Statistical Analysis Plan Version 3 I5Q-JE-CGAP

# A Phase 3, Long-Term, Open-Label Safety Study of LY2951742 (Galcanezumab) in Japanese Patients with Migraine

NCT02959190

Approval Date: 16-Jul-2019

# 1. Statistical Analysis Plan for Protocol: I5Q-JE-CGAP A Phase 3, Long-Term, Open-Label Safety Study of LY2951742 (Galcanezumab) in Japanese Patients with Migraine



LY2951742 (Galcanezumab)

Study I5Q-JE-CGAP is a long-term (12 month) Phase 3, multisite, randomized, open-label study of galcanezumab in Japanese patients with migraine. Episodic migraine patients will be rolled over from Study I5Q-JE-CGAN. Chronic migraine patients will be enrolled separately from the extension of Study I5Q-JE-CGAN.


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I5Q-JE-CGAP

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

Approval Date: 16-Jul-2019 GMT

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# 3. Revision History

Followings are major changes (e.g. change of definition, a new analysis specifically for this study) from SAP Version 2 to SAP Version 3. Minor updates (e.g. clarification of definitions, and adding listings, adding examples for clarification) were not listed in general.

- Section 5.4.1: Analysis population for X% responder analysis was clarified.
- Section 5.4.3.1: MSQ responder analysis was modified. For MSQ Role Function-Restrictive domain responder analysis, cutoff value was changed from 25 (for both EM and CM patients) to 17.14 for CM patients (the cutoff for EM patients remains the same as 25) to align global studies I5Q-MC-CGAG (CGAG) and I5Q-MC-CGAI (CGAI).
- Section 5.4.3.4: There was a typo. PSMQ-M was collected at Month 16 (SP IV). Hence, it was added. Descriptive summary for Month 16 was added (Table CGAP. 5.5 and Section 5.5.11.4)
- Section 5.5.1: For efficacy and QoL analysis, analysis arm was changed. Originally (SAP Ver.2) it was statistical models (MMRM, GLIMMIX, logistic regression) with 4 arms (EM120, EM240, CM120, CM240). The updated analysis (SAP Ver. 3) are,
  [1] Statistical models with 2 arms (CM120, CM240)
  [2] Descriptive summary for 6 arms (LY120/LY120, LY240/LY240, PLA/LY120, PLA/LY240, CM120, CM240)
  The reason of this change is as follows; Based on the interim DBL and SAP Ver.2 analysis, we conducted preliminary analysis, i.e., the model based analysis (4 arms). Because the impact of the baseline difference (EM and CM patients) on post baseline estimation was not well captured as expected. In addition. All listings will be by 6 arms instead of 4 arms unless otherwise specified.
  Note: Originally, descriptive summary for 6 arms was planned in SAP Version 1.
- Section 5.5.1: For safety analysis, treatment definition in statistical models are clarified as 4 arms (EM120, EM240, CM120, CM240).
- Section 5.5.1: For listing, 6 arms (LY120/LY120, LY240/LY240, PLA/LY120, PLA/LY240, CM120, CM240) will be used. Originally, it was planned with 4 arms (EM120, EM240, CM120, CM240).
- Section 5.5.1: For descriptive summary, standard error was added, in addition to standard deviation.
- Section 5.5.1.1: Treatment definition as covariate was clarified for efficacy, QoL, and safety.
- Section 5.5.1.1: Covariate for QoL analysis was clarified.
- Section 5.5.1.1: Log-rank test was updated. Stratification factor was deleted. Treatment comparison is CM120 vs CM240 only.
- Section 5.5.1.1: Kaplan-Meier plot was clarified based on 6 arms.
- Section 5.5.1.4, Table CGAP. 5.4:
  - For TEAEs in SP III for EM patients, baseline was corrected from “CGAP Visit 3” to “CGAN Visit 1 to CGAP Visit 3”.

  - For FEAEs in SP IV for EM patients, baseline was corrected from "CGAP Visit 3 to CGAP Visit 16" to "CGAN Visit 1 to CGAP Visit 16".
  - For Treatment emergent immunogenicity in SP III for EM patients, baseline was corrected from "CGAN Visit 3" to
    - EM (LY120/LY120, LY240/LY240): CGAN Visit 3
    - EM (PLA/LY120, PLA/LY240): CGAP Visit 3
  - For Treatment emergent immunogenicity in SP III and IV combined for EM patients, baseline was corrected from "CGAP Visit 3" to
    - EM (LY120/LY120, LY240/LY240): CGAN Visit 3
    - EM (PLA/LY120, PLA/LY240): CGAP Visit 3
- Section 5.5.4: "number of MHD or headache days with acute medication use" was added.
- Section 5.5.10: Efficacy/health outcome related analysis were clarified to align with changes in Section 5.5.1. Table CGAP. 5.5 was updated, as well. Mainly analysis in SP III/IV combined were modified. More specifically, MMRM and GLIMMIX analysis in SP III/IV are replaced by descriptive summary except MHD analysis. Eventually, analysis in SP III were conducted by both MMRM/GLIMMIX (2 arms) and descriptive summary (6 arms) and analysis in SP IV by descriptive summary only (6 arms). Other notable changes in the table were as follows:
  - The title of "PGI-I (adjusted for PGI-S)" analysis was renamed as "PGI-I" because "adjusted for PGI-S" was irrelevant for the descriptive summary.
  - Analysis of "Number of headache days", "PGI-I", "MIDAS individual items", and "30% response rate" in SP III/IV (descriptive summary) were newly added.
  - "PSMQ-M" and "PSMQ-M responder" analysis for SPIII/SPIV was added.
  - Analysis of "Distribution of response rate at Month 12", "PGI-S responder", "MIDAS 50% responder", and "MSQ Role Function-Restrictive responder" in SP III (descriptive summary) were newly added.
  - The title of "MSQ Role Function-Restrictive responder" was renamed to add separate cutoff values for EM and CM as "MSQ Role Function-Restrictive responder (>=25 for EM or 17.14 for CM)".
  - Descriptive Summary of MSQ individual score (Q1 to Q14) was added.
  - The title of "Number of days with acute medication use" was wrong. It was corrected as "Number of MHD or headache days with acute medication use."
- Section 5.5.11: Efficacy/health outcome related analysis were clarified to align with changes in Section 5.5.1.

- Section 5.5.12.1.1: Following TFLs were added for 6 arms display:
  - TEAEs (SP III) by SOC/PT
  - TEAE by considered to be related to investigational product by investigator (SP III)
- Section 5.5.12.1.1.1: Figure of duration of Potential Hypersensitivity Events for each PT (SPIII/IV) was added.
- Section 5.5.12.1.4: For qualitative ECG analysis, baselines for SP IV analysis were corrected:
  - EM patients: from "assessment day <=Visit 12" to "assessment day <=Visit 16"

  - CM patients: from "assessment day <=Visit 12" to "assessment day <=Visit 16"
- Section 5.5.12.1.6: Immunogenicity analysis population was specified as 6 arms.
- Section 5.5.13: Subgroup analysis for self-injection patients was specified as descriptive summary only for efficacy/health outcome. Safety and Demographics TFLs were specified.
- Section 5.8.1: For interim analysis, efficacy/health outcome related analysis were clarified to align with changes in Section 5.5.1. "Change from Baseline in the Number of Days with Acute Medication Use" was deleted because such information was not collected.

# 4. Study Objectives

## 4.1. Primary Objective

Table CGAP. 4.1 shows the primary objective and endpoints of the study. Table CGAP. 4.2 provides definitions for the terms referenced below.

## 4.2. Secondary Objectives

Table CGAP. 4.1 shows the secondary objectives and endpoints of the study. Table CGAP. 4.2 provides definitions for the terms referenced below.

**Table CGAP. 4.1 Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary**<br>To evaluate the long-term safety and tolerability of galcanezumab 120 mg/month or 240 mg/month in patients with migraine for 1 year of treatment. | Analysis of:<br>• treatment-emergent adverse events (TEAEs)<br>• discontinuation rates<br>• vital signs and weight<br>• electrocardiograms (ECGs)<br>• laboratory measures<br>• other safety parameters, including suicidality using the Columbia Suicide Severity Rating Scale (C-SSRS) |
| **Secondary**<br>• To characterize the long-term pharmacokinetics, pharmacodynamics and immunogenicity of galcanezumab<br><br>• To evaluate the long-term effectiveness of galcanezumab in the prevention of migraine | • Assessment of serum concentrations of galcanezumab to enable a pharmacokinetic evaluation<br>• Assessment of plasma concentrations of CGRP to enable a pharmacodynamic evaluation of target engagement of galcanezumab<br>• Assessment of the development and consequences of ADA to galcanezumab in patients exposed to drug<br>• Mean change from baseline (Visit 3) in the number of migraine headache days<br>• Mean change from baseline in the number of headache days<br>• Proportion of patients meeting 50% response criteria (reduction of at least 50% in the number of migraine headache days)<br>• Mean change from baseline in PGI of illness as measured by PGI-S |

| Objectives | Endpoints |
|---|---|
| • To evaluate the long-term effect of galcanezumab on quality of life | • Patient's global impression of improvement as measured by PGI-I<br>• Mean change from baseline in the number of monthly migraine headache days requiring medication for the acute treatment of migraine headache<br>• Mean change from baseline to endpoint in the evaluation of the MIDAS total score and individual items<br>• Mean change from baseline to endpoint in the MSQ (v2.1) total score and individual domains<br>• Descriptive summary at each visit for HCRU and employment status |
| • To evaluate patient satisfaction with medication<br>• To evaluate safety and residual treatment effect during the post-treatment follow-up period | • Satisfaction with medication using the PSMQ-M<br>• Analysis of safety parameters<br>• Time to first loss of response (when patient no longer meets 50% response criteria) during the post-treatment follow-up phase |

Abbreviations: ADA = anti-drug antibodies; CGRP = Calcitonin gene-related peptide; C-SSRS = Columbia Suicide Severity Rating Scale; ECGs = Electrocardiograms; HCRU = Health Care Resource Utilization; MIDAS = Migraine Disability Assessment test; MSQ (v2.1) = Migraine Specific Quality of Life Questionnaire version 2.1; PGI-I = Patient Global Impression of Improvement; PGI-S = Patient Global Impression of Severity; PSMQ-M = Patient Satisfaction with Medication Questionnaire-Modified; TEAEs = treatment-emergent adverse events.

**Table CGAP. 4.2 Migraine and Headache Endpoint Definitions**

| Diagnosis | Definition/Criteria |
|---|---|
| Migraine headache (patients with EM only) | A headache, with or without aura, of ≥30 minutes duration with both of the following required features (A and B):<br>A. At least 2 of the following headache characteristics:<br>• Unilateral location<br>• Pulsatile quality<br>• Moderate or severe pain intensity<br>• Aggravation by or causing avoidance of routine physical activity<br>AND<br>B. During headache at least 1 of the following:<br>• Nausea and/or vomiting<br>• Photophobia and phonophobia<br><br>*(Definition adapted from the IHS ICHD-3 beta)* |
| Probable migraine headache (patients with EM only) | A headache missing 1 of the migraine features in the IHS ICHD-3 beta definition such that 1 feature in criteria A is missing or 1 feature in criteria B is missing; i.e., meet at least 2 A criteria and none of the B criteria, or meet 1 of the A criteria and at least 1 of the B criteria. |
| Migraine headache (patients with CM only) | A headache, with or without aura, of ≥30 minutes duration which meets criteria A and B or meets criterion C:<br>A. At least 2 of the following headache characteristics:<br>• Unilateral location<br>• Pulsatile quality<br>• Moderate or severe pain intensity<br>• Aggravation by or causing avoidance of routine physical activity<br>AND<br>B. During headache at least 1 of the following:<br>• Nausea and/or vomiting<br>• Photophobia and phonophobia<br>OR<br>C. The headache is believed by the patient to be migraine at onset and is relieved by a triptan or ergot derivative<br><br>*(Definition adapted from the IHS ICHD-3 beta)* |

| Diagnosis | Definition/Criteria |
|---|---|
| Probable migraine headache (patients with CM only) | A headache missing 1 of the migraine features in the IHS ICHD-3 beta definition such that 1 feature in criteria A is missing or 1 feature in criteria B is missing; that is, meet at least 2 A criteria and none of the B criteria or meet 1 of the A criteria and at least 1 of the B criteria. It must not meet criterion C. |
| Migraine headache day | A calendar day on which a **migraine headache or probable migraine headache** occurred. |
| Headache day | A calendar day on which any type of headache occurs, (including migraine headache, probable migraine headache, and non-migraine headache). |
| Migraine headache days with abortive (acute) medication use | Calendar days on which migraine or probable migraine occurs requiring abortive (acute) medication. |
| Migraine headache days or headache days with abortive (acute) medication use | Calendar days on which any types of headache occurs requiring abortive (acute) medication. |

Abbreviations: CM = chronic migraine; EM = episodic migraine; ICHD = International Classification of Headache Disorders; IHS = International Headache Society.

# 5. A Priori Statistical Methods

## 5.1. Study Design

Study CGAP is a multisite, randomized, open-label, trial with 4 study periods.

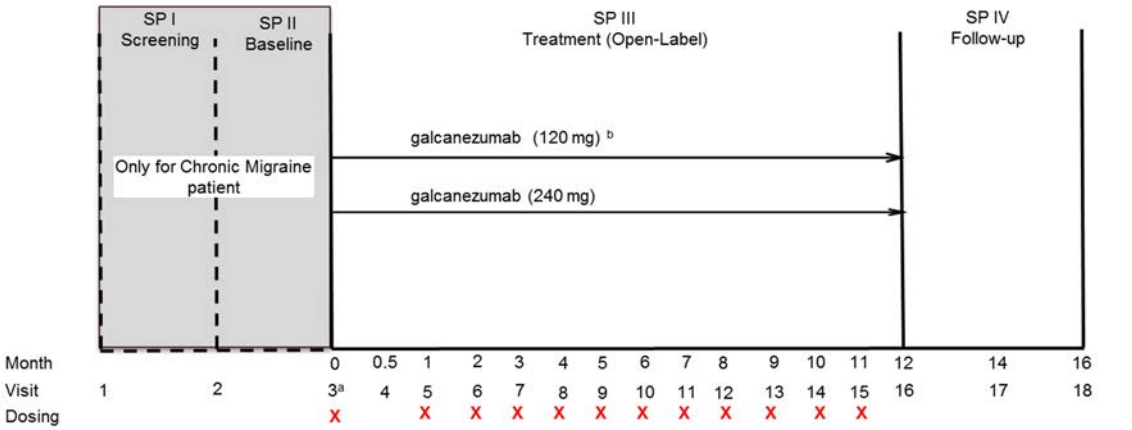
### *5.1.1. EM Patients*

Figure CGAP.5.1 illustrates the study design for EM patients. A major part of this study is a roll over study from parental Study I5Q-JE-CGAN (CGAN) for EM patients who complete Study Period III in Study CGAN, and are willing to continue the study.

The end-of-treatment phase of Study CGAN (Visit 12 of Study CGAN) is equal to the Visit 3 of Study CGAP. The beginning of Study CGAP for EM patients is Visit 3, not Visit 1; Visit 3 is the first injection visit for both EM patients and CM patients in Study CGAP.

All visits except Visit 3 in Study Periods III and IV, patients will use a paper-based headache diary (paper diary) provided by the sponsor, which can take information of the frequency of headaches, migraine headaches, and medication for migraine or headache. Investigators are responsible for data integrity of the paper diary.

At Visit 3, ePRO (electronic Patient-Reported Outcomes) diary will be used as Visit 12 of Study CGAN. It is used to record information of the frequency of headaches, migraine headaches, and medication for migraine or headache.



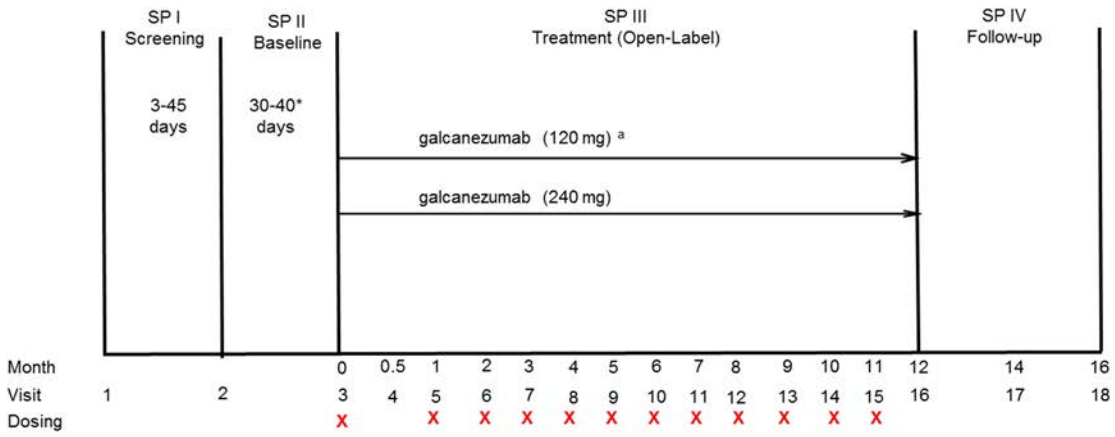

Abbreviation: SP = study period.
[a]Patients who roll over from Study CGAN will start at Visit 3.
[b]Patients assigned to 120 mg arm who are from placebo arm in Study CGAN have 240 mg loading dose at Visit 3 and who are from 120 mg (+ 240 mg loading dose) arm in Study CGAN have no 240 mg loading dose but have one 120 mg dose and one placebo dose at Visit 3.
Note: The Visit 3 injections are under blind condition for all patients. From Visit 5, patients receive either one 120 mg injection (120 mg arm) or two 120 mg injections (240mg arm) without blinding.

**Figure CGAP.5.1. Study I5Q-JE-CGAP protocol design for EM patients.**

### *5.1.2. CM Patients*

Figure CGAP.5.2 illustrates the study design for CM patients.

In Study Periods II, III and IV, patients will use a paper diary provided by the sponsor.




Abbreviation: SP = study period.
*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).

Note: The Visit 3 injections are under blind condition for all patients. From Visit 5, patients receive either one 120 mg injection (120 mg arm) or two 120 mg injections (240mg arm) without blinding

**Figure CGAP.5.2. Study I5Q-JE-CGAP protocol design for CM patients.**

## 5.2. Determination of Sample Size

Approximately 300 patients (approximately 150 patients per arm; approximately 240 patients with EM and approximately 60 patients with CM) will be enrolled for the purposes of regulatory registration, to ensure at least 100 patients per arm with 1 year of exposure. It is assumed that 30% of patients will not complete a 12-month treatment period.

### *5.2.1. EM Patients*

Approximately 240 EM patients will be rolled over from Study CGAN (120 patients for the CGAP 120-mg arm, 120 patients for the CGAP 240-mg arm).

### *5.2.2. CM Patients*

Approximately 60 patients with CM will be enrolled (30 patients for the CGAP 120-mg arm, 30 patients for the CGAP 240-mg arm).

## 5.3. Randomization and Treatment Assignment

### *5.3.1. EM Patients*

There will be 2 treatment arms; galcanezumab 120 mg/month, and galcanezumab 240 mg/month. The patients will be randomized in a 1:1 ratio to receive 120 mg/month of galcanezumab, or 240 mg/month of galcanezumab at Visit 3 of Study CGAN for the patients who roll over from Study CGAN. Patients who were in the galcanezumab treatment arms for Study CGAN continue with the same dose in Study CGAP, while patients who were in the placebo arm in Study CGAN are randomized to 120 mg or 240 mg at Visit 3 of Study CGAN

(randomization ratio = 1:1). If patients who roll over from Study CGAN are confirmed eligible, the patients will begin a 12-month treatment period (Study Period III).

### 5.3.2. CM Patients

Patients meeting all eligibility requirements will be randomized to receive galcanezumab 120 mg/month, or galcanezumab 240 mg/month in a 1:1 ratio.

## 5.4. Endpoints

### 5.4.1. Efficacy Endpoints

Migraine and headache endpoints are defined in Table CGAP. 4.2. Each month is defined as a 30-day period with migraine or headache measures normalized from the visit intervals.

Information recorded in the paper diary, the possible responses and the assignment to the type of headache is presented in Table CGAP. 5.1 (EM patients) and Table CGAP. 5.2 (CM patients). The medication will be recorded and the headache information will be summarized for eCRF as shown below. Note that the exception is EM patients at CGAP Visit 3. It will be based on CGAN Visit 12 information, as stated in CGAP Protocol Section 2, Schedule of Activities, footnote [a]. The paper diary collected following information:

During Study Period III:

- Number of diary days completed by the patient since the last visit?
- How many migraine headache days did the subject experience since the last visit?
- How many headache days did the subject experience since the last visit?
- How many days did the subject take any pain medication for migraine or headache since the last visit?
- How many days did the subject take any pain medication for migraine since the last visit?

During Study Period IV for assessment of first 30 days in the 60-day period since last visit:

- Number of diary days completed by the patient during Days 1-30 of the 60-day period since the last visit?
- How many migraine headache days did the subject experience during Days 1-30 of the 60-day period since the last visit?
- How many headache days did the subject experience during Days 1-30 of the 60-day period since the last visit?
- How many days did the subject take any pain medication for migraine or headache during Days 1-30 of the 60-day period since the last visit?
- How many days did the subject take any pain medication for migraine during Days 1-30 of the 60-day period since the last visit?

During Study Period IV for assessment of second 30 days in the 60-day period since last visit:

- Number of diary days completed by the patient during Days 31-60 of the 60-day period since the last visit?

- How many migraine headache days did the subject experience during Days 31-60 of the 60-day period since the last visit?
- How many headache days did the subject experience during Days 31-60 of the 60-day period since the last visit?
- How many days did the subject take any pain medication for migraine or headache during Days 31-60 of the 60-day period since the last visit?
- How many days did the subject take any pain medication for migraine during Days 31-60 of the 60-day period since the last visit?

**Table CGAP. 5.1 Diary Questions, Responses, and Assignment to Headache Type for Episodic Migraine Patients**

| QUESTION | RESPONSES | HEADACHE ASSIGNMENT |
|---|---|---|
| Q1. Yesterday, did you have a headache that lasted for thirty minutes or more? | Yes | Migraine if at least 2 from migraine Criteria A and at least 1 from migraine Criteria B. |
| | No[a] | |
| Q2. Enter the total number of hours you had a headache yesterday (closest value). | Range 1 to 24 (hours) | If the response ≥1 (or when Q1 = Yes), 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 |
| Yesterday, was the headache throbbing or pounding? | Yes | Migraine Criteria A |
| | No | |
| Yesterday, was the headache just on the right or left side of your head? | Yes | Migraine Criteria A |
| | No | |
| Yesterday, was the headache made worse by your usual daily activity | Yes | Migraine Criteria A |
| | No | |
| Q4. Yesterday, did the headache come with sensitivity to light and sound? | Yes | Migraine Criteria B |
| | No | |
| Q5. Yesterday, did you feel sick to the stomach or throw-up with the headache? | Yes | Migraine Criteria B |
| | No | |
| Q6. Yesterday, did you take any medicine for your headache? | Yes | Medication will only count as headache medication on a day a headache occurred. |
| | No | |

**Table CGAP. 5.2 Diary Questions, Responses, and Assignment to Headache Type for Chronic Migraine Patients**

| QUESTION | RESPONSES | HEADACHE ASSIGNMENT |
|---|---|---|
| Q1. Yesterday, did you have a headache that lasted for thirty minutes or more? | Yes | Migraine if condition [1] or [2] is met<br>[1] at least 2 from Migraine Criteria A and at least 1 from Migraine Criteria B<br>[2] Migraine Criteria C. |
| | No[a] | |
| Q2. Enter the total number of hours you had a headache yesterday. (closest value) | Range 1 to 24 (hours) | If the response ≥1 (or when Q1 = Yes), 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 |
| Yesterday, was the headache throbbing or pounding? | Yes | Migraine Criteria A |
| | No | |
| Yesterday, was the headache just on the right or left side of your head? | Yes | Migraine Criteria A |
| | No | |
| Yesterday, was the headache made worse by your usual daily activity | Yes | Migraine Criteria A |
| | No | |
| Q4. Yesterday, did the headache come with sensitivity to light and sound? | Yes | Migraine Criteria B |
| | No | |
| Q5. Yesterday, did you feel sick to the stomach or throw-up with the headache? | Yes | Migraine Criteria B |
| | No | |
| Q6. Yesterday, did you take any medicine for your headache? | Yes | Medication will only count as headache medication on a day a headache occurred. |
| | No | |
| Q7. Do you believe you experienced a migraine AND it was relieved by a triptan or ergot derivative? | Yes | Migraine Criteria C |
| | No | |

Abbreviation: Q = question.

[a] If "No" is answered for Q1, then the patients will skip the other questions.

### Efficacy Measure: the Number of Monthly Migraine Headache Days

One of the efficacy measures is the number of monthly migraine headache days. A migraine headache day is defined as a calendar day on which a **migraine or probable migraine** occurs.

The number of monthly migraine headache days will be summarized from the daily diary data for each patient in that period (including 30 days of daily data from the baseline period prior to randomization, 12 months of daily data during the treatment phase, and 4 months of daily data during the post-treatment phase).

The daily data will be aggregated, and the number of migraine headache days will be provided for each of the 30-day periods. In calculating the number of migraine headache days for each period, if the period is not equal to 30 days, the number of migraine headache days will be

normalized by multiplying the number of migraine headache days by (30/x) where "x" is the total number of non-missing diary days in the period.

For SP III, Month 1 period data is based on headache information from Visit 3 up to on Visit 5-1 day. Month 2 period data is based on headache information from Visit 5 up to Visit 6 – 1 day. Month 3, to Month 12 will be defined similarly.

For the 4 months of the post-treatment period, the monthly interval will be derived as below. Firstly, the 2-month visit interval (60 days) will be split into two 1-month periods for efficacy measures. Day 1 (the first day of post-treatment period) to Day 30 will be for the first 1-month period and Day 31 to Day 60 for the second 1-month period. Even if diary is recorded longer than 60 days, these will be ignored.

For patients who discontinued early during the post-treatment phase, if the date of discontinuation is within 30 days of previous visit date, all data between the previous visit date and the discontinuation date will go to 1 monthly period; if the date of discontinuation is more than 30 days of the previous visit date, then the first 30 days will be the first monthly period, and the rest will be considered as part of the second monthly period (up to 60 days).

Example 1: A patient has 64 days between Visit 17 and Visit 18. He completes the study on Visit 18. Then he has:

- 1st half month = diary data from Day 1 to Day 30
- 2nd half month = diary data from Day 31 to Day 60

Example 2: A patient has 44 days between Visit 17 and Visit 18. He discontinues the study on Visit 18 (i.e., disposition is not marked as completed). Then he has:

- 1st half month = diary data from Day 1 to Day 30
- 2nd half month = diary data from Day 31 to Day 44

Additionally, if the compliance rate for each monthly interval is ≤50%, then all endpoints to be derived from the diary data for that 1-month period will be considered missing. For the post-treatment phase, the derived 1-month periods (resulting from splitting 2-month visit interval) will be treated similarly.

For a patient who discontinued early in the treatment phase, the compliance rate for the last month of that study period will be calculated with the denominator of the maximum of 30 and the total number of calendar days in that month, i.e., max(30, the total number of calendar days in that month).

For a patient who discontinued early in the post-treatment phase, the compliance rate for the last month of that study period will be calculated with the denominator of 30. (For example, as shown above in Example 1, Visit 17 and Visit 18 can be split into 2 months. Each of them can

have 30 days as maximum duration.) For the rest of months and patients, the compliance rate will be calculated as described in Section 5.5.7.

**The Other Efficacy Measures**

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

- **Number of headache days** is calculated as the number of calendar days in a 30-day period on which a headache occurs.
- **Number of migraine headache days with abortive (acute) medication use** is calculated as the number of calendar days in a 30-day period on which migraine or probable migraine occurs and abortive (acute) medication is used.
- **Number of MHD or headache days with abortive medication use** is calculated as the number of calendar days in a 30-day period on which MHD or headache occurs and an abortive medication is used.
- An **X% responder** is defined as Yes, if any patient who has a ≥X% reduction in the total number of migraine headache days in a 30-day period relative to baseline period, as No if otherwise. Therefore, if the percent change from baseline in the number of migraine headache days is ≥X%, the patient will be counted as an X% responder. In other words, if the response rate defined above in a month is ≥X%, then the patient will be an X% responder in that month. Indicators of X% responders will be derived for X = 0, 5, 10, …, 95, and 100.

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

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

  If the denominator is zero, then such patients will be excluded from the analysis.
- **Time to first loss of 50% response in the post-treatment phase (in months)** is calculated for 50% responders (at Month 12) as the time from the end of treatment phase to the first month in Study Period IV at which these patients no longer meet the 50% response criteria. Patients who continue meeting the criteria until the end of the study will be censored.

## 5.4.2. Other Efficacy Measures

### 5.4.2.1. Patient Global Impression

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

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

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

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

PGI-S responder at each visit is defined as having a severity decrease from baseline of at least 2 points on the 7-point scale at the specific visit.

## 5.4.3. Quality of Life Questionnaires

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

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

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

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

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

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

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

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

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

The total score of all 3 domains will be calculated as the sum of raw scores of 3 domains. If any of the 3 domain scores is missing, then total score will be missing.

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

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

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

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

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

- Emotional Function(range of 3 to 18):

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

- Total Score (range of 14 to 84):

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

The MSQ Role Function-Restrictive domain responder is defined as patients with the change from baseline subscore >=25 for EM patients and >=17.14 for CM patients.

#### 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' lives, including days of work or school missed, days with productivity at work or school reduced to half or more, days with household work missed, days with productivity in household work reduced to half or more, and days missed family/social/ leisure activities. Each question is answered as a numeric number of days during the past 3 months of assessment, ranging from 0 to 90. The answers to all 5 questions will be added up to a total MIDAS score. No imputation is needed when calculating the total score, as patients are not allowed to send partial data.

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

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

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

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

1. Hospital emergency room visits since your last study visit (planned assessment visit) (YES/NO)
    a. If yes, how many times did you go to a hospital emergency room?
    b. How many of these times going to a hospital emergency room were related to your migraine headaches?
2. Overnight stays as a patient in a hospital since your last study visit (planned assessment visit) (YES/NO)
    a. If yes, how many different times were you as a patient in a hospital overnight?
        - How many days total were you in the hospital for overnight stay?
    b. How many of these times, as a patient in a hospital overnight, were related to your migraine headaches?
    c. How many days total, as a patient in a hospital overnight, were related to your migraine headaches?
3. Any other visits with a healthcare professional that occurred since your last study visit (planned assessment visit) (YES/NO)
    a. If yes, how many different times did you visit a healthcare professional?
    b. How many of these times, visiting a healthcare professional, were related to your migraine headaches?

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

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

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

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

There will be no imputation for missing values.

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

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

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

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

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

Positive response for each item are defined as follows:

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

The PSMQ-M will be collected at Month 1, Month 6, Month 12, and Month 16.

### *5.4.4. Safety Endpoints*

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

### *5.4.5. Immunogenicity Endpoints*

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

The definition of baseline is as follows:

EM patients: CGAN Visit 3

CM patients: CGAP Visit 3

### *5.4.6.* CCI


### *5.4.7. Pharmacokinetic Assessment*

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

## 5.5. Statistical Analyses

The SAP Version 1 was approved prior to first patient visit and SAP Version 2 prior to the interim database lock. The SAP Version 3 was created after reviewing preliminary analysis results based on SAP Version 2, using the interim database lock. The SAP supersedes the

statistical plans described in the protocol. PK/PD analysis is out of scope in this Section. Detail of the analysis is specified in Section 5.4.6 and Section 5.4.7.

### 5.5.1. General Considerations

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

Unless specified otherwise, data will be reported by the following treatment groups.

- EM120: EM patients who are randomized to galcanezumab 120 mg in Study CGAP
- EM240: EM patients who are randomized to galcanezumab 240 mg in Study CGAP
- CM120: CM patients who are randomized to galcanezumab 120 mg in Study CGAP
- CM240: CM patients who are randomized to galcanezumab 240 mg in Study CGAP

For some reports, following groups will be used:

- LY120/LY120: Study CGAN 120 mg galcanezumab with a loading dose/Study CGAP 120 mg galcanezumab with placebo injection for a loading dose
- LY240/LY240: Study CGAN 240 mg galcanezumab/Study CGAP 240 mg galcanezumab
- PLA/LY120: Study CGAN placebo/Study CGAP 120 mg galcanezumab with a loading dose
- PLA/LY240: Study CGAN placebo/Study CGAP 240 mg galcanezumab
- EM_ALL: all EM patients from Study CGAN (= EM120 + EM240)
- CM_ALL: all CM patients started from Study CGAP (= CM120 + CM240)
- LY_ALL: all patients (EM_ALL + CM_ALL)

Frequency tables such as AE or TEAEs will be sorted by total (LY_ALL) in decreasing frequency.

When 4 arms (EM120, EM240, CM120, CM240) are displayed and statistical comparisons are made, then it will be based on (EM120 vs EM240, CM120 vs CM240), unless otherwise specified.

When 3 arms (EM_ALL, CM_ALL, LY_ALL) are displayed and statistical comparisons are made, then it will be based on EM_ALL and CM_ALL, unless otherwise specified.

For efficacy and QoL analysis, descriptive statistics will be used. They will be displayed by 6 arms (LY120/LY120, LY240/LY240, PLA/LY120, PLA/LY240, CM120, CM240). There will be no statistical comparison among arms. In the summary of continuous variables, the mean, standard deviation, standard error, minimum, median, and maximum will be reported.

For efficacy and QoL analysis, in addition to the descriptive statistics, when statistical model is used such as MMRM, GLIMMIX, logistic regression, then 2 arms (CM120, CM240) will be used with statistical comparisons between arms.

For safety analysis, when statistical model is used such as MMRM, or ANCOVA, then 4 arms (EM120, EM240, CM120, CM240) will be used without any statistical comparisons between arms.

For listings, they will be displayed by 6 arms (LY120/LY120, LY240/LY240, PLA/LY120, PLA/LY240, CM120, CM240), unless otherwise specified.

All statistical tests will be conducted at a 2-sided alpha level of 0.05, and 95% confidence intervals will be provided, if appropriate. No adjustments for multiplicity will be applied to any safety or effectiveness analyses.

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

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

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

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

For categorical efficacy variables without repeated measures, comparisons between treatment groups will be performed using logistic regressions.

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

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

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

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

For EM patients' analysis, baseline is Study CGAP Visit 3 (Study CGAN Visit 12) assessment, unless otherwise specified with some exception (e.g., immunogenicity analysis). If baseline data is not available at Study CGAP Visit 3 (e.g., height), then baseline assessment of CGAN will be used.

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

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

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

Summary tables will display each arm (EM120, EM240, CM120, CM240). In addition, if the summary is sorted by total (LY_ALL), then the "LY_ALL" will be shown (e.g. summary of TEAE, summary of pre-existing condition).

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

For PGI-I, PGI-S, MSQ, MIDAS, and MHD related analysis with repeated measurement in SP III (continuous and binary outcomes), "overall (month 1-12)" will be shown for treatment comparisons at the final DBL.

#### 5.5.1.1. Adjustments for Covariates

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

Treatment definition used for statistical models is 2 arms (CM120, CM240) for efficacy and QoL analysis and 4 arms (EM120, EM240, CM120, CM240) for safety analysis unless otherwise specified.

An MMRM analysis refers to a restricted maximum likelihood (REML)-based, mixed-effects repeated measures analysis using all the longitudinal (continuous response variable) observations at each post-baseline visit.

Unless otherwise specified (e.g. PGI-I analysis), the MMRM models will include the fixed, categorical effects of treatment (CM120, CM240), month, and treatment-by-month interaction, as well as the continuous, fixed covariates of baseline value and baseline-by-month interaction.

For efficacy and QoL analysis, except for migraine headache days, the baseline number of MHD (continuous) is added as a covariate for the MMRM model specified above.

The GLIMMIX models for the repeated binary outcomes will include the fixed, categorical effects of treatment, month, and treatment-by-month interaction, as well as the continuous, fixed covariate of baseline value. In addition, the baseline number of MHD is added as a continuous covariate.

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

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

- For MSQ Role Function-Restrictive responder (change from baseline >=25 for EM patients or change from baseline >= 17.14 for CM patients) analysis, the baseline number of MHD (continuous) and baseline score of MSQ Role Function-restrictive are added as covariates.

For time to event analysis of 50% response (Time to first loss of 50% response in post-treatment phase), log rank test will be used (CM120 vs CM240). Kaplan-Meier plot is based on 6 arms.

#### 5.5.1.2. Handling of Dropouts or Missing Data

No imputation method will be used for a visit if a certain measure at the visit is determined as missing. For example, if the compliance rate for each monthly interval is ≤50%, then all endpoints to be derived from the diary data for that 1-month period will be considered missing: otherwise, the endpoints at that month (visit) is not missing.

Please refer to Section 5.4.1 for approach to handling missing diary data for derivation of the number of migraine headache days and other efficacy measures.

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

#### 5.5.1.3. Analysis Populations

Analysis populations are defined below:

**All Patients:** All patients who signs informed consent.

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

**Intent-to-Treat (ITT) Population**: All patients who are randomized at Visit 3 and received at least 1 dose of the study drug. Patients in the ITT population will be analyzed according to the treatment 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 IV) as indicated by entering any post-treatment visit. Patients in the post-treatment population will be analyzed according to the treatment that they were randomized to at Visit 3. Post-treatment Population is a subset of ARP.

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

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

**Safety Population**: This is the same as the ITT population except the assigned arm definition. It is determined by modal treatment the patient received during the treatment period (up to the injection visits if they discontinue early). For determining modal treatment, do not consider the loading dose visit for PLA/LY120 and CM120 patients (newly assigned to LY120-mg treatment group), but do consider it for LY120/LY120, LY240/LY240, PLA/LY240, CM240 patients.

(See arm definitions in Section 5.5.4.) If there are 2 or more modes, then add the loading dose visit and recalculate the mode. If there is still a tie, the highest dose of the modes is to be used**.**

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

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

PPS will be used to create summary table of mean change from baseline in the number of migraine headache days for sensitivity analysis purpose (descriptive summary only).

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

Unless otherwise specified, statistical analysis for efficacy will be carried out for 12 months treatment phase (Study Period III), 4 months post-treatment phase (Study Period IV) as well as 12 months treatment and 4 months post-treatment phase combined (Study Period III/IV). Detail analysis plan is in Table CGAP. 5.5. Unless otherwise specified, following analysis population will be used:

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

#### 5.5.1.4. Baseline and Post-Baseline Definition

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

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

| Study Period/Analysis | Patient Population | Baseline Observation | Post-baseline Observation(s) |
|---|---|---|---|
| **Study Period III** | | | |
| Efficacy analyses | ITT Population with a baseline and at least 1 post-baseline observation | Visit 3 | All Visits 3.01–16 |
| Mean change from baseline in the number of migraine headache days | PPS Population with a baseline and at least 1 post-baseline observation | Visit 3 | All Visits 3.01–16 |
| Quality of Life analyses | ITT Population with a baseline and at least 1 post-baseline observation | Visit 3 | All Visits 3.01–16 |
| TEAEs | Safety Population | EM: CGAN Visit 1 – CGAP Visit 3<br><br>CM: All Visits 1–3. Pre-existing condition that is still ongoing at Visit 1 should be evaluated as baseline values. | All Visits 3.01–16 |
| Serious Adverse Events, Discontinuations due to Adverse Events | Safety Population | NA | All Visits 3.01–16 |
| C-SSRS categorical analyses | Safety population with a baseline and at least 1 post-baseline C-SSRS assessment | EM:<br>Recent History: CGAP Visit 3<br><br>All Prior History: All CGAN Visits 1-12 **including** lifetime[a]<br><br>CM:<br>Recent History: All CGAP Visits 1–3 **excluding** lifetime[a] | All Visits 3.01–16 |

| Study Period/Analysis | Patient Population | Baseline Observation | Post-baseline Observation(s) |
|---|---|---|---|
| | | All Prior History: All CGAP Visits 1 – 3 **including** lifetime[a] | |
| C-SSRS categorical analyses for improvement | Safety population with a baseline and at least 1 post-baseline C-SSRS assessment | EM: Visit 3<br><br>CM: Last of CGAP Visit 1-3. | Last of 3.01–16 |
| 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 post-baseline observation | EM: Visit 3<br>CM: All Visits 1–3 | All Visits 3.01–16 |
| Treatment emergent immunogenicity | Safety Population. ADA follow-up cohort (See Section 5.5.12.1.6) | EM (LY120/LY120, LY240/LY240): CGAN Visit 3<br>EM (PLA/LY120, PLA/LY240): CGAP Visit 3<br>CM: Visit 3 | All Visits 3.01–16 |
| Treatment emergent changes in vital signs, weight, and ECGs | Safety Population with a baseline and at least 1 post-baseline observation | EM: Visit 3<br>CM:<br>Low: Minimum value from Visits 1–3<br><br>High: Maximum value from Visits 1–3 | Low:<br>Minimum value from Visits 3.01–16<br><br>High:<br>Maximum value from Visits 3.01–16 |
| Continuous safety analyses | Safety Population with a baseline and at least 1 post-baseline observation | EM: Visit 3<br>CM: Last of Visits 1–3 | Scheduled visits:<br>3< Visits ≤16 |
| **Study Period III and IV combined** | | | |
| Efficacy analyses | ITT Population with a baseline and at least 1 post-baseline observation | Visit 3 | All Visits 3.01-18 |
| Quality of Life analyses | ITT Population with a baseline and at least 1 post-baseline observation | Visit 3 | All Visits 3.01-18 |

| Study Period/Analysis | Patient Population | Baseline Observation | Post-baseline Observation(s) |
|---|---|---|---|
| Continuous safety analyses | Safety Population with a baseline and at least 1 post-baseline observation | EM: Visit 3<br>CM: Last of Visit 1- 3 | All Visits 3.01-18 |
| Treatment emergent immunogenicity | ADA follow-up cohort (See Section 5.5.12.1.6) | EM (LY120/LY120, LY240/LY240): CGAN Visit 3<br>EM (PLA/LY120, PLA/LY240): CGAP Visit 3<br>CM: Visit 3 | All Visits 3.01–18 |
| **Study Period IV** | | | |
| Continuous safety analyses – change from baseline to LOCF endpoint (ANCOVA) | Post-treatment Population with a baseline and at least one post-baseline observation | EM: Last of Visits 3-16<br>CM: Last of Visits 1-16 | Last Visit: 16.01-18 |
| FEAEs | Post-treatment Population | EM: All Visits in CGAN Visit 1 - 16.<br><br>CM: All Visits 1- 16. Pre-existing condition that is still ongoing at Visit 1 should be evaluated as baseline values. | All Visits 16.01–18 |
| Serious Adverse Events, Discontinuations due to Adverse Events | Post-treatment Population | NA | All Visits 16.01–18 |
| Follow-up emergent abnormal laboratory values | Post-treatment Population with normal laboratory values at all nonmissing baseline visits (with respect to direction being analyzed) and who have at least 1 post-baseline observation | EM:<br>All Visits 3- 16<br><br>CM:<br>All Visits 1- 16 | All Visits 16.01–18 |
| Follow-up emergent changes in vital signs, weight and ECGs | Post-treatment Population with a baseline and at least 1 post-baseline observation | EM:<br>Low: Minimum value from Visits 3–16<br><br>High: Maximum value | Low: Minimum value from Visits 16.01–18<br><br>High: Maximum value from Visits 16.01–18 |

| Study Period/Analysis | Patient Population | Baseline Observation | Post-baseline Observation(s) |
|---|---|---|---|
| | | from Visits 3–16<br><br>CM:<br>Low: Minimum value from Visits 1–16<br><br>High: Maximum value from Visits 1–16 | |
| C-SSRS categorical analyses | Post-treatment Population with a baseline and at least 1 post-baseline C-SSRS assessment | EM:<br>Recent History: CGAP Visit 3-16<br><br>All Prior History: All CGAN Visits 1-12 **including** lifetime[a] and All CGAP Visits 3.01-16<br><br>CM:<br>Recent History: All CGAP Visits 1–16 **excluding** lifetime[a]<br><br>All Prior History: All CGAP Visits 1-16 **including** lifetime[a] | All Visits 16.01–18 |
| C-SSRS categorical analyses for improvement | Post-treatment Population with a baseline and at least 1 post-baseline C-SSRS assessment | EM:<br>Last of CGAP Visits 3.01-16<br>CM:<br>Last of CGAP Visits 3.01-16 | Last of 16.01–18 |

Abbreviations: ADA = Anti-Drug Antibody; CM = chronic migraine; C-SSRS = Columbia Suicide Severity Rating Scale; EM = episodic migraine; FEAE = follow-up emergent adverse event; ITT = intent-to-treat; PPS = per protocol set; TEAE = treatment emergent adverse event.

Note: Visit 3.01 indicates the first unscheduled visit occurring after Visit 3 and prior to Visit 4. Other visits can be interpreted in a similar manner. For example, Visit 12.01 indicates the first unscheduled visit occurring after Visit 12 and prior to Visit 13. For efficacy and quality of life measures without unscheduled visits data point, Visit 3.01 indicates scheduled collection visits after visit 3.

[a] Lifetime is captured in the C-SSRS visit 1 CRF (EM: CGAN visit 1, CM: CGAP visit 1).

### *5.5.2. Patient Disposition*

For disposition summary, treatment group is based on (EM120, EM240, CM120, CM240, LY_ALL)

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

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

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

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

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

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

### *5.5.3. Important Protocol Deviations*

For protocol deviation summary, treatment group is based on (EM120, EM240, CM120, CM240, LY_ALL)

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

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

Summary of important protocol deviations will be made for

- Baseline and SP III
- SP IV

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

- Baseline and SP III
- SP IV

It is based on 4 arms (EM120, EM240, CM120, CM240).

### *5.5.4. Patient Characteristics*

For baseline patient characteristics summary, treatment groups are based on

[Group 1] EM120, EM240, CM120, CM240

[Group 2] LY120/LY120, LY240/LY240, PLA/LY120, PLA/LY240

[Group 3] EM_ALL, CM_ALL, LY_ALL

Hence, each summary will be created for these three groups.

If statistical comparisons are conducted, then following arm will be compared:

Group1: EM120 vs EM240, CM120 vs CM240.

Gropu2: None.

Group3: EM_ALL vs CM_ALL

Note that source of patient characteristics at baseline for EM patients are defined in the CGAP Protocol Section 2, Schedule of Activities, unless otherwise specified. For example, height is from CGAN Visit 3, and age is from CGAP Visit 3.

The following patient characteristics at baseline will be summarized

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

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

- Baseline MHD category per 30 day (<8, >=8) (EM: CGAN Month 6. CM: Visit 2 to Visit 3)
- Years since migraine diagnosis (EM: CGAP Visti3. CM: Visit 3)
- Migraine and headache related measures (EM: CGAN Month 6. CM: Visit 2 to Visit 3).
  - number of migraine headache days
  - number of migraine headache days with abortive (acute) medication use
  - number of migraine headache days or headache days with abortive (acute) medication use
  - number of headache days
- PGI-S (EM: CGAN Month 6. CM: Visit 3)
- MIDAS (total, each question) (EM: CGAN Month 6. CM: Visit 3)
- MSQ (total, 3 subscores) (EM: CGAN Month 6. CM: Visit 3)
- Previous migraine prevention treatment (Yes, No, Yes and did not fail, Yes and fail >=1, Yes and fail >=2) (EM: CGAN Visit 1, CM: Visit 1)
- Number of previous migraine prevention treatment fail (EM: CGAN Visit 1, CM: Visit 1)
- Past usage (yes/no) or current usage (yes/no) of followings: Alcohol, caffeine, nicotine replacement therapy, and tobacco and nicotine combined. (EM: CGAN Visit 1, CM: Visit 1)

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

- Medical history except primary medical conditions (at ICF). Medical history is defined as illness (es) that ended prior to the signing of informed consent (EM: CGAP Visit 3, CM: Visit 1). It will be summarized by preferred term (PT).

- Pre-existing condition (at ICF). Pre-existing conditions are those AEs existing at the study entry. It will be summarized by preferred term (PT) (EM: CGAP Visit 3, CM: Visit 1)

- Number of Comorbid conditions other than migraine. Comorbid conditions other than migraine are those AEs existing before Visit 3 and continuing after Visit 3 other than migraine. (i.e., not contained "migraine" as PT). If it ends on Visit 3, then it is not a comorbid condition. The count is based on PT. (2 events with different LLT but the same PT will be counted as one comorbid condition.) (EM: CGAP Visit 3, CM: Visit 3)

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

Listing of Subjects Demographic will be created.

### *5.5.5. Exposure to Investigational Product*

For exposure summary, treatment group is based on (EM120, EM240, CM120, CM240)

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

- Beginning of Month 1 (Visit 3)
- Beginning of Month 2 (Visit 5)
- Beginning of Month 3 (Visit 6)
- Beginning of Month 4 (Visit 7)
- Beginning of Month 5 (Visit 8)
- Beginning of Month 6 (Visit 9)
- Beginning of Month 7 (Visit 10)
- Beginning of Month 8 (Visit 11)
- Beginning of Month 9 (Visit 12)
- Beginning of Month 10 (Visit 13)
- Beginning of Month 11 (Visit 14)
- Beginning of Month 12 (Visit 15)

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

- For treatment phase (Study Period III), duration of exposure in days is calculated as: treatment phase last visit date – first date IMP administered + 1.
- For treatment phase (Study Period III), number and percentage of patients with 1, 2, continuing up to 12 doses injected.

Comparisons between treatments for duration of IMP exposure will be performed using an ANOVA with treatment in the model.

Number of patients with 1 dose, 2, 3, …, 12 doses injected will be compared between treatment groups with the Fisher's exact test.

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

Listing of treatment exposure with Randomization Scheme and Codes will be created.

### *5.5.6. Treatment Compliance*

For treatment compliance summary, treatment group is based on (EM120, EM240, CM120, CM240)

Treatment compliance will be calculated for Study Period III as:

$$\frac{\text{number of completed scheduled dosing visits in which the patient received planned injections} * 100}{\text{number of completed scheduled dosing visits, including any skipped dosing visits before the last dosing visit (Visit 15, inclusive) or early discontinuation visit (exclusive)}}$$

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

### *5.5.7. Patient Reported Outcomes Diary Compliance*

For diary compliance summary, treatment group is based on (EM120, EM240, CM120, CM240)

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

- SP III: baseline, Month 1,…, Month 12, overall (Month 1 through Month 12) for ITT population
- SP IV: Month 13,…, Month 16, overall (Month 13 through Month 16) for post treatment population

Diary compliance at each 1-month period (including baseline, Month 1, 2, 3, up to Month 16) as well as for Study Period III overall (Month 1 through Month 12) will be calculated. Diary compliance at each period is calculated as:

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

"Expected number of diary days in the period" is based on actual visit date for that particular period (Month)

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

For each patient, overall diary compliance for SP III is average of monthly compliance in SP III (Month 1,…, Month 12). If he discontinues early, then ignore the rest of the month. In this case, the last month compliance is based on max (30, the total number of calendar days in that month) (See Section 5.4.1).

Expected number of Diary days for Month 13, Month 14, Month 15, and Month 16 in SP IV is 30 days. Note that 2-month visit interval (e.g. Month 13 and Month 14) will be split into two one-month interval as defined in Section 5.4.1. The section explains how to handle early discontinuation case.

For each patient, overall diary compliance for SP IV is average of monthly compliance in SP IV (Month 13,…, Month 16). If he discontinues early, then ignore the rest of the month. In this case, the last month compliance is based on 30 days as the denominator (See Section 5.4.1)

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

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

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

### *5.5.8. Previous Migraine Prevention Therapy and Previous Migraine Acute Treatment*

For previous migraine prevention therapy summary, treatment group is based on (EM120, EM240, CM120, CM240)

The proportion of patients who received previous migraine prevention therapy, and the proportion of patients with response to the previous migraine prevention therapy within each of

the 6 categories (to enter this trial, medical history event, adequate response, inadequate response, no response, and treatment availability) will be summarized for ITT patients. (Those reasons are captured at EM: CGAN Visit 1, CM: CGAP Visit 1). Treatment group comparisons will be done using the Fisher's exact test.

Previous migraine prevention therapies are migraine prevention therapies that started prior to the date of the first injection and stopped prior to or at the date of first injection (CGAN Visit 3 for EM patients, CGAP Visit 3 for CM patients) which has indication recorded in the CRF (prior therapy migraine medication, or concomitant medication) as one of the followings:
[1] "Primary study condition" (except acute treatment)
[2] Corresponding medical history event (preferred term) that includes "migraine" (except acute treatment)
[3] Corresponding adverse event (preferred term) that includes "migraine" (except acute treatment)

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

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

Previous migraine acute treatment during baseline (EM: CGAN Month 6, CM: SP II) will be summarized by following categories (can be multiple classes):

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

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

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

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

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

For concomitant therapy summary, treatment group is based on (EM120, EM240, CM120, CM240)

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

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

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

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

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

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

As mentioned in the previous section, the definition/categorization of the migraine prevention therapy and migraine acute treatments will be reviewed by medical before unblinding.

### *5.5.10. Efficacy Analyses*

Table CGAP. 5.5 summarize the planned analysis for SP III, SP III and SP IV combined, and SP IV for efficacy analysis. All response rates are derived from migraine headache days unless otherwise specified. There will be no multiplicity adjustment for statistical test.

For summary of EM and CM patients, descriptive summary based on 6 arms (LY120/LY120, LY240/LY240, PLA/LY120, PLA/LY240, CM120, CM240) will be shown (SPIII and SPVI combined).

In addition, for CM patients, the statistical models such as MMRM or GLIMMIX will be used for some analysis with the treatment arm (CM120, CM240). In particular, only "number of MHD" analysis will be conducted by a statistical model (MMRM) as SP III and SP IV combined analysis. The other "analysis in SP III and SP IV combined" are by descriptive analysis.

Kaplan-Meier plot is based on 6 arms. The associated log-rank test is based on (CM120, CM240) only.

If analysis results would be considered less informative, then such results may not be provided in CSR.

**Table CGAP. 5.5 Efficacy variables and Analysis Methods**

| Efficacy Variables | Analysis in SP III | Analysis in SP III/IV | Analysis in SP IV only |
|---|---|---|---|
| Number of MHD | MMRM | MMRM/ D | NA |
| Number of MHD with acute medication use | MMRM | D | NA |
| Number of MHD or headache days with acute medication use | MMRM | D | NA |
| Number of headache days | MMRM | D | NA |
| PGI-S | MMRM | D | NA |

| | | | |
|---|---|---|---|
| PGI-I | MMRM | D | NA |
| MSQ Total | MMRM | D | NA |
| MSQ Role Function-Restrictive domain | MMRM | D | NA |
| MSQ Role Function-Preventive domain | MMRM | D | NA |
| MSQ Emotional Function domain | MMRM | D | NA |
| MSQ each question summary | NA | D | NA |
| MIDAS Total (sum of item 1, 2, 3, 4, and 5) | MMRM | D | NA |
| MIDAS individual items (item 1, 2, 3, 4, 5, A, and B) | MMRM | D | NA |
| HCRU Summary | NA | D | NA |
| HCRU Migraine related events/100-patients-year | NA | D | NA |
| HCRU Employment status | NA | D | NA |
| PSMQ-M | NA | D | NA |
| PSMQ-M responder | NA | D | NA |
| X% response rate (X=50, 75, or 100) | GLIMMIX | D | NA |
| 30% response rate | GLIMMIX | D | NA |
| Distribution of response rate (Month 12) | GLIMMIX/ D | NA | NA |

| | | | |
|---|---|---|---|
| Time from the end of SP III to no longer meeting 50% response criterion | NA | NA | KM/log-rank test |
| PGI-S responder (2>= improvement) | GLIMMIX/ D | NA | NA |
| MIDAS 50% responder | GLIMMIX/ D | NA | NA |
| MSQ Role Function-Restrictive responder (>=25 for EM or 17.14 for CM) | Logistic regression/ D | NA | NA |

Abbreviation D: Descriptive summary based on 6 arms (LY120/LY120, LY240/LY240, PLA/LY120, PLA/LY240, CM120, CM240); GLIMMIX= generalized linear mixed model: KM= Kaplan-Meier plots; MIDAS = Migraine Disability Assessment test; MMRM = mixed-effects repeated measures analysis; MSQ (v2.1) = Migraine Specific Quality of Life Questionnaire version 2.1; PGI-I = Patient Global Impression of Improvement; PGI-S = Patient Global Impression of Severity;

Note 1: For MMRM, GLIMMIX, log-rank test, and logistic regression, analysis are based on 2 arms (CM120, CM240).

Note 2: Kaplan-Meier plots are based on 6 arms.

**Continuous Efficacy Measures**

For the continuous efficacy measures, the change from baseline to each post-baseline period will be estimated for each treatment from repeated measures analyses as described below, using PROC MIXED. When the objective is to assess overall mean change during the treatment phase, the endpoint will be estimated as the main effect of treatment from the MMRM analysis across Months 1-12 using Month 1 up to Month 12 data.

An MMRM analysis refers to a restricted maximum likelihood (REML)-based, mixed-effects repeated measures analysis using all the longitudinal observations at each post-baseline monthly visit. The MMRM models will include the fixed, categorical effects of treatment (CM120, CM240), month, and treatment-by-month interaction, as well as the continuous, fixed covariates of baseline value and baseline-by-month interaction.

An unstructured covariance structure will be used to model the within-patient errors. The Kenward-Roger (Kenward and Roger 1997) approximation will be used to estimate denominator degrees of freedom. If the model does not converge, the Fisher scoring algorithm will be implemented by specifying the SCORING option (SCORING=5) in SAS. If the model still fails

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

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

Hence we fit the model by the following order:

[1] unstructured covariance with the default fitting,

[2] unstructured covariate with the Fisher scoring,

[3] toeph covariance with the default fitting,

[4] toeph covariance with the Fisher scoring

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

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

[7] toep covariance with the default fitting,

[8] toep covariance with the Fisher scoring

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

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

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

The analysis "Mean change from baseline (Visit 3) in the number of migraine headache days" result will be plotted by treatment arm (horizontal-axis= month, vertical-axis = change from baseline).

**Binary Efficacy Measures**

For the repeated binary efficacy measures such as responder indicators based on the number of migraine headache days, the visitwise binary responder indicators will be analyzed using a

categorical, pseudo-likelihood-based repeated measures analysis. This analysis will be implemented using the GLIMMIX procedure in SAS to compare treatments and include the fixed, categorical effects of treatment (CM120, CM240), month, and treatment-by-month interaction, as well as the continuous, fixed covariate of baseline value.

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

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

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

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

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

For the repeated binary secondary efficacy measures where the objective is to assess the proportion of patients with X% response during the first 6-month (or 12-month) treatment phase, the endpoint for comparing treatment arms will be estimated as the main effect of treatment from the categorical MMRM analysis across Months 1-12 using Month 1 up to Month 12 data.

**Time to Event Measures**

For the following time to event measures, a Kaplan-Meier curve of the time to event will be provided.

- Time to first loss of 50% response in post-treatment phase (SP III completer only)

It is calculated for patients who are Month 12 50% responders to the first month in Study Period IV at which these patients no longer meet the 50% response criteria. Patients who continue meeting the criteria until the end of the study will be censored.

**Distribution of Response Rates**
Overall x% response rate during the treatment phase will be estimated for X=0, 5, 10,…, 95, and 100, using descriptive summary and GLIMMIX model as described earlier in this section. These estimated response rates will be plotted and points within each treatment arm will be connected to show a curve of response rates. No statistical comparisons will be conducted among different treatment arms.

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

PGI-S responder analysis will be conducted.

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

## *5.5.11. Quality-of-Life (QoL) Analyses*

For QoL summary, the analysis arm and methods are the same as the one used in the efficacy analysis.

For both EM and CM patients, descriptive summary based on 6 arms (LY120/LY120, LY240/LY240, PLA/LY120, PLA/LY240, CM120, CM240) will be shown.

In addition, for CM patients, the statistical models such as MMRM, GLIMMIX, and logistic regression will be used for some analysis with the treatment arm (CM120, CM240).

The analysis method and periods are specified in Table CGAP. 5.5. MMRM, GLIMMIX, and logistic regression models are specified in Section 5.5.1.1 and Section 5.5.10.

### 5.5.11.1. MSQ

The mean change from baseline to each post-baseline visit for Study Period III for MSQ total score and domain (overall Month 1-12) will be analyzed by the MMRM model. The descriptive summary will be created (SP III/IV).

MSQ Role Function-Restrictive domain responders in SP III (month 12) will be analyzed by logistic regression. The descriptive summary will be created (SP III) (month 12).

Descriptive Summary of MSQ individual score (Q1 to Q14) will be created.

#### 5.5.11.2. MIDAS

For SP III, the mean change from baseline to each post-baseline visit (month 3, 6, 9, 12) and overall will be analyzed by the MMRM model. (response variables are total score, each item 1, 2, 3, 4, 5, A, and B). The descriptive summary will be created (SP III/IV).

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

#### 5.5.11.3. HCRU

For HCRU, descriptive summary of Question 1-3 will be created. Analysis period is SP I/II/III/IV combined. It includes baseline (EM: CGAP Visit 3 data. CM: over the last 6 months period from Visit 3 data), SP III (12 months period), and SP IV (4 months period) with ITT population. In particular, for each period, the summary of following will be created:

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

Summary of HCRU related to migraine will be created (SP III/IV). The unit is per 100 patient years. 100 patient year is defined as

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

Descriptive summary of working status (Question 4) will be created for each month: Analysis period is SP III/IV combined. It includes month 0 to month 12, month 14, and month 16 with ITT population.

#### 5.5.11.4. PSMQ-M

Summary of each item, as well as positive response defined in Section 5.4.3.4 will be created using descriptive statistics for each month (month 1, 6, 12, 16) in SP III/IV.

### *5.5.12. Safety Analyses*

The safety analyses will be conducted for Study Period III, Study Period IV, as well as Study Periods III and IV combined. Treatment group is based on 4 arms (EM120, EM240, CM120, CM240), unless otherwise specified. AE related tables will be sorted by LY_ALL. In such cases, LY_ALL will be displayed in the table.

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

- Adverse events
  - hypersensitivity events
  - injection sites
  - upper respiratory tract infections
- Suicide-related thoughts and behaviors
- Vital signs and weight
- Laboratory measurements
- ECGs
- Antibodies (ADA and NAb)

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

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

#### 5.5.12.1. Categorical Safety Variables

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

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

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

#### *5.5.12.1.1. Adverse Events*

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

Follow-up emergent adverse events (post-treatment emergent adverse events) are defined similarly. They are events that first occurred or worsened during the follow-up period (Study Period IV) when compared to the baseline (SP I, SP II, and SP III). Pre-existing condition that is still ongoing at Visit 1 for CM patients should be evaluated as baseline values. (See detail definitions in Table CGAP. 5.4)

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

Following summary will be created:

- Overview of AE (SP III)
- TEAEs (SP III)
  - By PT by decreasing frequency
  - By SOC/PT
  - By maximum severity/PT
- FEAEs (SP IV)
  - By PT by decreasing frequency
  - By SOC/PT
  - By maximum severity/PT
- TEAEs by considered to be related to investigational product by investigator (SP III)
- Treatment Emergent Adverse Events that started on Treatment phase and Continuing in Post-Treatment Phase (SP III, SP IV combined)
- SAEs (SP III, SP IV separately)
- AEs leading to discontinuation (SP III, SP IV separately)

Following tables are created by 6 arms (with LY_ALL) without statistical tests:

- TEAEs (SP III) by SOC/PT
- TEAE by considered to be related to investigational product by investigator (SP III)

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

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

#### 5.5.12.1.1.1. Potential Hypersensitivity events

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

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

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

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

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

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

- During drug administration

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

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

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

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

Figure of duration of Potential Hypersensitivity Events for each PT (SP III/IV) will be created.

#### 5.5.12.1.1.2. Adverse Events Related to Injection Site

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

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

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

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

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

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

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

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

Figure of duration of Injection Site related Adverse Events for each PT (SP III/IV) will be created.

#### 5.5.12.1.1.3. Upper Respiratory Tract Infections

Upper respiratory tract infections will be defined using all the PTs from the 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 (SP III and SP IV separately) and resulting in study drug discontinuation (SP III) will be summarized by treatment group using MedDRA PTs. Events will be ordered by decreasing frequency.

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

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

### *5.5.12.1.2. Suicide-Related Thoughts and Behaviors*

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

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

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

The number and percent of patients who experienced at least 1 of various comparative measures during treatment will be presented and compared for Study Period III and summarized for Study Period IV. Comparative measures include followings:

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

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

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

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

Composite endpoints based on the above categories are defined below.

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

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

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

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

- Treatment emergent suicidal ideation compared to recent history:
  An increase in the maximum suicidal ideation score during treatment (Visits 3.01 to 16 for Study Period III; Visits 16.01 to 18 for Study Period IV) from the maximum suicidal ideation category during the screening and lead-in periods (EM patients: C-SSRS scales taken at CGAP Visit 3 for Study Period III; CM patients: C-SSRS scales taken at CGAP Visits 1 to 3 excluding "lifetime" for Study Period III; EM patients: C-SSRS scales taken at CGAP Visits 3 to 16 for Study Period IV, CM patients: C-SSRS scales taken at Visits 1 to 16 excluding "lifetime" for Study Period IV). Recent history excludes "lifetime" scores from the Baseline C-SSRS scale or Baseline/Screening C-SSRS scale.
- Treatment emergent suicidal ideation compared to all prior history:
- The same definition above except the baseline includes "lifetime" scores. See Table CGAP. 5.4 for more detail.

- Treatment emergent serious suicidal ideation compared to recent history:
  An increase in the maximum suicidal ideation score to 4 or 5 on the C-SSRS during treatment (Visits 3.01 to 16 for Study Period III; Visits 16.01 to 18 for Study Period IV) from not having serious suicidal ideation (scores of 0-3) during the screening and lead-in periods (EM patients: C-SSRS scales taken at CGAP Visit 3 for Study Period III, CM patients: C-SSRS scales taken at CGAP Visits 1 to 3 excluding "lifetime" for Study Period III; EM patients: C-SSRS scales taken at CGAP Visits 3 to 16 for Study Period IV, CM patients: C-SSRS scales taken at Visits 1 to 16 excluding "lifetime" for Study Period IV). Recent history excludes "lifetime" scores from the Baseline C-SSRS scale or Baseline/Screening C-SSRS scale.

- Treatment emergent serious suicidal ideation compared to all prior history:
- The same definition above except the baseline includes "lifetime" scores. See Table CGAP. 5.4 for more detail.

- Emergence of serious suicidal ideation compared to recent history:
  An increase in the maximum suicidal ideation score to 4 or 5 on the C-SSRS during treatment (Visits 3.01 to 16 for Study Period III; Visits 16.01 to 18 for Study Period IV) from no suicidal ideation (scores of 0) during the screening and lead-in periods (EM patients: C-SSRS scales taken at CGAP Visit 3 for Study Period III, CM patients: C-SSRS scales taken at CGAP Visits 1 to 3 excluding "lifetime" for Study Period III; EM patients: C-SSRS scales taken at CGAP Visits 3 to 16 for Study Period IV, CM patients: C-SSRS scales taken at Visits 1 to 16 excluding "lifetime" for Study Period IV). Recent history excludes "lifetime" scores from the Baseline C-SSRS scale or Baseline/Screening C-SSRS scale.
- Improvement in suicidal ideation at endpoint compared to baseline:
  A decrease in suicidal ideation score at endpoint (the last measurement during treatment; Visits 3.01 to 16 for Study Period III; the last measurement during open-label phase Visits 16.01 to 18 for Study Period IV) from the baseline measurement (EM patients: CGAP Visit 3 for Study Period III, CM patients: the last non missing measure during CGAP Visit 1 to 3 for Study Period III; Both EM and CM patients: the last non-missing measure during Visits 3.01 to 16 for Study Period IV).
- Emergence of suicidal behavior compared to all prior history:
  The occurrence of suicidal behavior (Categories 6-10) during treatment (Visits 3.01-16 for Study Period III; Visits 16.01 to 18 for Study Period IV) from not having suicidal behavior (Categories 6-10) prior to treatment (EM patients: All CGAN Visits 1-12 including "lifetime" for Study Period III, all CGAN Visits 1-12 including "lifetime" and All CGAP Visits 3.01-16 for Study Period IV. CM patients: All CGAP Visits 1-3 including "lifetime" for Study Period III, All CGAP Visits 1 to 16 including "lifetime" for Study Period IV).

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

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

#### *5.5.12.1.3. Vital Signs and Weight*

Vital signs collected during the study include systolic and diastolic blood pressure, pulse, and temperature. Blood pressure and pulse will be measured in triplicate, in the sitting position, and

should be measured prior to blood draws. The 3 sitting blood pressure measurements and 3 pulse values will be averaged and used as the value for that visit. If the measurements are less than three, the averaged values on the available data will be used.

The number and percent of patients meeting criteria for treatment-emergent abnormalities in vital signs and weight at any time during study will be summarized (SP III and SP IV separately). Treatment group comparisons will be performed using the Fisher's exact test for SP III. Table CGAP. 5.6 displays the criteria used to define treatment emergent changes in vital signs and weight. The last column of the table displays the patient populations defined by baseline categories, the treatment emergent categorical changes will be analyzed for each of those patient populations for SP III. The criteria generally consist of 2 parts, an absolute threshold and a change from baseline amount. The baseline and post-baseline definitions for vital signs analyses are in Table CGAP. 5.4.

**Table CGAP. 5.6 Criteria for Treatment-Emergent Categorical Changes in Vital Signs**

| Parameter | Direction | Criteria | Patients Population defined by Baseline Categories |
|---|---|---|---|
| Systolic BP (mm Hg) (sitting) | Low | ≤90 and decrease ≥20 | All patients; >90; ≤90 |
| | High | ≥140 and increase ≥20 | All patients; <140, ≥140 |
| | PCS High | ≥180 and increase ≥20 | All Patients; <180, ≥180 |
| | Sustained Elevation | ≥140 and increase ≥20 at 2 consecutive visits | All patients; <140; ≥140 |
| Diastolic BP (mm Hg) (sitting) | Low | ≤50 and decrease ≥10 | All patients; >50; ≤50 |
| | High | ≥90 and increase ≥10 | All patients; <90, ≥90 |
| | PCS High | ≥105 and increase ≥15 | All Patients; <105, ≥105 |
| | Sustained Elevation | ≥90 and increase ≥10 at 2 consecutive visits | All patients; <90; ≥90 |
| Systolic BP or Diastolic BP (mm Hg) (sitting) | Sustained Elevation | Meeting criteria for systolic BP for 2 consecutive visits or meeting criteria for diastolic BP for 2 consecutive visits or both | All Patients |
| Pulse (bpm) (sitting) | Low | <50 and decrease ≥15 | All patients; ≥50; <50 |
| | High | >100 and increase ≥15 | All patients; ≤100; >100 |
| | Sustained Elevation | >100 and increase ≥15 at 2 consecutive visits | All patients; ≤100; >100 |
| Weight (kg) | Low | (Loss) decrease ≥7% | All patients |
| | High | (Gain) increase ≥7% | All patients |
| Temperature (° C) | Low | <35.6° C and decrease ≥1.1° C | All patients; ≥35.6° C |
| | High | ≥38.3° C and increase ≥1.1° C | All patients; <38.3° C |

Abbreviations: BP = blood pressure; bpm = beats per minute; F = degrees Celsius; 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 $QT/RR^{⅓}$. The Large Clinical Trial Population Based QT Correction (QTcLCTPB) (msec) will be calculated with the formula as $QT/RR^{0.413}$. For the QTc calculations, the unit for QT is milliseconds and the unit for RR is seconds. For patients with QRS ≥120 milliseconds at any time during the study (including baseline and SP IV), the QTc interval (e.g., QTcF and QTcLCTPB) will be excluded from the analyses (change from baseline to LOCF endpoint analysis, categorical analysis).

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

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

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

Table CGAP. 5.7 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) and at least one post-baseline result will be included.
- For Treatment emergent high analyses: Patients with all normal or low values at baseline (no high values) and at least one post-baseline result will be included.
- For Treatment emergent increase analyses: Patients with a baseline and at least 1 post-baseline result will be included.

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

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

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

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

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

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

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

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

For SPIII and SP IV summaries, the baseline qualitative ECG status is defined as the status at last available qualitative ECG assessment during the baseline period (EM: assessment day =Visit 3 for SP III, and assessment day <=Visit 16 for SP IV. CM: assessment day <=Visit 3 for SP III, and assessment day <=Visit 16 for SP IV). A category is a collection of possible descriptions (findings) of one qualitative aspect of an ECG. A category name is the name of the qualitative aspect of the ECG (for example, Rhythm, Conduction, Morphology, Ischemia, and so forth). A finding is 1 of the possible specific descriptions (for example, Sinus Bradycardia, Acute Septal Infarction) within a category.

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

#### *5.5.12.1.5. Laboratory Tests*

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

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

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

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

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

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

- The percentages of patients with an Alkaline phosphatase (ALP) greater than or equal to 2 times (2×) the Covance ULN during post-baseline period will be summarized for all patients with a post-baseline value.
- The percentages of patients with a total bilirubin (TBIL) measurement greater than or equal to 2 times (2×) ULN during post-baseline period will be summarized for all patients with a post-baseline value.

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

The analysis of elevation in ALT, AST, ALP, and TBIL will contain 3 subsets:

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

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

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

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

#### *5.5.12.1.6. Immunogenicity*

The summary TFLs will be based on 6 arms (LY120/LY120, LY240/LY240, PLA/LY120, PLA/LY240, CM120, CM240). To evaluate the changes in immunogenicity data of

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

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

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

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

Analysis of each period includes:

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

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

The following will also be created:

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

### 5.5.12.2. Continuous Safety Measures

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

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

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

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

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

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

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

### *5.5.13. Subgroup Analyses*

Some TFLs listed below for patients with self-injection experience will be created for 4 arms (EM120, EM240, CM120, CM240).

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Efficacy/ health outcome measures (descriptive summary):

- Mean change from baseline (Visit 3) in the number of migraine headache days(Table)
- Mean change from baseline (Visit 3) in the number of migraine headache days (Figure)
- Mean change from baseline in the number of headache days
- Mean change from baseline in the number of monthly migraine headache days requiring medication for the acute treatment of migraine headache
- Treatment Compliance

- PSMQ-M summary

AE related summary:

- Duration of Treatment-Emergent Adverse Events Related to Injection Sites (Figure)
- Duration of Treatment-Emergent Adverse Events Related to Hypersensitivity Events (Figure)
- Treatment-Emergent Adverse Events Related to Injection Sites by PT
- Treatment-Emergent Adverse Events Related to Injection Sites by Max Severity by PT
- Treatment-Emergent Hypersensitivity Events by PT
- Treatment-Emergent Hypersensitivity Events by Max severity by PT
- Treatment-Emergent Adverse Events by PT
- Treatment-Emergent Adverse Events by Max Severity by PT
- Listing of Adverse Events Leading to Discontinuation and Serious Adverse Events
- Listing of Subjects with Treatment-Emergent or Post-Treatment Emergent Adverse Events

Demographics:

- Baseline Demographics and Disease Characteristics - Continuous Variables
- Baseline Demographics and Disease Characteristics - Categorical Variables

## 5.6. Interim Analyses

At least 1 interim analysis is planned after the database lock for Study CGAN. The interim analysis will be conducted to support regulatory submission prior to all patients completing the CGAP study.

## 5.7. Unblinding Plan

CGAP is an open label study. However EM patients' injection at CGAP Visit 3 will be kept blind until the earliest timing of an interim CGAN database lock (DBL) (if it takes place), the final CGAN DBL, or the interim CGAP DBL (if it takes place).

The earliest timing of the interim CGAP DBL (if it takes place) or the final CGAP DBL will be equal to or later than the earliest timing of the interim CGAN DBL (if it takes place) or the final CGAN DBL. This guarantees that all CGAN patients finish the CGAN double blind treatment period (Study Period III) and the data in CGAN Study Period III is locked.

When the interim CGAN DBL, the final CGAN DBL, or the interim CGAP DBL takes place, then an unblinding occurs. The unblinding will reveal the CGAP Visit 3 injection, as well as CGAN treatment arms for EM patients.

During the CGAP study, some members are unblinded (Table CGAP. 5.8). They do not have direct interaction with sites. They will not be allowed to join meetings which may affect the

other members' blind condition, such as trail level safety review (TLSR) and data review meetings.

**Table CGAP. 5.8 Unblinded Members through CGAP Study**

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

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

The CGAP interim analysis will be conducted by the CGAP unblinded study members. They do not have direct interaction with sites (Table CGAP. 5.9) after the unblinding. These members will become unblinded after the earliest timing of the interim CGAN DBL, the final CGAN DBL, or the CGAP interim DBL. All study personnel with direct interaction with sites after the unblinding are kept blinded to the interim analysis results.

**Table CGAP. 5.9 Unblinded Members Unblinded after the Earliest Timing of the Interim CGAN DBL, the Final CGAN DBL, or the CGAP Interim DBL**

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

| | | |
|---|---|---|
| | preparation | |
| CTPM | CSR/PMDA consultation preparation | TFL |
| PPM | CSR/PMDA consultation preparation | TFL |
| Regulatory | CSR/PMDA consultation preparation | TFL |
| Data Management | CSR/PMDA consultation preparation | CLUWE/TFL |

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

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

### *5.8.1. Report to be Generated at Interim Analysis*

At the time of interim analysis, all randomized patients will have had the chance to complete Month 6 (Visit 10) in Study Period III. Analyses conducted at the interim analysis do not include any data from Study Period IV, unless otherwise specified. Efficacy/health outcome results are up to Month 6 data in SP III. Safety/protocol deviation results are based on all data during SP III.

For efficacy/health outcome analysis in SP III (continuous/binary outcomes using MMRM/GLIMMIX), overall (month 1-6) will be shown for treatment comparisons at the interim DBL instead of overall (month 1-12). They will be estimated as the main effect of treatment using Month 1 up to Month 6 data.

**Disposition**

- Patient Allocation by Investigator Site
- Summary of Patient Dispositions for Treatment Phase
- Listing of Subjects who discontinued for Treatment Phase or Post-Treatment Phase
- Listing of Patient Population by Treatment

**Baseline Demographic**

- Baseline Demographics and Disease Characteristics - Continuous Variables
- Baseline Demographics and Disease Characteristics - Categorical Variables
- Listing of Subjects Demographic

**Efficacy/Health outcome**

- Change from Baseline in the Number of Migraine Headache Days by 2 arms (CM120, CM240) using MMRM
- Change from Baseline in the Number of Migraine Headache Days by 2 arms (CM120, CM240) using MMRM (Figure)
- Descriptive Summary of Number of Migraine Headache Days (monthly raw values and change from baseline monthly values) by 6 arms (LY120/LY120, LY240/LY240, PLA/LY120, PLA/LY240, CM120, CM240)
- Descriptive Summary of Number of Migraine Headache Days (monthly raw values) by 6 arms (Figure)
- Descriptive Summary of Number of Migraine Headache Days (change from baseline monthly values) by 6 arms (Figure)
- Change from Baseline in the Number of Migraine Headache Days with Acute Medication Use by 2 arms (CM120, CM240) using MMRM
- Change from Baseline in the Number of Headache Days by 2 arms (CM120, CM240) using MMRM
- Distribution of Response Rates Based on Number of Migraine Headache Days by 2 arms (CM120, CM240) using GLIMMIX
- Distribution of Response Rates Based on Number of Migraine Headache Days by 2 arms (CM120, CM240) using GLIMMIX (Figure)
- Estimated Proportion of 50% Responders for Migraine Headache Days by 2 arms (CM120, CM240) using GLIMMIX
- Estimated Proportion of 75% Responders for Migraine Headache Days by 2 arms (CM120, CM240) using GLIMMIX
- Estimated Proportion of 100% Responders for Migraine Headache Days by 2 arms (CM120, CM240) using GLIMMIX
- Change from Baseline in Migraine-Specific Quality of Life Questionnaire - Role Function-Restrictive Domain Score by 2 arms (CM120, CM240) using MMRM
- Change from Baseline in Patient Global Impression - Severity Scores by 2 arms (CM120, CM240) using MMRM

**Safety: AE**

- Overview of Adverse Events
- Adverse Events Leading to Discontinuation
- Serious Adverse Events
- Adverse Events Related to Injection Sites Leading to Discontinuation
- Adverse Events Leading to Discontinuation for Upper Respiratory Tract Infections
- Treatment-Emergent Adverse Events Related to Injection Sites by Max Severity
- Treatment-Emergent Adverse Events (sort by Preferred Term)
- Listing of Adverse Events Leading to Discontinuation and Serious Adverse Events

**Safety: Lab**

- Abnormal Changes in Hepatic Laboratory Measures at Any Time
- Treatment-Emergent Abnormal Laboratory Measures at Any Time
- Listing of Subjects with abnormal Laboratory Results
- Listing of Subjects with abnormal Hepatic Laboratory Results

**Safety: ECG**

- Shift Table Summary of Qualitative ECG Abnormalities by Finding Category
- Summary of Qualitative ECG Abnormalities - From Baseline Normal to Post-Baseline Abnormal
- Change from Baseline to LOCF Endpoint in ECG Intervals and Heart Rate
- Treatment-Emergent Abnormalities for ECG Intervals and Heart Rate at Any Time
- Listing of Subjects with Treatment or Post-Treatment Emergent ECG findings
- Listing of Subjects with QRS >=120 Milliseconds at Any Time
- Listing of Abnormal Qualitative ECG by Finding Category

**Safety: Other**

- C-SSRS summary and/or listing

**Protocol Deviations**

- Summary of Important Protocol Deviations in SP III
- Summary of Important Protocol Deviations in SP IV
- Listing of Important Protocol Deviations in SP III
- Listing of Important Protocol Deviations in SP IV

### *5.8.2. Report to be Generated at Final Database Lock*

For the final database lock, all TFLs will be created. At the timing of the final database lock, all randomized patients will have had a chance to complete or discontinue 12 months of treatment period (Study Period III) and 4 months of the post-treatment period (Study Period IV.)

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

## 5.9. Clinical Trial Registry Analyses

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

Analyses provided for the CTR requirements include the following:

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

- 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

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

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

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.

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