with a baseline and at least one postbaseline observation	Visit 2	All Visits 2.01–15
Quality of Life Analyses (Repeated analysis)	ITT Population and patients with a baseline and at least one postbaseline observation	Visit 2	All Visits 2.01–15

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 II and III Combined			
Efficacy Analyses	ITT Population and patients with a baseline and at least one postbaseline observation	Visit 2	All Visits 2.01-17
Quality of Life Analyses	ITT Population and patients with a baseline and at least one postbaseline observation	Visit 2	All Visits 2.01-17
Continuous Safety Analyses (Repeated Measures)	ITT Population and patients with a baseline and at least one postbaseline observation	Visit 2	All Visits 2.01-17
Treatment-emergent Immunogenicity	ITT Population	Visit 2	All Visits 2.01-17
Study Period III			
TEAEs	Post-treatment Population	All Visits 1- 15	All Visits 15.01–17
Serious Adverse Events, Discontinuations due to Adverse Events	Post-treatment Population	NA	All Visits 15.01–17
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 one postbaseline observation	All Visits 1- 15	All Visits 15.01–17
Treatment-emergent Immunogenicity	Post-treatment Population	All Visits 1- 15	All Visits 15.01–17
Treatment-emergent Changes in Vital Signs and Weight	Post-treatment Population and patients with a baseline and at least one postbaseline observation	Low: Minimum value from Visits 1–15 High: Maximum value from Visits 1–15	Low: Minimum value from Visits 15.01–17 High: Maximum value from Visits 15.01–17

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

Note: Visit 2.01 indicates the first unscheduled visit occurring after Visit 2 and prior to Visit 3. Visit 15.01 indicates the first unscheduled visit occurring after Visit 15 and prior to Visit 16.

[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 two treatment groups for Study Period II and Study Period III both overall and by visit. Reasons for discontinuation will be compared between treatment groups using CMH test for study period II with the ITT population. Descriptive statistics only will be presented for the treatment groups in Study Period III with post-treatment population.

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

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

5.5.3. Protocol Violations

Listings of subjects with significant protocol violations will be provided for the overall ITT population. The following list of significant protocol violations will be determined from the clinical database and from the Lilly clinical/medical group:

- Lack of informed consent or late informed consent
- Violations of inclusion/exclusion criteria
- Significant violations of study drug dosing as determined by the Lilly clinical/medical group
- Significant violations of prohibited concomitant medication usage as determined by the Lilly clinical/medical group
- Other significant protocol violations as determined by the Lilly clinical/medical group

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 month at baseline, including
    - number of migraine headache days
    - number of headache days
    - number of migraine headache days with pain medication for migraine or headache
- Number and percent of patients
    - with high (≥8) vs low-frequency (<8) of migraine headache days
    - fulfilling chronic migraine criteria, episodic migraine criteria, and other
    - with at least two preventive drug failures

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

Comparisons between treatment groups will be performed using CMH test for categorical data and ANOVA with treatment and pooled investigative site 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 CMH 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, Visits 1 and 2.

5.5.5. Exposure to Investigational Product

Patients will receive the investigational medicinal product (IMP) monthly at Visit 2, and Visits 4-14.

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:

- Duration of exposure in days calculated as (Last date IMP administered – First date IMP administered+30 days), 30 days were added because IMP half-life is about 30 days.
- Number and percentage of patients with different doses injected.
- Number of patients with autoinjector
- Number and percentage of injections using prefilled syringe versus autoinjector

Comparisons between treatments for duration of IMP exposure, and number of patients with different doses injected will be performed using an ANOVA with treatment and pooled investigative site in the model.

In addition, injections that are not administered will be listed.

5.5.6. Treatment Compliance

Treatment compliance will be calculated for Study Period II as:

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

Comparisons between two treatments for treatment compliance will be performed using an ANOVA with treatment and pooled investigative site in the model. For this analysis, partial dose (for example, a patient assigned 240mg only got one injection) will be considered as no dose received.

5.5.7. Previous Migraine Prevention Therapy

The proportion of patients who received previous migraine prevention therapy, and the proportion of patients with response to the previous migraine prevention therapy within each of the four categories (adequate response, inadequate response, no response, and treatment availability) will be summarized for all ITT patients. Treatment group comparisons will be done using CMH test.

5.5.8. Concomitant Therapy

The proportion of patients who received concomitant medication collected from eCRF will be summarized for all ITT patients for Study Period II and Study Period III separately. Treatment group comparisons will be done using CMH test for Study Period II with ITT population. Descriptive statistics only will be presented for the treatment groups in Study Period III with post-treatment population.

5.5.9. Safety Analyses

The primary analysis will evaluate long-term safety and tolerability of LY2951742 120mg and 240mg in patients suffering from migraine.

As the primary analysis, the safety analyses will be conducted for Study Period II, Study Period III, as well as Study Period II and III combined.

- For Study Period II and Study Period III separately, the safety analyses outlined in the following sub-sections will be conducted.
- For Study Period II and Study Period III combined, only the change from baseline with MMRM analysis and time to event analysis (Section 5.5.9.3) will be conducted.

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

- AEs
- TEAEs
    - By PT by decreasing frenquencies
    - By SOC
    - By maximum severity
    - By considered to be related to investigational produce by investigator
- SAEs
- AEs leading to discontinuation

- Suicide-Related Thoughts and Behaviors
- Vital signs and weight
- Laboratory measurements
- ECGs
- Antibodies (ADA and NAb)

The baseline and postbaseline for all safety measures are described in Table CGAJ.5.2 unless specified otherwise.

5.5.9.1. Categorical Safety Variables

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

- Study Period II: Comparisons between treatment groups for all categorical safety measures will be made using CMH test with the ITT population.
- Study Period III: Descriptive statistics only will be presented for the treatment groups with post-treatment population.

5.5.9.1.1. Adverse Events

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

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

5.5.9.1.1.1. Allergic Reactions/Hypersensitivities

Allergic reactions/hypersensitivities will be defined using the following terms:

- Broad and narrow terms in the Anaphylactic reaction SMQ (20000021)
- Broad and narrow terms in the Angioedema SMQ (20000024)
- Broad and narrow terms in the Severe cutaneous adverse reactions SMQ (20000020)
- Broad and narrow terms in the Hypersensitivity SMQ(20000214)

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 allergic reactions / hypersensitivities by maximum severity will be summarized by treatment groups using MedDRA PT nested within the SMQ.

The number and percentage of patients with TEAEs of allergic reactions/hypersensitivities by timing will be summarized using MedDRA PT nested within the SMQ. Events will be ordered by decreasing frequency within the SMQ. Note the timing of the allergic reactions / hypersensitivities is collected through eCRF and categorized into the following four 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 demonstration
- Reaction >14 days.

The relationship between the development of TEAE of allergic reactions/hypersensitivities and treatment emergent ADA within LY2951742 dose groups will be examined.

5.5.9.1.1.2. Injection Site Reactions

Injection site reactions will be defined using terms from the MedDRA High Level Term Injection site reactions.

The number and percentage of patients with treatment-emergent injection site reactions, serious adverse events related to injection site reactions, and injection site reaction adverse events 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 treatment-emergent injection site reactions by maximum severity will be summarized by treatment groups using MedDRA PT nested within the High Level Term. For each patient and injection site reaction event, the maximum severity for the MedDRA level being displayed (PT) is the maximum post-baseline severity observed from all associated LLTs mapping to that MedDRA level.

The number and percentage of patients with treatment-emergent injection site reactions by device type (syringe versus auto-injector) will be summarized by treatment groups using MedDRA PT nested within the High Level Term.

The relationship between the development of TEAE of injection site reactions and treatment-emergent adverse event of allergic reactions/hypersensitivities will be examined for all treatment groups. Additionally, the relationship between the development of TEAE of injection site reactions and treatment emergent ADA will be examined for LY2951742 group.

5.5.9.1.1.3. Infections

Infections will be defined using all the PTs from the Infections and Infestations SOC as defined in MedDRA.

The number and percentage of patients with TEAEs, SAEs, and AEs resulting in study drug discontinuation will be summarized by treatment group using MedDRA PTs. Events will be ordered by decreasing frequency in the LY2951742 group.

The number and percentage of patients with TEAEs by maximum severity will be summarized by treatment group using MedDRA PTs.

The number and percentage of patients experiencing a TEAE of infection who are treated with anti-infectives (including antibiotics, antifungals, antivirals, or antiprotozoals, etc.) will be presented by treatment group using MedDRA PTs nested within SOC. Final list of anti-infectives will be provided by medical.

The relationship between TEAEs-infections and other clinical, laboratory, and hematology parameters will be examined and a listing will be provided.

5.5.9.1.2. 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 one of various composite measures during treatment phase and post-treatment follow-up phase separately 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 one of various comparative measures during treatment will be presented and compared for Study Period II only. Comparative measures include treatment-emergent suicidal ideation compared to recent history, treatment-emergent serious suicidal ideation compared to recent history, emergence of serious suicidal ideation compared to recent history, improvement in suicidal ideation at endpoint compared to baseline, and emergence of suicidal behavior compared to all prior history.

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

Category 1 – Wish to be Dead
Category 2 – Non-specific Active Suicidal Thoughts
Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Category 5 – Active Suicidal Ideation with Specific Plan and Intent
Category 6 – Preparatory Acts or Behavior
Category 7 – Aborted Attempt
Category 8 – Interrupted Attempt
Category 9 – Actual Attempt (non-fatal)
Category 10 – Completed Suicide.

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

Composite endpoints based on the above categories are defined below.

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

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

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

For Study Period II only, 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 from the maximum suicidal ideation category during the screening and lead-in periods (C-SSRS scales taken at or before baseline excluding "lifetime"). Recent history excludes "lifetime" scores from the Baseline C-SSRS scale or Baseline/Screening C-SSRS scale.

- Treatment-emergent serious suicidal ideation compared to recent history:
  An increase in the maximum suicidal ideation score to 4 or 5 on the C-SSRS during treatment phase during the screening and lead-in periods from not having serious suicidal ideation (scores of 0-3) (C-SSRS scales taken at or before baseline excluding "lifetime"). Recent history excludes "lifetime" scores from the Baseline C-SSRS scale or Baseline/Screening C-SSRS scale.
- Emergence of serious suicidal ideation compared to recent history:
  An increase in the maximum suicidal ideation score to 4 or 5 on the C-SSRS during treatment phase from no suicidal ideation (scores of 0) during the screening and lead-in periods (C-SSRS scales taken at or before baseline excluding "lifetime"). Recent history excludes "lifetime" scores from the Baseline C-SSRS scale or Baseline/Screening C-SSRS scale.
- Improvement in suicidal ideation at endpoint compared to baseline:
  A decrease in suicidal ideation score at endpoint (the last measurement during treatment) from the baseline measurement (the measurement taken just prior to treatment). This analysis should only be performed for a non-lifetime baseline measurement.
- Emergence of suicidal behavior compared to all prior history:
  The occurrence of suicidal behavior (Categories 6-10) during treatment from not having suicidal behavior (Categories 6-10) prior to treatment (including "lifetime"). Prior to treatment includes "lifetime" and/or "screening" scores from the Baseline C-SSRS scale, Screening C-SSRS scale, or Baseline/Screening C-SSRS scale, and any "Since Last Visit" from the Since Last Visit C-SSRS scales taken prior to treatment.

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. 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 one treatment group.

5.5.9.1.3. 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 three sitting blood pressure measurements and three pulse values will be averaged and used as the value for that visit.

Table CGAJ.5.3 displays the criteria used to define treatment-emergent changes in vital signs and weight. The last column of the table displays the patient populations defined by baseline categories, the treatment emergent categorical changes will be analyzed for each of those patient populations. The criteria generally consist of two parts, an absolute threshold and a change from baseline amount. The baseline and postbaseline definitions for vital signs analyses are in Table CGAJ.5.2.

Table CGAJ.5.3. Criteria for Treatment-Emergent Categorical Changes in Vital Signs

Parameter	Direction	Criteria	Patients Population defined by Baseline Categories
Systolic BP (mm Hg) [1] (sitting)	Low	≤90 and decrease ≥20	All patients; >90; ≤90
	High	≥140 and increase ≥20	All patients; <140, ≥140
Diastolic BP (mm Hg) [1] (sitting)	Low	≤50 and decrease ≥10	All patients; >50; ≤50
	High	≥90 and increase ≥10	All patients; <90, ≥90
Pulse (bpm) [1] (sitting)	Low	<50 and decrease ≥15	All patients; ≥50; <50
	High	>100 and increase ≥15	All patients; ≤100; >100
Weight (kg)	Low	(Loss) decrease ≥7%	All patients
	High	(Gain) increase ≥7%	All patients
Temperature (° F)	Low	<96° F and decrease ≥2° F	All patients
	High	≥101° F and increase ≥2° F	All patients

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

5.5.9.1.4. Electrocardiogram Intervals and Heart Rate

Analyses of corrected QT (QTc) interval will be calculated using two correction formulas. The QTcF (msec) will be calculated with Fridericia's formula as $QT/RR^{1/3}$. The Large Clinical Trial Population Based QT Correction (QTcLCTPB) (msec) will be calculated with the formula as $QT/RR^{0.413}$. For the QTc calculations, the unit for QT is milliseconds and the unit for RR is seconds. For patients with QRS ≥120 milliseconds at any time during the study, the QTc interval will be excluded from the analyses. A listing of ECG data for patients with QRS ≥120 milliseconds at any time during the study will be provided.

The 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 CGAJ.5.4 displays the criteria for treatment-emergent changes in ECG intervals, heart rate and QTcLCTPB. For QTcLCTPB, the treatment-emergent low and high criteria are listed by gender and age range, based on Lilly reference ranges.

- 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 one postbaseline result will be included.

The baseline and postbaseline visits are summarized in Table CGAJ.5.2.

Table CGAJ.5.4. Criteria for Treatment-Emergent Changes in ECG Intervals and Heart Rate

Parameter	Direction	Criteria	
Heart Rate (bpm)	Low	<50 and decrease ≥15	
	High	>100 and increase ≥15	
PR Interval (msec)	Low	<120	
	High	≥220	
QRS Interval (msec)	Low	<60	
	High	≥120	
QTcF (msec)	Low	Males: <330	Females: <340
	High	Males: >450	Females: >470
		>500msec	
	Increase	Increase >30 msec	
		Increase >60 msec	
QTcLCTPB (msec)[1]	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	

In addition, descriptive summary of qualitative ECG abnormalities will be conducted which will include summaries of 11 ECG categories (Axis, Rhythm, Conduction, Ischemia, Infarction, Injury, Morphology, U-waves, T-waves, ST Segment, and Other Abnormalities) of qualitative findings at any time postbaseline. A category is a collection of possible descriptions (findings) of one qualitative aspect of an ECG. A category name is the name of the qualitative aspect of the ECG (for example, Rhythm, Conduction, Morphology, Ischemia, and so forth). A finding is one of the possible specific descriptions (for example, Sinus Bradycardia, Acute Septal Infarction) within a category.

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

5.5.9.1.5. Laboratory Tests

The incidence rates of patients with treatment-emergent abnormal, high, or low laboratory values based on Covance reference ranges at any time post-baseline and at LOCF endpoint will be assessed using CMH test s 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 upper limit of normal (ULN) during the treatment period will be summarized for all patients with a post-baseline value.
- The percentages of patients with a total bilirubin (TBL) 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 TBL≥2× ULN, in the absence of significant cholestasis (i.e. AlkP< 2× ULN), and in the absence of other causes of liver injury

The analysis of elevation in ALT, AST and total bilirubin will contain two subsets:

- patients whose nonmissing maximum baseline value is less than or equal to 1× ULN
- patients whose nonmissing maximum baseline value is greater than 1× ULN.

5.5.9.1.6. Immunogenicity

To evaluate the changes in immunogenicity data (Anti-LY2951742 Antibody (hereafter "Anti-Drug Antibody (ADA)," Neutralizing ADA (hereafter "Neutralizing Antibody (NAb)") after

treatment, the following statistical analyses are planned for comparison between treatment groups.

- To compare the proportions of positive results between treatment groups using a CMH test. This analysis will be done at each sample collection time point and for each immunogenicity analyte (ADA and NAb).
- To compare the incidence of treatment-emergent immunogenicity between treatment groups for Study Period III. This analysis will be done for each immunogenicity analyte (ADA and NAb). The baseline and post-baseline definitions for each study period is shown in Table CGAJ.5.2. Treatment-emergent immunogenicity 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 the overall treatment-emergent ADA, treatment-induced ADA, and treatment-boosted ADA will be compared between treatment groups.
- To assess the relationship between immunogenicity and treatment emergent Allergic Reactions/Hypersensitivities as summarized in Section 5.5.9.1.1.1.
  - A tabular summary of the incidence for these treatment emergent Allergic Reactions/Hypersensitivities events will be provided for patients with and without both any immunogenicity (and positive ADA) and treatment-emergent immunogenicity (as defined above).
  - Timing of the treatment emergent Allergic Reactions/Hypersensitivities events relative to the development of ADA (or treatment emergent ADA) will also be summarized.
- To summarize the onset of treatment-induced ADA by treatment groups.

  ADA Onset is defined as the time period between the initial administration of the study drug and the first instance of treatment-induced ADA

5.5.9.2. Continuous Safety Measures

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

When ANCOVA is used to analyze continuous safety measures, 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 LBSEQID) will be used in the model for mean change from last baseline value to LOCF endpoint.

For vital signs only, the mean change from baseline will be analyzed for both Study Period II and Study Period II/III using a repeated measures analysis with a model similar to that used for efficacy analysis described in Section 5.5.10.

5.5.9.3. Time to Event Safety Measures

A Kaplan-Meier curve of the time to development of treatment-emergent ADAs at Study Period II and Study Period II/III will be provided for both LY2951742 groups. Treatment emergent ADA is defined in Section 5.5.9.1.6. Time to development of treatment-emergent ADAs (in days) will be defined as Date of development of treatment-emergent ADAs – Date of randomization + 1. If a patient has not developed treatment-emergent ADAs, they will be censored at the date of the last immunogenicity assessment. If they did not have an immunogenicity assessment, they will be censored at the date of randomization.

5.5.10. Efficacy Analyses

5.5.10.1. Continuous Efficacy Measures

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

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

- Heterogeneous Toeplitz
- Heterogeneous First-order autoregressive
- Toeplitz
- First-order autoregressive

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

All the planned continuous efficacy outcomes for Study Period II and Study Period II/III include the following:

- Mean change from baseline in
  - the number of migraine headache days;
  - the number of headache days;
  - the frequency of medication use for the acute treatment of migraines or headaches;
- Patient's global impression of illness as measured by PGI-I.

5.5.10.2. Binary Efficacy Measures

For categorical (binary) efficacy measures including X% response (X could be 30, 50, 75, and 100), the visitwise 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, and treatment-by-month interaction, as well as the continuous, fixed covariate of baseline value of the measure from which the binary variable is derived.

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 Fishers 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.

The binary secondary efficacy measures such as X% response at LOCF endpoint in the 6-month treatment phase will be calculated for each treatment group. Treatment group differences will be assessed using CMH test.

5.5.11. Health Economics Analyses

The mean change from baseline to each postbaseline visit for Study Period II and Study Period II/III for MSQ (including Role Function-Restrictive, Role Function-Preventive, Emotional Function, and total score), and MIDAS (item scores and total score) as defined in Section 5.4.3.3 will be evaluated using MMRM as described in Section 5.5.10.1. Indicators of MSQ domain responders and MIDAS responders defined in Section 5.4.3 will be analyzed using GLIMMIX as described in Section 5.5.10.2.

Injection specific questionnaire PSMQ-M and SQAAQ will be summarized for Study Period II.

HCRU scores will be analyzed with a repeated measures negative binomial regression anlaysis using PROC GLIMMIX in SAS. The model will include treatment, pooled investigative site, month, and treatment-by-month interaction, the continuous fixed covariates of baseline, baseline-by-month interaction, and an offset term of log(number of calendar days during past 6 visits / 180). In case of non-convergence, pooled investigative site and/or baseline-by-month interaction may be excluded from the model.

Employment status in HCRU will be summaried for both Study Period II and Study Period III. SQAAQ will also be summarized by device (autoinjector vs syringe).

5.6. Interim Analyses

No interim analysis is planned for Study CGAJ before the completion of open-label treatment phase. However, an interim analysis may be conducted in support of regulatory submissions if necessary. Interim data snapshots will be provided as supplemental safety data to support external DMC safety reviews across all Phase 3 migraine prevention studies.

At the completion of treatment phase, safety, tolerability, and effectiveness of LY2951742 will be evaluated. The analyses at the completion of treatment phase will be considered the primary analyses of the study.

Early database lock may occurr to support regulotary submission for cluster headache indication.

5.7. Unblinding Plan

Not applicable. CGAJ is an open-label study.

5.8. Reports to be generated

5.8.1.1. Reports to be Generated for Safety Data Review Before Final Database Lock

For safety data reviews at the timing of interim analyses of CGAG/CGAH/CGAI, the TFLs listed in Table CGAJ.5.5 will be generated. Additional analysis may be requested as deemed necessary.

Table CGAJ.5.5. List of Safety Analyses to be Conducted at Timing of Interim Analyses of CGAG/CGAH/CGAI

Index	Tables	Section Number	Notes
1	Patient disposition	Section 5.5.2	For Study Period II only
2	Patient Characteristics	Section 5.5.4	
3	Exposure to Investigational Product	Section 5.5.5	
5	Concomitant Therapy	Section 5.5.8	For Study Period II only

List of Safety Analyses to be Conducted at Timing of Interim Analyses of CGAG/CGAH/CGAI (Concluded)

Index	Tables	Section Number	Notes
6	Safety AE Analysis • TEAE by SOC and by decreasing frequency • TEAE by Maximum Severity • TEAE of Allergic Reactions/Hypersensitivity by decreasing frequency • TEAE of Injection Site reactions by decreasing frequency within High Level Term • SAE by decreasing frequency • DCAE by decreasing frequency	Section 5.5.9.1.1	For Study Period II only
7	Safety C-SSRS Analysis • Suicidal ideation and Behavior • Treatment emergent Suicidal ideation and Behavior	Section 5.5.9.1.2	For Study Period II only
8	Safety vital signs and Weight Analysis • Change from baseline in Vital signs o MMRM • Change from baseline in Vital Signs and Weight (LOCF) • Categorical analysis of Vital signs and weight	Section 5.5.9.1.3	For Study Period II only
9	Safety ECG and Heart Rate Analysis • Change from baseline in ECG intervals and HR (LOCF) • Categorical analysis of ECGs • Qualitative changes of ECGs	Section 5.5.9.1.4	For Study Period II only
10	Safety Laboratory Analysis • Change from baseline in Laboratory measures (LOCF) • Categorical analysis of Laboratory measures	Section 5.5.9.1.5	For Study Period II only

Abbreviations: AE = adverse event; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; HR = heart rate; LOCF = last observation carried forward; MMRM = mixed model repeated measure; SAE = serious adverse event; SOC = system organ class; TEAE = treatment emergent adverse event.

5.8.1.2. Report to be Generated at end of Treatment Phase and at Final Database Lock

For analysis at the completion of treatment phase, the following analyses including tables, figures and listings will be conducted for all 100% randomized patients who have had a chance to complete 12 months of treatment period:

- Patient disposition as specified in Section 5.5.2 for Study Period II
- Concomitant Therapy as specified in Section 5.5.8 for Study Period II.
- All the safety, efficacy, and health economics analyses for Study Period II.

For final database lock, the following analyses including tables, figures and listings will be conducted for all 100% randomized patients who have had a chance to complete 12 months of treatment and 4 months of post-treatment period:

- Patient disposition as specified in Section 5.5.2 for Study Period III.

- Concomitant Therapy as specified in Section 5.5.8, but for Study Period III only.
- All the safety, efficacy, and health economics analyses, for Study Period III, as well as Study Period II/III.

Analyses at final lock combined with the analysis at the completion of treatment phase will be used in the final CSR.

5.9. Clinical Trial Registry Analyses

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

Analyses provided for the CTR requirements include the following:

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

- An adverse event is considered 'Serious' whether or not it is a treatment emergent adverse event (TEAE).
- An adverse event is considered in the 'Other' category if it is both a TEAE and is not serious. For each Serious AE 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

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

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

Guy W. ECDEU assessment manual for psychopharmacology, revised 1976. Rockville, MD: National Institute of Mental Health, Psychopharmacology Research Branch. p 217-222. Available at: https://archive.org/details/ecdeuassessmentm1933guyw. Accessed September 29, 2014.Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics. 1997;53:983-997.

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

Molenberghs G and Verbeke G. Models for Discrete Longitudinal Data. 2005. Springer Series in Statistics.

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