Statistical Analysis Plan: I5Q-MC-CGAR (v3)

Statistical Analysis Plan for Protocol I5Q-MC-CGAR: A Phase 3b Multicenter, Single-Arm, Open-Label Safety Study of LY2951742 in Patients with Episodic or Chronic Cluster Headache

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1.   Statistical Analysis Plan for Protocol I5Q-MC-CGAR: A Phase 3b Multicenter, Single-Arm, Open-Label Safety Study of LY2951742 in Patients with Episodic or Chronic Cluster Headache

Galcanezumab (LY2951742)

Study CGAR is a Phase 3b multicenter, single-arm, open-label safety study of galcanezumab 300 mg in outpatients with episodic or chronic cluster headache who completed study I5Q-MC-CGAL or I5Q-MC-CGAM. The study has 2 study phases (SP): SP I (screening phase), and SP II (open-label treatment phase).

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Protocol I5Q-MC-CGAR
Phase 3b

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly:
12 July 2016
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly:
31 Jan 2018
Statistical Analysis Plan Version 3 electronically signed and approved by Lilly on date provided below.

Approval Date: 02-Mar-2021 GMT

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved on 12 July 2016 prior to first patient visit.

Statistical Analysis Plan Version 2 was approved prior to the database lock for the interim analysis supporting cluster headache indication submission. The overall changes and rationale for the changes incorporated in Version 2 are as follows:

- LY2951742 was replaced by galcanezumab in the body of the SAP.
- Analysis populations are updated. Evaluable analysis set is renamed to GMB-treated population; continuous treatment exposure population set is removed.
- GMB-treated time and off-treatment time are defined, and the safety analyses will be performed during the GMB-treated time in addition to the whole open-label treatment phase including both GMB-treated time and off-treatment time.
- The list of protocol deviations in Section 5.9 was moved to Appendix 1 with a complete list of important protocol deviations.
- Safety analyses are reduced to summaries of AE overview, TEAE, SAE, and DCAE, since detailed planned analyses of Study CGAR safety data are more thoroughly described in PSAP for cluster headache indication in the context of combining the safety data from the originating studies with the safety data from Study CGAR.
- Section 5.17. Reports to Be Generated at Each Interim and Final Database Lock was added.
- Other minor corrections, modifications, and clarifications were made.

Statistical Analysis Plan Version 3 was approved prior to the final study database lock. The overall changes and rationale for the changes incorporated in Version 3 are as follows:

- General formatting and grammatical edits were made to improve clarity.
- The PGI-I analyses in Section 5.13 were updated to remove a graphical display; a tabular summary will be presented instead, without 95% confidence intervals.
- The description of the EQ-5D-5L questionnaire was updated in Section 5.14 to provide additional details for the derivation of the health state index scores. A description of the correlation analyses of EQ-5D-5L with PGI-I and cluster headache status was also added to meet the stated tertiary objectives.
- The following safety analysis descriptions were added in Section 5.16, to be consistent with the analysis approaches described in the SAPs for the other Emgality Phase 3 cluster headache studies:
  - Potential hypersensitivity events (Section 5.16.2)
  - AEs related to injection sites (Section 5.16.3)
  - Upper Respiratory Tract Infections (Section 5.16.4)
  - Suicide-related thoughts and behaviors (Section 5.16.5)
  - Vital signs and weight (Section 5.16.6)

- o   Electrocardiogram Intervals and Heart Rate (Section 5.16.7)
- o   Laboratory tests (Section 5.16.8)
- o   Immunogenicity (Section 5.16.9)
- The data cutoff dates for the two interim database locks were added in Section 5.17.1 for the interim locks used to support the regulatory submission and safety update report, respectively.
- The list of important protocol deviations in Appendix 1 were updated to align with the current version of the Trial Issue Management Plan (Version 12).

4. Study Objectives

4.1. Primary Objective

The primary objective of this study is to evaluate the safety of open-label galcanezumab within the context of expected medical practice in eligible patients with episodic or chronic cluster headache. Safety will be assessed using treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), as well as suicidal ideation and behaviors utilizing the Columbia-Suicide Severity Rating Scale (C-SSRS).

4.2. Secondary Objectives

Characterize the reasons for discontinuation and frequency of adverse events (AEs) of interest for galcanezumab. The AEs of interest are those related to injection sites, hypersensitivity events, and upper respiratory tract infections.

Characterize the immunogenicity of galcanezumab. The immunogenicity will be assessed by the assessment of anti-drug antibodies (ADA) to galcanezumab, their relationship with AEs, and neutralizing ADA to galcanezumab.

4.3. Tertiary Objectives

Evaluate the effectiveness of galcanezumab by the assessment of the proportion of patients reporting a score of 1 ("very much better") or 2 ("much better") on the Patient Global Impression of Improvement (PGI-I) 1 month after receiving their first dose.

Evaluate the effect of LY2951742 on health values by the analyses of the European Quality 5-Dimensions 5-levels (EQ-5D-5L) on (1) health state index values; (2) each dimension of the descriptive system and dichotomized level responses; (3) European Quality Visual Analogue Scale (EQ-VAS) current health score; and (4) correlations with PGI-I, cluster headache status.

5.   A Priori Statistical Methods

5.1.   Study Design

5.2.   Determination of Sample Size

The sample size for this study is not based on statistical or power considerations. This is an open-label safety study for patients who previously enrolled in and completed studies CGAL or CGAM. Therefore, the sample size is determined by the number of patients completing studies CGAL and CGAM who choose to enroll in this study.

5.3.   Randomization and Treatment Assignment

All patients will receive the same treatment: galcanezumab 300 mg (GMB 300mg). Every month, the decision whether to administer a monthly dose will be based upon the study investigator's judgment.

5.4.   General Considerations

General aspects of statistical analyses are described below.

Unless otherwise specified, analyses will be conducted in the GMB-treated population, which includes all patients who are enrolled and receive at least 1 dose of study drug in Study CGAR, and analyses will be presented with 1 treatment arm. Safety analyses will be performed during the GMB-treated time and during the whole open-label treatment phase (SP II), which includes both GMB-treated time plus off-treatment time. GMB-treated time is composed of monthly dosing intervals, that is, the time from a GMB dose to the next monthly visit. The time between the first monthly visit that a dose is not administered and the dosing re-initiation visit is counted as off-treatment time. Baseline will be the time during SP I prior to receiving the first dose in this study. For safety analyses during the open-label treatment phase, any time after the first dose of GMB 300 mg will be considered as postbaseline period no matter if it is during an on-treatment or off-treatment month. For safety analyses during the GMB-treated time, only events that occurred during the GMB-treated time will be considered as postbaseline values.

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

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP or clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

5.5.   Adjustments for Covariates

Statistical modeling of data using covariates is not anticipated in this study. However, such modeling may be performed as post hoc analyses if deemed appropriate.

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5.6. Handling of Dropouts or Missing Data

Last-observation-carried-forward (LOCF) will be used in handling of missing data when it is applicable. For those patients who are lost to follow-up, or who drop out of the study, the analyses will include all data up to the point of their last data collection.

5.7. Multicenter Studies

Statistical modeling of data using country or site as covariates is not anticipated in this study. However, such modeling may be performed as post hoc analyses if deemed appropriate.

5.8. Patient Disposition

The number and percentage of GMB-treated patients who discontinue early will be tabulated along with reasons for discontinuation.

Patient allocation and reasons for discontinuation by investigator will also be listed.

5.9. Important Protocol Deviations

Summary and listing of subjects with important protocol deviations will be provided for the GMB-treated population.

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

5.10. Patient Characteristics

The following patient characteristics at baseline will be summarized for all GMB-treated patients:

- Demographics (age, gender, race, ethnicity, height, weight, body mass index, country, region)
  Note: Age, gender, race, and ethnicity will be based upon the information from the parent trial.
- Baseline disease characteristics:
  - number of cluster headache attacks yesterday
  - mean pain severity of cluster headache attacks yesterday
  - mean duration of cluster headache attacks yesterday
  - was abortive treatment used?

Pre-existing conditions will be summarized. Pre-existing conditions are medical events ongoing at the time of informed consent.

Note: The reference to yesterday defines a 24-hour period from midnight to midnight the day before the assessment date.

5.11. Treatment Exposure and Compliance

This open-label study dosing will be based upon the study investigator's judgment and there will not be any formal computation of treatment compliance. Total number of monthly doses administered will be summarized for the GMB-treated population. Treatment received will also be reported in an individual subject listing by providing the date, time, and the injection dose administered.

5.12. Concomitant Therapy

The proportion of patients who receive concomitant medication will be summarized using the WHODRUG dictionary preferred term (PT) and will be presented in the order of decreasing frequency of usage. If there are different PTs for salt forms of a preventive or abortive medication, these PTs will be combined for the medication in the presentation. Concomitant therapies are those that started on or continued after the date of first dose of study medication. All records will be used in the above summary even if frequency, dose, or dates of use are missing.

5.13. Efficacy Analyses

Descriptive summaries of the PGI-I, a 7-point scale, with 1=very much better and 7=very much worse (Guy 1976) will be presented at each time point collected during postbaseline, as described in the schedule of activities. It will be summarized as both a categorical and continuous variable.

The proportion of patients reporting a score of 1 ("very much better") or 2 ("much better") on the PGI-I 1 month after receiving their first dose will be reported.

5.14. Health Outcomes/Quality-of-Life Analyses

The European Quality of Life 5-Dimensions 5-Levels (EQ-5D-5L) questionnaire is a widely used, generic patient-rated scale that assesses current health status at the time of questionnaire completion, that is "today" (The EuroQol Group 1990; Herdman et al. 2011). The questionnaire consists of 2 parts. The first part assesses 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that have 5 possible levels of response (no problems, slight problems, moderate problems, severe problems, extreme problems). Answers to these 5 dimensions define a patient's health state. Given a patient's health state, the patient's country-specific health state index value can be obtained from the country-specific value set.

A country-specific value set is derived from valuation research that aims to measure how health is valued by people in a country. The valuation research includes a representative sample of participants from the general population in that country. In the valuation study participants are asked to value health by reviewing EQ-5D health states. The result from the valuation study is a value set for that country. The value set is essentially a set of weights to each of the levels in each EQ-5D dimension. A high weight means that people in that country believe that such a score has a high impact on health-related quality of life.

The health state index value is a single value on a scale from less than 0 (where zero is a health state equivalent to death; negative values are valued as worse than dead) to 1 (perfect health), with higher scores indicating better health utility. The UK population-based and US population-based health state index values are calculated based on the value sets from https://euroqol.org/wp-content/uploads/2018/02/EQ-5D-5L_Crosswalk_Value_Sets.xls

The second part of the questionnaire consists of a visual analog scale (VAS) on which the patient rates their perceived health state from 0 (the worst health you can imagine) to 100 (the best health you can imagine).

Descriptive statistics (n, mean, standard deviation [SD], range, median, 25th and 75th percentiles, min, max) for EQ-5D-5L Health State Index overall score based on US and UK population, scores for each of the 5 EQ-5D-5L dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and EQ-5D-5L VAS current health score will be provided by visit. The number and percentage of patients with dichotomized responses (problems, no problems) for each of the 5 EQ-5D-5L dimensions will also be provided by visit.

To assess the correlation of EQ-5D-5L Health State Index Scores and VAS current health score with PGI-I and cluster headache status, the following analyses will also be performed:

- A correlation analysis between mean change from baseline in EQ-5D-5L with PGI-I at month 1, using Spearman's rank correlation coefficient.
- An Analysis of Variance (ANOVA) comparing mean change from baseline in EQ-5D-5L by cluster headache status (active or remission) at month 1 and month 6.

5.15. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

Bioanalytical and Pharmacokinetic/Pharmacodynamic (PK/PD) methods are not applicable to this SAP. An analysis of PK/PD data is not planned as part of this SAP but will be documented separately according to global PK/PD procedures.

5.16. Safety Analyses

For purposes of the cluster headache regulatory submission, analyses of Study CGAR safety data are more thoroughly assessed in the context of combining the safety data from the parent studies with the safety data from Study CGAR. The planned integrated analyses are described in separate documents. For the purpose of Study CGAR alone, the safety and tolerability of treatment will be summarized by the following:

- AEs
  - TEAEs
    - by PT
    - by PT nested within system organ class (SOC)
  - SAEs, by PT nested within SOC
  - AE leading to discontinuation, by PT nested within SOC
  - Potential hypersensitivity events

- o AEs related to injection sites
- Suicide-related thoughts and behaviors
- Vital signs and weight
- ECGs
- Laboratory measurements
- Anti-drug antibodies (ADA) and neutralizing ADA (NAb)

Unless otherwise specified, safety analyses will be conducted for the GMB-treated population during GMB-treated time and GMB-treated time plus off-treatment time. Categorical safety analyses will include both scheduled and unscheduled visits.

5.16.1. Treatment-Emergent Adverse Events

Treatment-emergent AEs are defined as the reported AEs that first occurred or worsened during the postbaseline phase compared with baseline phase. For events occurring on the day of first administration of study drug, the case report form collected flag will be used to determine whether the event was pre-treatment versus post-treatment. For each TEAE, the severity level of the event (mild, moderate, or severe) will be determined by patient or physician opinion. The Medical Dictionary for Regulatory Activities (MedDRA) Lowest Level Term (LLT) will be used in the treatment-emergent computation. For each LLT, the maximum severity at baseline will be used as the baseline severity. If the maximum severity during postbaseline is greater than the maximum baseline severity, the event is considered to be treatment emergent. For events with a missing severity during the baseline period, it will be treated as "mild" in severity; for events with a missing severity during the postbaseline period, it will be treated as 'severe" for TEAE computation. For each patient and TEAE, the maximum severity for the MedDRA level being displayed (PT, High Level Term, or SOC) is the maximum postbaseline severity observed from all associated LLTs mapping to that MedDRA level.

For events that are male- or female-specific, the denominator and computation of the percentage will only include patients from that specific sex.

5.16.2. Potential Hypersensitivity Events

Potential hypersensitivity events will be defined using the following terms (standard MedDRA query [SMQ]):

- 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)

A listing of patients having an event identified from these analyses will be medically reviewed to determine if the terms identified represent events likely hypersensitivity in nature. Listings should include information on timing of event relative to latest dose of study drug administration, the event term from this query, other AEs for the patient and timing, any abnormal laboratory findings, concomitant medication, medical history and pre-existing

conditions. Only those that are judged medically to be events likely hypersensitivity in nature will be included in the final summary.

The number and percentage of patients with likely hypersensitivity TEAEs will be summarized by treatment groups using MedDRA PT nested within the SMQ. Events will be ordered by decreasing frequency within the SMQ.

5.16.3. Adverse Events Related to Injection Sites

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

The number and percentage of patients with TEAEs related to injection sites will be summarized using MedDRA PT. Events will be ordered by decreasing frequency of PT term.

5.16.4. 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.

5.16.5. Suicide-Related Thoughts and Behaviors

Postbaseline suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent, based on the C-SSRS, will be summarized for the GMB-treated population during GMB-treated time and GMB-treated time plus post-treatment time. In particular, for each of the following events, the number and percent of patients with the event will be enumerated: 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 will be presented and compared. These include suicidal behavior (completed suicide, non-fatal suicidal attempts, interrupted attempts, aborted attempts, and preparatory acts or behavior), suicidal ideation (active suicidal ideation with specific plan and intent, active suicidal ideation with some intent to act without specific plan, active suicidal ideation with any methods [no plan] without intent to act, non-specific active suicidal thoughts, and wish to be dead), and suicidal ideation or behavior.

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.

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

5.16.6. Vital Signs and Weight

Vital signs collected during the study include systolic and diastolic blood pressure (BP), pulse, and temperature. BP and pulse measurements will be taken when the patient is in a sitting position. Three measurements of sitting BP and pulse will be collected at approximately 30 to 60 second intervals at every office visit and the 3 sitting BP measurements and 3 pulse values will be averaged and used as the value for that visit.

Table CGAR.5.1 displays the criteria used to define categorical changes of interest in vital signs and weight. The last column of the table displays the patient population for each analysis based on baseline categories. The number and percent of patients meeting these criteria will be summarized.

The criteria to identify patients with treatment-emergent abnormal changes generally consist of 2 parts, an absolute threshold and a change from baseline amount.

- The absolute threshold in the criteria is based on 1) minimum postbaseline when the direction is low; 2) maximum postbaseline when the direction is high.

- The change from baseline amount in the criteria is 1) decrease from baseline to minimum postbaseline when the direction is low; 2) increase from baseline to maximum postbaseline when the direction is high.

The baseline for systolic BP, diastolic BP, and pulse is defined as the last non-missing baseline value during the baseline period.

For categorical changes of interest in temperature and weight, the baseline values are defined below:

- For the analyses of categorical changes of interest in temperature and weight,

  o the baseline is defined as the minimum value during baseline period when the direction is low

  o the baseline is defined as the maximum value during the baseline period when the direction is high

Table CGAR.5.1.   Categorical Changes of Interest in Vital Signs and Weight

Parameter	Direction	Criteria	Patients Population defined by Baseline Categories
Systolic BP (mm Hg) (sitting)	Low	≤90 and decrease ≥20	>90; ≤90; All patients
	High	≥140 and increase ≥20	<140; ≥ 140; All patients
	PCS High	≥180 and increase ≥20	<180; ≥ 180; All patients
	Sustained Elevation	≥140 and increase ≥20 at 2 consecutive visits	<140; ≥ 140; All patients
Diastolic BP (mm Hg) (sitting)	Low	≤50 and decrease ≥10	>50; ≤50; All patients
	High	≥90 and increase ≥10	<90; ≥ 90; All patients
	PCS High	≥105 and increase ≥15	<105; ≥ 105; All patients
	Sustained Elevation	≥90 and increase ≥10 at 2 consecutive visits	<90; ≥ 90; All patients
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	≥50; <50; All patients
	High	>100 and increase ≥15	≤100; >100; All patients
	Sustained Elevation	>100 and increase ≥15 at 2 consecutive visits	≤100; >100; All patients
Weight (kg)	Low	(Loss) decrease ≥7%	All patients
	High	(Gain) increase ≥7%	All patients
Temperature (° F)	Low	<96° F and decrease ≥2° F	≥ 96° F
	High	≥101° F and increase ≥2° F	<101° F

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

5.16.7. Electrocardiogram Intervals and Heart Rate

Analyses of QTc interval, Fridericia's corrected QT interval (QTcF) (msec), will be calculated with Fridericia's formula as $QT/RR^{\frac{1}{3}}$. For the QTc calculations, the unit for QT is milliseconds and the unit for RR is seconds. For patients with QRS ≥120 milliseconds at any time during the study, the QT and QTc interval will be excluded from the analyses.

The baseline for ECG is defined as the last non-missing baseline value during the baseline period. This baseline definition for ECG applies to all analyses (quantitative and qualitative).

The number and percent of patients meeting criteria for treatment-emergent abnormalities in ECG intervals (PR, QRS, and QTcF) and heart rate will be summarized.

Table CGAR.5.2 displays the criteria for treatment-emergent changes in ECG intervals and heart rate.

- For treatment-emergent low analyses: patients with normal or high values at baseline (no low values) will be included.

- For treatment-emergent high analyses: patients with normal or low values at baseline (no high values) will be included.

- For treatment-emergent increase analyses: patients with a baseline and at least one postbaseline result will be included.

Table CGAR.5.2.   Criteria for Treatment-Emergent Changes in ECG Intervals and Heart Rate

Parameter	Direction	Criteria	
Heart Rate (bpm)	Low	<50 and decrease ≥15	
	High	>100 and increase ≥15	
PR Interval (msec)	Low	<120	
	High	≥220	
QRS Interval (msec)	Low	<60	
	High	≥120	
QTcF (msec)	Low	Males: <330	Females: <340
	High	Males: >450	Females: >470
	PCS High	>500msec	
	Increase	Increase >30 msec	
		Increase >60 msec	
		Increase >75 msec	

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Abbreviations: bpm = beats per minute; ECG = electrocardiogram; PCS = Potentially Clinically Significant; QTcF = Fridericia's corrected QT interval.

In addition, qualitative ECG abnormalities will be evaluated which will include 11 ECG categories (axis, rhythm, conduction, ischemia, infarction, injury, morphology, U-waves, T-waves, ST Segment, and other abnormalities) of qualitative findings. A category is a collection of possible descriptions (findings) of one qualitative aspect of an ECG. A category name is the name of the qualitative aspect of the ECG (for example, rhythm, conduction, morphology, ischemia, and so forth). A finding is one of the possible specific descriptions (for example, sinus bradycardia, acute septal infarction) within a category.

A shift table summary of qualitative ECGs at any time will be produced, to assess shifts from baseline normal to postbaseline abnormal for the overall ECG and for each of the 11 finding categories mentioned above.

Patients with the following are excluded from ECG analyses: lead reversals or <9 leads, nonmatching demographic data, and those suggesting patient identification errors.

5.16.8. Laboratory Tests

The number and percent of patients with treatment-emergent abnormal, high, or low laboratory values for each laboratory test based on Covance reference ranges will be summarized.

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

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

5.16.9. Immunogenicity

In the immunogenicity assay process, each sample is potentially examined multiple times, according to a hierarchical procedure, to produce a sample ADA assay result and potentially a sample NAb assay result. The cut points used, the drug tolerance of an assay, and the possible values of titers are operating characteristics of the assay.

It can be the case that the presence of high concentrations of galcanezumab will affect the measurements of the presence of ADA or NAb, and conversely high levels of ADA or NAb may affect the measurement of GMB concentration. Thus an GMB drug concentration, assessed from

a sample drawn at the same time as the ADA sample, plays a key role in clinical interpretation of a sample when the laboratory result is Not Detected.

5.16.9.1. Definitions of Patient ADA Status

Patient evaluable for TE ADA: A patient is evaluable for TE ADA if the patient has a non-missing baseline ADA result, and at least 1 non-missing postbaseline.

TE ADA positive (TE ADA+) patient: A patient who is evaluable for TE ADA is TE ADA+ if either of the following holds:

- **Treatment-induced:** The patient has baseline status of ADA Not Present and at least one postbaseline status of ADA Present with titer ≥ 20 (that is, 2* MRD where for this ADA assay the MRD, the minimum required dilution of the ADA assay, is 10).

- **Treatment-boosted:** The patient has baseline and postbaseline status of ADA Present, with the postbaseline titer being 2 dilutions (4-fold) greater than the baseline titer. That is, the patient has baseline status of ADA Present, with titer 1:B, and at least one postbaseline status of ADA Present, with titer 1:P, with P/B ≥ 4.

5.16.9.2. Immunogenicity Analyses to be Performed

To evaluate changes in immunogenicity data (ADA and NAb) after treatment, the number and percent of TE ADA evaluable patients who are TE ADA+ in Study CGAR will be tabulated.

The following analyses are planned:

- The incidence of TE ADA+ patients in CGAR postbaseline, by previous TE ADA status in the parent study (CGAL or CGAM) and at CGAR baseline. Because patients who enter Study CGAR will have differing levels of previous GMB exposure (0 to 15 months), this immunogenicity analysis will categorize patients in 3 groups, according to their previous GMB exposure in the parent study:
  - Study CGAL patients who received placebo (0 months of GMB treatment)
  - Study CGAL patients who received GMB (2 months of GMB treatment)
  - Study CGAM patients (12 or 15 months of GMB treatment)
- A listing of patients with TE ADA in CGAR postbaseline, including ADA and NAb results from both the parent study and CGAR.

5.17. Reports to Be Generated at Each Interim and Final Database Lock

5.17.1. Report to Be Generated at Interim Database Locks

Two interim locks will occur prior to the final database lock for CGAR, to support the regulatory submission and safety update report, respectively. The first lock will occur after all patients in both parent studies (CGAL and CGAM) have had the chance to complete the double-blind treatment phase, and the corresponding Synopsis CSR will include any data up to the cutoff date of 27 March 2018. The second lock for a safety update report will include any data up to the

cutoff date of 04 September 2018. The analyses for these two interim locks will focus on the following topics:

- patient disposition
- patient characteristics
- exposure to investigational products
- AE overview, TEAE, SAE, and DCAE

5.17.2. Report to Be Generated at Final Database Lock

For final database lock, all analyses defined in this SAP, including tables, figures, and listings, will be generated.

5.18. 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 that will be converted to an XML file. Both Serious Adverse Events and 'Other' Adverse Events are summarized: 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 "Serious" AE and "Other" AE, for each term, 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 the 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. Reference

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7. Appendices

Appendix 1.   Important Protocol Deviations

Category (sCTMS)	Sub Category (sCTMS)	Trial-specific Term	Source
Informed Consent	Informed consent not obtained	NA	Programmable/Non-programmable–Monitor identified
Informed Consent	Revoke Consent	NA	Non-programmable–Monitor identified
Eligibility	Inclusion/Exclusion	Exclusionary cardiovascular-related condition	Programmable/Non-programmable–Monitor identified
Eligibility	Inclusion/Exclusion	Exclusionary hepatobiliary elevation	Programmable/Non-programmable–Monitor identified
Eligibility	Inclusion/Exclusion	Positive exclusionary UDS for any substances of abuse	Programmable/Non-programmable–Monitor identified
Eligibility	Inclusion/Exclusion	Inadvertent enrollment	Non-programmable–Monitor identified
Study Procedures	Excluded Con Meds	Use of verapamil at doses higher than allowed at baseline and during study	Programmable/Non-programmable–Monitor identified
Study Procedures	Other	C-SSRS not completed at required visits	Programmable/Non-programmable–Monitor identified
Study Procedures	Other	Missing all 3 BP, or all 3 Pulse	Programmable/Non-programmable–Monitor identified
Study Procedures	Other	Missing scheduled ECG	Programmable/Non-programmable–Monitor identified
Study Procedures	Other	Discontinuing without the 1 month post injection office visit (Event List F)	Programmable/Non-programmable–Monitor identified

Category (sCTMS)	Sub Category (sCTMS)	Trial-specific Term	Source
Safety	SAEs	Site did not appropriately report SAEs	Nonprogrammable – Monitor identified
Safety	Other	Female patients who are dosed who have a positive urine and/or serum pregnancy test	Programmable
Investigational Product	Patient took medication not fit for use	Patient received drug that was declared "Not Fit for Use"	Nonprogrammable – Monitor identified
Investigational Product	Other	Administering galcanezumab less than 21 days between doses	Programmable
Investigational Product	Dosing Error	Other Significant violations of study drug dosing	Nonprogrammable – Monitor identified
Investigational Product	Other	IP lost or stolen	Nonprogrammable – Monitor identified
Administrative/ Oversight	Suspected Misconduct	NA	Nonprogrammable – Monitor identified
Administrative/ Oversight	Suspected Misconduct	Suspected Fraud	Nonprogrammable – Monitor identified
Administrative/ Oversight	Suspected Misconduct	Suspected falsification of data	Nonprogrammable – Monitor identified
Administrative/ Oversight	Other	C-SSRS scale administered by unqualified rater	Nonprogrammable – Monitor identified
Administrative/ Oversight	Other	Quality issue at site or vendor	Nonprogrammable – Monitor identified
Administrative Oversight	Other	Privacy Breach	Nonprogrammable – Monitor identified

Abbreviations: BP = blood pressure; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; IP = investigational product; NA = Not Applicable; SAE = serious adverse event.

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