Protocol I5Q-MC-CGAR(a)

A Phase 3b Multicenter, Single-Arm, Open-Label Safety Study of LY2951742 (galcanezumab) in Patients with Episodic or Chronic Cluster Headache

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LY2951742 (galcanezumab)

Study CGAR is a Phase 3b multicenter, single-arm, open-label safety study of galcanezumab 300 mg in patients with episodic or chronic cluster headache who completed study I5Q-MC-CGAL or I5Q-MC-CGAM.

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Table of Contents

Section **Page**

List of Tables

Table **Page**

List of Figures

Figure **Page**

List of Appendices

Appendix **Page**

1. Synopsis

Title of Study:
A Phase 3b Multicenter, Single-Arm, Open-Label Safety Study of LY2951742 (galcanezumab) in Patients with Episodic or Chronic Cluster Headache

Rationale:
Galcanezumab is a humanized monoclonal antibody that selectively binds to and neutralizes calcitonin gene-related peptide (CGRP) that has been identified for clinical development in pain conditions relevant to the CGRP pathway such as migraine and cluster headache. The similarities between migraine and cluster headache, the role of CGRP in both disorders, and the clinical efficacy observed with galcanezumab to date for the preventive treatment of migraine support the evaluation of galcanezumab for the treatment of cluster headache.

The aim of this study is to assess the long-term safety and tolerability of galcanezumab 300 mg administered up to once monthly in episodic or chronic cluster headache patients who have completed Study I5Q-MC-CGAL (CGAL) or Study I5Q-MC-CGAM (CGAM).

Objective(s)/Endpoints:

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).

Summary of Study Design:

Briefly, Study I5Q-MC-CGAR (CGAR) is a Phase 3b single-arm, open-label safety study of galcanezumab 300 mg in outpatients with episodic or chronic cluster headache who completed Study CGAL or Study CGAM. This study will consist of 2 study phases (SP): SP I is the screening phase to confirm patients meet the inclusion/exclusion criteria, and SP II is the open-label treatment phase during which patients can receive galcanezumab 300 mg administered subcutaneously (SC) up to once a month. Within the paradigm of a once-monthly dosing regimen, the decision to dose at each monthly interval will be determined by the investigator.

Treatment Arms and Duration:

One treatment arm: galcanezumab 300 mg administered SC up to once a month as determined by the study investigator based on clinical symptoms and response.

Number of Patients:

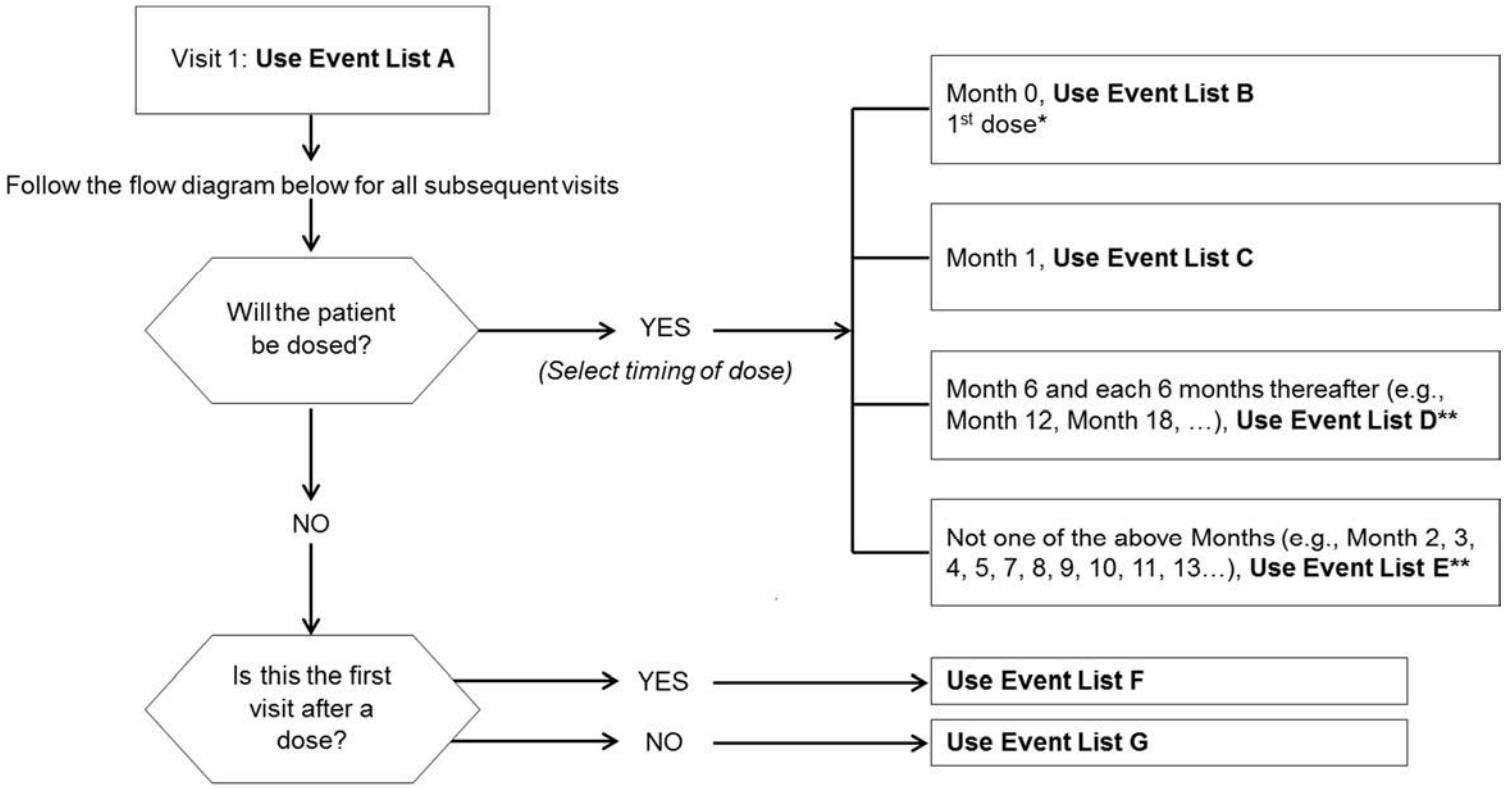
This is an open-label safety study for patients who previously enrolled in and completed Study CGAL or Study CGAM. Therefore, the sample size is determined by the number of patients completing Studies CGAL and CGAM who choose to enroll in this study.

Statistical Analysis:

Unless otherwise specified, analyses will be conducted on the evaluable analysis set, which includes all enrolled patients receiving at least 1 dose of the investigational product.

The primary analyses will include summaries of TEAEs, SAEs, and suicidal ideation and behaviors assessed by solicited questioning using the C-SSRS.

2. Schedule of Activities



*Approximately 1 week after the 1st dose at Month 0, a Telephone visit will occur (**Use Event List G**).
**If treatment was halted per protocol during the study, the following procedures: ECG, immunogenicity, PK, hematology, clinical chemistry, HbA_{1c} and urine pregnancy, are to be completed prior to reinitiation of dosing (see Section 5.1 for additional details).

Figure 2.1. CGAR visit flow diagram.

Table 2.1. Schedule of Activities, Protocol I5Q-MC-CGAR

Study Phase	**SP I**	**SP II**					
		Dosing Visits				**Non-dosing visits**	
Events	**Event List A**	**Event List B**	**Event List C**	**Event List D**	**Event List E**	**Event List F**	**Event List G**
Visit	**Visit 1[a,b,c,d]**	**Month 0 1st Dose**	**Month 1**	**Month 6 and every 6 Months thereafter (e.g., Month 12, 18…)**	**Months not listed in Event List B, C, or D (e.g., Month 2, 3, 4, 5, 7, 8…)**	**The first visit after a dose**	**Dose is not administered; Telephone visit**
Informed consent	X						
Inclusion/exclusion criteria	X						
Medical history and pre-existing conditions	X						
Electrocardiogram[e]	X	X		X		X	
Physical examination[f]	X	X	X	X	X	X	
Weight	X			X		X	
Waist and hip circumference	X						
Vitals[g]	X	X	X	X	X	X	
Hematology[e]	X			X		X	
Clinical chemistry[e]	X			X		X	
Urinalysis[e]	X			X		X	

Study Phase	SP I	SP II					
		Dosing Visits				Non-dosing visits	
Events	Event List A	Event List B	Event List C	Event List D	Event List E	Event List F	Event List G
Visit	Visit 1[a,b,c,d]	Month 0 1st Dose	Month 1	Month 6 and every 6 Months thereafter (e.g., Month 12, 18…)	Months not listed in Event List B, C, or D (e.g., Month 2, 3, 4, 5, 7, 8…)	The first visit after a dose	Dose is not administered; Telephone visit
HbA_{1C}[e]	X			X		X	
FSH	X						
Serum pregnancy[k]	X					X	
Urine pregnancy test[e, k] (performed by site)		X		X			
Urine drug screen[k]	X						
Immunogenicity[e]		X	X	X		X	
PK sampling[e]		X	X	X		X	
PGI-I			X	X		X	
EQ-5D-5L	X	X	X	X		X	
Cluster headache status	X	X	X	X	X	X	
C-SSRS/SHSF, SHFU[h]	X	X	X	X	X	X	
AEs	X[i]	X	X	X	X	X	X
SAEs	X	X	X	X	X	X	X

Study Phase	SP I	SP II					
		Dosing Visits				Non-dosing visits	
Events	**Event List A**	**Event List B**	**Event List C**	**Event List D**	**Event List E**	**Event List F**	**Event List G**
Visit	**Visit 1[a,b,c,d]**	**Month 0 1st Dose**	**Month 1**	**Month 6 and every 6 Months thereafter (e.g., Month 12, 18…)**	**Months not listed in Event List B, C, or D (e.g., Month 2, 3, 4, 5, 7, 8…)**	**The first visit after a dose**	**Dose is not administered; Telephone visit**
Concomitant medications	X	X	X	X	X	X	
Administer LY2951742[j]		X	X	X	X		

Abbreviations: AE = adverse event; C-SSRS = Columbia-Suicide Severity Rating Scale; EQ-5D-5L = European quality 5-dimensions 5-levels; FSH = follicle stimulating hormone; HbA_{1C} = hemoglobin A1C; ND = not done; PGI-I = Patient Global Impression of Improvement; PK = pharmacokinetics; SAE = serious adverse event; SHFU = Self-Harm Follow-up Form; SHSF = Self-Harm Supplement Form; V = visit.

a If the last visit of the parent study is also the first visit of Study CGAR, then ECGs, vitals, weight, hematology, clinical chemistry, urinalysis, HbA_{1C}, and serum pregnancy, C-SSRS, and SHSF/SHFU from the last visit of the parent study will also be used for the first visit of CGAR. All other study procedures in Event List A need to be completed at V1 of CGAR.

b If the last visit of the parent study is ≤2 weeks from V1 of CGAR, the hematology, chemistry, HbA_{1C}, and urinalysis do not need to be repeated. All other study procedures in Event List A need to be completed at V1 of CGAR.

c If the last visit of the parent study is >2 weeks from V1 of CGAR, all study procedures in Event List A need to be completed at the first visit of CGAR.

d After V1, if V2 does not occur within 3 months of V1 (e.g., patient enters V1 in remission), prior to V2 an ECG, hematology, clinical chemistry, urinalysis, urine drug screen, HbA_{1C}, and serum pregnancy must be collected and eligibility confirmed again prior to dosing at V2.

e If treatment was halted per protocol during the study, the following procedures: ECG, immunogenicity, PK, hematology, clinical chemistry, HbA_{1c} and urine pregnancy, are to be completed prior to reinitiation of dosing (see Section 5.1 for additional details).

f Directed physical examination only if needed.

g Vital signs include body temperature, blood pressure, and pulse. Blood pressure and pulse will be measured in triplicate in the sitting position and should be measured prior to blood draws.

h The C-SSRS and SHSF (SHFU when applicable) will be completed at scheduled and unscheduled office visits.

i At V1, record AEs that are on-going from the previous trial.

j Patients should remain in the office for 30 minutes of observation following the first LY2951742 injection of the study; injections of LY2951742 are to occur after all other visit procedures are completed.

k May be repeated during the study at the discretion of the investigator.

3. Introduction

3.1. Study Rationale

Study CGAR is a Phase 3b study to assess the long-term safety and tolerability of galcanezumab 300 mg in patients with episodic or chronic cluster headache who have completed one of the Phase 3 double-blind, placebo-controlled studies, CGAL or CGAM.

Study CGAR will implement a dosing strategy to more closely approximate what may occur in clinical practice. For each patient, the study investigator will determine whether or not to dose galcanezumab 300 mg at each monthly interval based on clinical symptoms and response. Dosing will be no more frequent than once per month, and the investigator may choose to not dose galcanezumab for 1 or more months at their clinical discretion based on clinical efficacy. As such, some patients may receive monthly long-term treatment with galcanezumab for a period of months or years during the study, while others may have 1 or more months of galcanezumab dose-free intervals based on the investigator's judgment of clinical efficacy.

3.2. Background

Cluster headache is a rare but disabling primary headache disorder characterized by episodic attacks of intense unilateral headache and the frequent association of autonomic symptoms such as lacrimation, conjunctival injection, and nasal congestion (International Classification of Headache Disorders, Third edition, beta version [ICHD-3 2013]). The diagnosis of cluster headache is distinctly recognized and defined ICHD-3 (2013).

There are significant unmet needs for just about every clinical aspect of the patient with cluster headache, particularly related to the severity of the disease and treatment options. The majority of patients experiencing cluster headache attacks rate their pain intensity as near to or at the worst pain imaginable (using a Visual Analog Scale [VAS] 10-cm scale; Torelli and Manzoni 2003). Regarding treatment options, two main treatment modalities are typically used: acute/abortive treatments (used at the onset of individual cluster headache attacks to abort the attack) and prophylactic/preventive treatments (aimed to reduce cluster headache attack frequency). In the United States, there are no approved preventive medications.

Calcitonin gene-related peptide is a 37-amino acid neuropeptide member of a family of peptides that includes amylin, adrenomedullin and calcitonin. Calcitonin gene-related peptide is one of the most abundant peptides within the nervous system (McCarthy and Lawson 1990), and is highly expressed in trigeminal ganglion neurons. The association of CGRP with cluster headache was demonstrated in 2 studies of patients with either spontaneous or induced cluster headache attacks who were found to have elevated CGRP levels compared to controls (Edvinsson and Goadsby 1994; Fanciullacci et al.1995; Fanciullacci et al. 1997). The elevated CGRP levels were normalized after successful treatment with SC sumatriptan, oxygen inhalation, or spontaneous recovery.

Galcanezumab is a humanized monoclonal antibody that selectively binds to and neutralizes CGRP. Galcanezumab has been identified for clinical development in pain conditions relevant

to the CGRP pathway such as migraine; and in completed studies to date, galcanezumab was shown to alter plasma CGRP concentrations, which is consistent with the binding of the antibody (galcanezumab) to CGRP (Investigator's Brochure [IB] Section 3.1).

To date, more than 380 clinical trial participants with migraine and 84 healthy volunteers have been exposed to galcanezumab at single doses up to 600 mg and multiple doses up to 300 mg in 5 clinical trials of galcanezumab. In studies of patients with migraine (Studies I5Q-MC-ART1 [ART-01] and I5Q-MC-CGAB [CGAB]), efficacy data have demonstrated that galcanezumab had significantly greater mean reductions than placebo in migraine headache days and other efficacy parameters. Across clinical studies of galcanezumab, assessment of TEAEs indicates that galcanezumab has been well tolerated in both healthy subjects and in patients with episodic migraine. The AEs generally have been mild to moderate in severity. In the completed studies of patients with migraine, the most frequently reported TEAEs in either study included injection-site pain, upper respiratory tract infection, abdominal pain, dizziness, injection-site erythema, rash, hypertension, and nasopharyngitis. Analyses of laboratory values and cardiovascular monitoring of the clinical studies have shown no clinically important changes in tested parameters (IB Section 3.2).

3.3. Benefit/Risk Assessment

More information about the known and expected benefits, risks, and reasonably anticipated AEs of galcanezumab may be found in the IB. Information on AEs expected to be related to the investigational product may be found in Section 7 (Development Core Safety Information) of the IB. Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the study, may be found in Section 6 (Effects in Humans) of the IB.

4. Objectives and Endpoints

Table 4.1 shows the objectives and endpoints of the study.

Table 4.1. Objectives and Endpoints

Objectives	Endpoints
Primary To evaluate the safety of open-label galcanezumab within the context of expected medical practice in eligible patients with episodic or chronic cluster headache.	Analysis of: • TEAEs • SAEs • Suicidal ideation and behaviors assessed by solicited questioning using the C-SSRS
Secondary To characterize the reasons for discontinuation and AEs of interest for galcanezumab.	Discontinuation rates
To characterize the immunogenicity of galcanezumab.	Analysis of: • Injection-site reactions • Allergy/hypersensitivity • Infections • The development and consequences of ADAs to galcanezumab, their relationship with AEs, and neutralizing ADAs to galcanezumab
Tertiary To evaluate the effectiveness of galcanezumab.	• 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.
To evaluate the effect of galcanezumab on health values.	EQ-5D-5L Analysis of: • Health state index values • Each dimension of the descriptive system and dichotomized level responses • EQ-VAS current health score • Correlations with PGI-I, cluster headache status

Abbreviations: ADA = anti-drug antibodies; C-SSRS = Columbia-Suicide Severity Rating Scale; EQ-5D-5L Analysis = European quality 5-dimensions 5-levels; EQ-VAS = European Quality Visual Analogue Scale; PGI-I = Patient Global Impression of Improvement; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

5. Study Design

5.1. Overall Design

Study CGAR is a Phase 3b single-arm, open-label safety study of galcanezumab 300 mg in outpatients with episodic or chronic cluster headache who completed Study CGAL or Study CGAM.

Please refer to the Protocol Operations Manual for information regarding the schedule of activities, study design, study tools, and patient scenario examples.

The study will consist of 2 SP:

- SP I is the screening phase to confirm patients meet the inclusion/exclusion criteria.
- SP II is the open-label treatment phase during which patients can receive galcanezumab 300 mg administered subcutaneously (SC) up to once a month.

Study Phase I: SP I is the screening phase. Patients will sign an informed consent document prior to completing any study-related screening procedures. SP I is the time from Visit (V)1 to V2. The minimum timeframe for SP1 needs to allow sufficient time for patients to washout of any excluded medications and to review subject eligibility. Visit 1 will be considered complete when the last procedure of the screening assessment for the patient is completed. Once Study CGAR is open for enrollment, potentially eligible patients may enter screening directly from the parent study, CGAL or CGAM. If a patient is not experiencing cluster headache attacks (e.g., in remission) they may wait to enter screening for CGAR until they anticipate experiencing or are experiencing a cluster headache attack. If patients had completed the parent study, CGAL or CGAM, prior to Study CGAR being open for enrollment, potentially eligible patients may still enter screening for Study CGAR. Study procedures for V1 (Event List A) of Study CGAR will be completed as follows:

- If the last visit of the parent study is also the first visit of Study CGAR, then electrocardiograms (ECGs), vitals, weight, hematology, clinical chemistry, urinalysis, hemoglobin A1C (HbA_{1C}), and serum pregnancy, C-SSRS, and Self-Harm Supplement Form/ Self-Harm Follow-up Form (SHSF/SHFU) from the last visit of the parent study will also be used for the first visit of Study CGAR.
- If the last visit of the parent study is ≤2 weeks from V1 of Study CGAR, the hematology, chemistry, HbA_{1C}, and urinalysis do not need to be repeated.
- If the last visit of the parent study is >2 weeks from V1 of Study CGAR, all study procedures in Event List A need to be completed at the first visit of Study CGAR.

Note: After V1, if V2 does not occur within 3 months of V1 (e.g., patient enters V1 in remission), prior to V2 an ECG, hematology, clinical chemistry, urinalysis, urine drug screen (UDS), HbA_{1C}, and serum pregnancy must be collected and eligibility confirmed prior to dosing at V2 (see footnote "d" in the SOA).

Study Phase II: SP II is the single-arm open-label treatment phase during which patients can receive galcanezumab 300 mg administered SC up to once a month. If a patient meets all eligibility requirements, a urine pregnancy screen will be conducted at the first dosing visit, prior to dosing to confirm that a female patient is not pregnant before administering investigational product. Following the first dose of galcanezumab, the patient should remain in the office for 30 minutes of observation. The site will have a scheduled telephone visit (V3) with the patient approximately 1 week after the first investigational product administration to collect spontaneously reported AEs.

Every month, the decision whether to administer a monthly dose will be based upon the study investigator's judgment, which is not limited to, but includes assessment of the patient's clinical symptoms and response as follows:

- Dosing is up to once monthly; more frequent dosing is not allowed. The full 300 mg dose is to be administered, changing the dose amount is not allowed.
- If the patient remits and dosing is halted, the patient may remain in the study, but they should have an office visit 1 month after the last dose to complete the procedures listed in

Event List F (Table 2.1). Dosing in this scenario may be reinitiated at the study investigator's discretion.

- Monthly telephone visits should be completed for patients who are not being dosed, but remain in the study (e.g., in remission).
- If dosing is temporarily interrupted due to a potential safety concern, dosing may be re-initiated at the study investigator's discretion following a discussion and agreement between the study investigator and Lilly Medical that re-initiation of dosing is appropriate.
    - At the office visit **prior to re-initiation of dosing** the following procedures: ECG, immunogenicity, pharmacokinetics (PK), hematology, clinical chemistry, HbA1c and urine pregnancy are to be collected. The urine pregnancy must be negative and the ECG should be evaluated for safety prior to dosing.

5.2. Number of Participants

Only patients who previously enrolled in and completed Study CGAL or Study CGAM are eligible for this study. Therefore, the maximum number of eligible participants is determined by the number of participants completing Studies CGAL and CGAM.

5.3. End of Study Definition

The study will continue in a specific region until any one of the following criteria is met:

- Sponsor decision
- Nonapproval from a regulatory agency in the country/region in which the patient is enrolled

5.4. Scientific Rationale for Study Design

Please refer to Section 3.1 for further information.

5.5. Justification for Dose

The dose level proposed for the study of galcanezumab in cluster headache is 300 mg administered once monthly. Based on inhibition of capsaicin-induced dermal blood flow (CIDBF) and pharmacokinetic/pharmacodynamic (PK/PD) modeling of plasma CGRP concentrations (target engagement) from prior studies, it is presumed that this dose regimen will provide a high degree of pharmacological activity (greater than 90% effective in inhibiting CIDBF; about 90% decrease from baseline in unbound plasma CGRP concentrations), and be sufficient to test the effectiveness of galcanezumab for the treatment of cluster headache. A dose of 300 mg once monthly is predicted to replicate the exposure and have the same effect on CIDBF and unbound plasma CGRP as 150 mg every 2 weeks (Q2W), which yielded evidence of efficacy in migraine (Study ART-01). The safety and tolerability of galcanezumab supports dosing at 300 mg once monthly. Additionally, the parent trials, Study CGAL and Study CGAM, utilized galcanezumab 300 mg once monthly dosing.

6. Study Population

Patients diagnosed with episodic or chronic cluster headache that were enrolled in **and** completed one of the parent studies, Study CGAL or Study CGAM, are potentially eligible for this study.

If the sponsor or investigator identifies a patient who did not meet enrollment criteria for Study CGAR and was inadvertently enrolled, a discussion must occur between the sponsor clinical research physician (CRP) and the investigator to determine if the patient may be considered for Study CGAR. If both agree it is medically appropriate for the patient to be considered for Study CGAR, the decision must be documented by the investigator.

All patients must meet the following selection criteria. Eligibility of patients for study enrollment will be based on medical history, physical examination, clinical laboratory tests, ECG, and the inclusion and exclusion criteria described below.

Individuals who do not meet the criteria for participation in this study (screen failure) may be considered for rescreen once, for selected criteria, with approval from Eli Lilly and Company (hereafter Lilly) Medical (see below).

Prospective approval of protocol deviations to enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

6.1. Inclusion Criteria

1. Patients who **participated in and completed** either Study CGAL or Study CGAM. A study completer is defined as follows:
    a. Study CGAL: a patient who has completed the double-blind treatment and post-treatment follow-up phases.
    b. Study CGAM: a patient who has completed the double-blind treatment, open-label extension and post-treatment follow-up phases. However, if a patient entered Study CGAM prior to Study CGAR being open for enrollment, they will be considered a completer if they completed the double-blind treatment and post-treatment follow-up phases (e.g., opted not to participate in the open-label extension).
2. Investigator judges the patient as reliable to follow all study procedures, keep all study visits, and be compliant with study requirements.
3. Reproduction:
    a. Women of child-bearing potential may participate in the study.
        i. Women of child-bearing potential must test negative for pregnancy (based on a urine pregnancy test) at the time of enrollment and must agree to use either 1 highly effective method of contraception or a combination of 2 effective methods of contraception during the study. Women may choose to use a double barrier method of contraception. Barrier methods without concomitant use of a spermicide are not reliable or an acceptable method. Thus, each barrier method must include use of a spermicide. It should be noted that the

use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.

b. Women not of child-bearing potential may participate in the study and include those who are:

   i. Infertile due to surgical sterilization (at least 6 weeks after hysterectomy, bilateral oophorectomy or tubal ligation), congenital anomaly such as mullerian agenesis, or

   ii. Post-menopausal, which is defined as:

      a. A woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had either

         i. cessation of menses for at least 1year, or

         ii. at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone (FSH) level >40 mIU/mL; or

      b. A woman 55 or older not on hormone therapy who has had at least 6 months of spontaneous amenorrhea; or

      c. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

c. Male patients agree to use at least 1 effective method of contraception during the study.

Note: If a male or female patient remits during the study and discontinues treatment, but remains in the study, they must continue to use a birth control as outlined above. At study termination, women and men must use birth control for at least 5 months following their last dose.

Please refer to the Protocol Manual of Operations for a list of the methods of contraception.

4. Throughout the study, agree to refrain from the use of drugs of abuse per United States Federal Guidelines (Schedule I) such as, but not limited to, cannabinoids, cannabis, psilocybin (mushrooms), Lysergic acid diethylamide (LSD) and 2-bromo-LSD.
5. Agree not to post any personal medical data related to the study or information related to the study on any website or social media site (for example, Facebook, Twitter, LinkedIn, Google+, etc.) until the entire trial has completed or you are otherwise informed by the study investigator.
6. Have given written informed consent.

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria:

7. Current enrollment in, or discontinuation within the last 30 days prior to V1 from, a clinical trial (with the exception of Study CGAL or Study CGAM) involving any investigational product or device, or concurrent enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
    a. Adequate washout (≥5 half-lives) of any investigational product is also required and may require >30 days depending on the half-life of the investigational product.
8. Use of therapeutic antibodies (except galcanezumab) during the course of the study (adalimumab, infliximab, trastuzumab, bevacizumab, etc.). Prior use of other therapeutic antibodies is allowed if an adequate washout has occurred (≥5 half-lives) prior to V2.
9. Lifetime history of migraine variants that could implicate or could be confused with ischemia; specifically, hemiplegic (sporadic or familial) migraine, ophthalmoplegic migraine, and basilar-type migraine defined by ICHD-3 beta.
10. Taking excluded medication(s) at V2. Excluded medications require an adequate washout (≥5 half-lives) prior toV2. The list of excluded medications is provided separately from the protocol.
11. Evidence of significant active or unstable psychiatric disease by medical history, such as bipolar disorder, schizophrenia, personality disorders or other serious mood or anxiety disorders. Patients with major depressive disorder or generalized anxiety disorder, whose disease state is considered stable and expected to remain stable throughout the course of the study, in the opinion of the investigator, may be considered for inclusion if they are not on excluded medication(s).
12. Are considered by the investigator to be at significant risk for suicide.
13. Women who are pregnant or nursing.
14. Any of the following cardiovascular-related conditions are exclusionary:
    a. Since enrolling in Study CGAL or Study CGAM or prior to V2 (enrollment), have ECGs showing acute abnormalities of:
        i. evidence of delayed ventricular repolarization including but not limited to a corrected QT (Fridericia's QT interval [QTcF]) interval >470 msec for women and >450 for men, **and/or**
        ii. evidence of atrioventricular (AV) depolarization of PR>220, or conduction delay of QRS>120, **and/or**
        iii. evidence of ischemia or any of the qualitative findings indicative of ST or J-point elevation, excluding those findings consistent with early repolarization (non-ischemic).

NOTE: Patients who meet 1 of the 14(a) ECG criteria during Study CGAL or Study CGAM may enroll in Study CGAR if the study investigator deems the finding not clinically significant.

b. History of myocardial infarction (MI), unstable angina (UA), percutaneous coronary intervention, coronary artery bypass graft, deep vein thrombosis/pulmonary embolism since enrolling in Study CGAL or Study CGAM and prior to V2 of Study CGAR, or have planned cardiovascular surgery or percutaneous coronary angioplasty or surgery for peripheral arterial disease.

c. Any lifetime history of vasospastic angina or stroke, or history of emergency room visit for chest pain in which an ischemic or cardiac event was not ruled out since enrolling in Study CGAL or Study CGAM and prior to V2 of Study CGAR.

d. Clinical evidence of peripheral vascular disease (e.g., Buerger's Disease) or a diagnosis of Raynaud's Disease or Raynaud's Phenomenon.

e. Have any history of intracranial or carotid aneurysm, intracranial hemorrhage, or stroke.

f. Have uncontrolled high blood pressure characterized by systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg on 2 or more blood pressure assessments prior to V2 of Study CGAR.

NOTE: Patients who meet the 14(f) blood pressure criteria during Study CGAL or Study CGAM may enroll in Study CGAR if the study investigator deems the finding not clinically significant.

15. Any of the following medical conditions are exclusionary:

a. Have a lifetime history of seizures (except for childhood febrile seizures).

b. Have a history or presence of any other medical illness including but not limited to any cardiovascular, hepatic, respiratory, hematological, endocrine, psychiatric or neurological disease, or any clinically significant laboratory abnormality, that in the judgment of the investigator indicates a medical problem that would preclude study participation.

c. Prior to V2, patients who have an elevation of ≥2× the upper limit of normal (ULN) for alanine aminotransferase (ALT), or ≥1.5× ULN for total bilirubin (TBL) or alkaline phosphatase (ALP) may be retested. The patient's results must be discussed with Lilly Medical and judged not clinically significant prior to enrollment.

NOTE: Patients with TBL ≥1.5× ULN are not excluded if they meet all of the following criteria for Gilbert syndrome:

1. Bilirubin is predominantly indirect (unconjugated) at screening (direct bilirubin within normal limits)
2. Absence of liver disease
3. ALT, aspartate aminotransferase (AST), and ALP ≤1× ULN at screening

4. Hemoglobin not significantly decreased at screening

d. Patients with a history of an intracranial tumor or head trauma must be discussed and judged not to indicate a medical problem that would preclude study participation by Lilly Medical prior to enrollment.

16. Any of the following drug- or alcohol-related conditions are exclusionary:

    a. History of use of psilocybin (mushrooms), LSD, or 2-bromo-LSD within 2 months prior to V2.

    b. Patients with a positive UDS for any substances of abuse prior to enrollment are excluded. Note: One retest may be performed if the UDS is positive for any prescribed substance. However, the results of the retest must be negative at or prior to enrollment at V2.

    c. Drug, alcohol, opioid, or barbiturate abuse/dependence since completing either Study CGAL or Study CGAM (excessive or habitual use as judged by the investigator), or currently using drugs of abuse (including, but not limited to opioids, barbiturates and cannabis), or any prescribed or over-the-counter medication in a manner that the investigator considers indicative of abuse/dependence. This exclusion criterion does not apply to tobacco and caffeine.

17. Employees of Lilly or investigational site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, parent, child or sibling, whether biological or legally adopted.

18. Known hypersensitivity to multiple drugs, monoclonal antibodies or other therapeutic proteins, or to galcanezumab or to any of the inactive ingredients.

19. Patients who were inadvertently enrolled in study CGAL/CGAM may not be eligible for enrollment in CGAR. Approval from Lilly Medical is required.

6.3. Lifestyle Restrictions

Patients are encouraged to abstain from alcohol consumption during active cluster periods.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be considered for rescreen once, with approval from Lilly Medical, for only the following criteria:

- Inclusion Criteria 4
- Exclusion Criteria 7
- Exclusion Criteria 8; patients with inadequate washout may be rescreened following an appropriate washout period.
- Exclusion Criteria 10; patients with inadequate washout may be rescreened following an appropriate washout period.

- Exclusion Criteria 11; patients with unstable mood or anxiety disorders may rescreen once that disorder is appropriately stabilized.
- Exclusion Criteria 12; these screen-fail patients may be considered for rescreen if the following conditions are met:
    - The patient was referred to an appropriate mental health professional and received treatment as necessary.
    - At least 6 months has elapsed since the screen-fail.
    - Are not considered by the investigator to be at significant risk for suicide at time of rescreening.
- Exclusion Criteria 13
- Exclusion Criterion 14(f); patients with uncontrolled high blood pressure may be considered for rescreen once their blood pressure is controlled in the opinion of the investigator and at <160/100; any use of antihypertensive medication and dose must be stable for at least 2 months prior to V2.
- Exclusion Criteria 16(b): If a patient fails eligibility due to a positive UDS, the patient may be considered for rescreen.

7. Treatments

7.1. Treatments Administered

All eligible subjects will receive galcanezumab 300 mg during the treatment phase (SP II). The treatment will be administered as three injections each containing 100 mg/1.0 mL by site personnel, during SPII.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the investigational agent(s) to the site personnel
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection
- returning all unused medication to Lilly or its designee at the end of the study

Note: In some cases, sites may destroy the material if, during the investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose clinical trial materials.

Possible injection sites include the abdomen, thigh, and upper arm. Buttocks may also be used, if more appropriate for SC injection than the other sites.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

7.1.1. Packaging and Labelling

Galcanezumab for injection, 100 mg/1.0 mL, will be supplied by the sponsor as disposable manual prefilled syringes (during SP II) in accordance with Current Good Manufacturing Practice (cGMP).

Packaging, Preparation, Labeling, and Storage

Galcanezumab solution for injection will be supplied by the sponsor or its designee in accordance with cGMP. Galcanezumab will be supplied as an injectable solution in 1-mL, single-dose, disposable manual syringes. Each syringe of galcanezumab will be designed to deliver 100 mg of galcanezumab. The disposable manual prefilled syringes of galcanezumab for injection, 100 mg/1.0 mL should be stored in the refrigerator (2° C to 8° C). The disposable manual prefilled syringes should be removed from the refrigerated storage and allowed to equilibrate to room temperature for approximately 30 minutes before administration.

Administration of Galcanezumab Using Disposable Manual Prefilled Syringe

Injections will be administered by the clinical staff. A dose will consist of three 1-mL disposable manual prefilled syringes, with each syringe containing 100 mg of galcanezumab, for a total of 300 mg galcanezumab.

7.1.2. Medical Devices

The manufactured medical device provided for use in this study is a disposable manual prefilled syringe.

7.2. Method of Treatment Assignment

All patients will receive the same treatment: galcanezumab 300 mg.

7.2.1. Selection and Timing of Doses

Investigational product (galcanezumab) will be administered as 3 SC injections of not more than once monthly during SP II at the discretion of the investigator. Less than 28 days between doses is a protocol violation.

Investigational product injections should only be administered after all other study procedures are completed for the given visit.

7.3. Blinding

This is an open-label study.

7.4. Dosage Modification

Not applicable.

7.5. Preparation/Handling/Storage/Accountability

Please refer to Section 7.1.1.

7.6. Treatment Compliance

To ensure treatment compliance, investigational product will be administered by site personnel. To document treatment administration each injection must be documented in the electronic case report form (eCRF) and follow the Schedule of Activities (Table 2.1).

7.7. Concomitant Therapy

The list of allowed/not allowed medications and procedures is provided separately in the Protocol Operations Manual. Patients should be instructed to consult with the investigator or study coordinator at the site before taking any new prescribed medications, over-the-counter (OTC) medications, or supplements. If the need for other concomitant medication arises, inclusion or continuation of the patient in the study may be at the discretion of the investigator after consultation with Lilly CRP/CRS or delegate.

7.8. Treatment After the End of the Study

7.8.1. Study Extensions

Not applicable.

7.8.2. Continued Access

Not applicable.

7.8.3. Special Treatment Considerations

Not applicable.

7.8.4. Patient Follow-Up in Pragmatic Trials

Not applicable.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

All patients are free to withdraw from participation in this study at any time and for whatever reason, specified or unspecified, and without prejudice.

Patients who discontinue early from the study should complete study procedures listed in Event List F in the Schedule of Activities.

8.1.1. Temporary Discontinuation from Study Treatment

This protocol allows for temporary interruption of treatment, based on clinical symptoms of efficacy and response as judged by the investigator (Section 5.1). Dosing in this scenario may be re-initiated at the study investigator's discretion. If dosing is temporarily interrupted due to a potential safety concern, dosing may be re-initiated at the study investigator's discretion following a discussion and agreement between the study investigator and Lilly Medical that re-initiation of dosing is appropriate.

8.1.2. Discontinuation of Inadvertently Enrolled

If the sponsor or investigator identify a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the sponsor CRP and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product.

8.2. Discontinuation from the Study

All patients may continue in the study and receive treatment with galcanezumab based on the study investigator's judgment of clinical symptoms and response until the end of the study (described in Section 5.3). In addition, the study investigator should consider study discontinuation for an individual patient for the following:

- Lack of benefit. The study physician should consider whether the patient is deriving benefit from galcanezumab.
- Safety concerns, including evaluation of overall risk-benefit.
- The investigator decides that the patient should be discontinued from the study for another reason.
- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).

- Subject decision. The patient requests to be withdrawn from the study.

Discontinuation of the investigational product for abnormal liver tests should be considered by the investigator when a patient meets 1 of the following conditions after consultation with the Lilly designated medical monitor:

- ALT or AST >8X ULN
- ALT or AST >5X ULN for more than 2 weeks
- ALT or AST >3X ULN and TBL level >2× ULN or prothrombin time >1.5X ULN
- ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

It is also recommended to consider discontinuation in a patient with ALP elevation which meets 1 of the following criteria and is deemed to be of liver origin and drug related:

- ALP >3X ULN
- ALP >2.5X ULN and TBL >2X ULN
- ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Patients who discontinue from the study early will have end-of-therapy procedures performed as shown in Event List F in the Schedule of Activities (Table 2.1).

8.3. Lost to Follow-Up

A patient will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site. Diligent attempts will be defined in the Protocol Operations Manual.

9. Study Assessments and Procedures

Section 2 lists the Visit Flow Diagram and Schedule of Activities, with the study procedures and their timing.

Appendix 2 lists the laboratory tests that will be performed for this study.

Appendix 3 lists the hepatic monitoring tests for treatment-emergent abnormalities for this study.

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

The Patient Global Impression of Improvement (PGI-I) requests patients to mark the box that best describes your cluster headache condition since you started taking this medicine. The options in the displayed boxes are represented on a seven-point scale, with 1=very much better and 7=very much worse (Guy 1976).

9.1.1. Appropriateness of Assessments

All efficacy and safety assessments have been well documented and are generally regarded as reliable, accurate, and relevant in this patient population.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the patient to discontinue the investigational product before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the informed consent form (ICF) is signed, study site personnel will record via eCRF the occurrence and nature of each patient's pre-existing conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should

record their assessment of the potential relatedness of each AE to protocol procedure, investigational product, via eCRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to investigational product, study device, or a study procedure, taking into account the disease, concomitant treatment or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, study device and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a patient's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF clarifying if possible, the circumstances leading to discontinuations of treatment.

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in 1 of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason: important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious, based upon appropriate medical judgment.
- when a condition related to the disposable manual prefilled syringe necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned.

Although all AEs occurring after signing the ICF are recorded in the eCRF, SAE reporting begins after the patient has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, it needs to be reported ONLY if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus. Pregnancy cases should be reported up to 5 months after last investigational product administration.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the patient summary eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Commission Clinical Trial Directive 2001/20/EC (United States Government Publishing Office [WWW]; European Commission [WWW]) and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.1.2. Adverse Event Monitoring with the Columbia-Suicide Severity Rating Scale, Self-Harm Supplement Form, and Self-Harm Follow-up Form

The C-SSRS and SHSF will be administered to assess and evaluate patients for suicide-related events (behavior and/or ideation) at every scheduled and unscheduled office visit as specified in the Schedule of Activities (Table 2.1). Before administering the C-SSRS (Posner et al. 2011), study site personnel will question the patient about any change in the pre-existing condition(s) and the occurrence and nature of any AEs. Nonserious AEs obtained through the questionnaire are recorded and analyzed separately. Only *serious* AEs and AEs leading to discontinuation elicited through the C-SSRS are to be recorded as AEs via eCRF. Serious adverse events must be reported to Lilly or its designee within 24 hours as SAEs. The SHSF captures the number of discrete events of suicidal behavior, possible suicidal behavior, or nonsuicidal self-injurious behavior recorded in the C-SSRS and must be completed at every visit. Additionally, the SHFU will be completed at any visit, including screening/baseline visits, when a suicidal or nonsuicidal self-injurious behavior is identified. At any time during the study, if a patient is considered to be at significant risk for suicide by the investigator, prompt referral of the patient to a mental health professional should be considered.

9.2.2. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Clinical staff must report a product complaint to the sponsor if a product quality issue is noted. Timeline expectations and instructions on how to report a product quality complaint are located on the provided study specific product complaint form. For an SAE attributable to a product quality issue or defect, the complaint must be reported within the same timeframe as the SAE.

9.3. Treatment of Overdose

Data not available.

9.4. Safety

9.4.1. Electrocardiograms

For each patient, 12-lead digital ECGs will be collected according to the Schedule of Activities (Table 2.1) as single ECGs for overread. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the subject meets entry criteria and for immediate subject management, should any clinically relevant findings be identified. Electrocardiograms may be obtained at additional times, when deemed clinically necessary.

Electrocardiograms will have a central overread. The investigator (or qualified designee) must document his/her review of the ECG printed at the time of evaluation, the final overread ECG report issued by the central ECG laboratory, and any alert reports.

9.4.2. Vital Signs

Blood pressure and pulse will be collected in triplicate according to the Schedule of Activities (

Table 2.1) and at unscheduled office visits. All sites will be provided with an automated blood pressure machine with several cuff sizes. The following guidelines will be used by investigative sites when measuring vital signs:

- Blood pressure and pulse must be measured before any blood draws.
- Blood pressure will be measured in sitting position with both feet resting on the floor after the patient has rested for at least 5 minutes.
- Blood pressure will be measured with a cuff that is appropriate to the size of the patient.
- Use the same arm for blood pressure collection throughout the study.
- Arm with cuff must be supported at approximately the heart level.
- Three sitting blood pressures and pulse measurements will be collected at approximately 30 to 60 second intervals.

9.4.3. Laboratory Tests

For each patient, laboratory tests detailed in (Appendix 2) should be conducted according to the Schedule of Activities Table 2.1).

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the patient receives the first dose of investigational product should be reported to Lilly or its designee as an AE via eCRF.

9.4.4. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CRP/clinical research scientist (CRS) will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist, and periodically review:

- trends in safety data
- laboratory analytes
- AEs including monitoring of injection site reactions, allergic reactions, and infections

If a study patient/subject experiences elevated ALT ≥3× ULN, ALP ≥2× ULN or elevated TBL ≥2× ULN, clinical and laboratory monitoring should be initiated by the investigator. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient/subject safety and comply with regulatory guidance, the investigator is to consult with the Lilly designated medical monitor regarding collection of specific recommended clinical information and follow-up laboratory tests (Appendix 3).

9.4.5. Samples for Immunogenicity Research

Where local regulations and ethical review boards (ERB) allow, blood samples for immunogenicity testing will be collected to determine antibody production against galcanezumab as specified in the Schedule of Activities (Table 2.1). Immunogenicity will be assessed by a validated assay designed to detect anti-drug antibody (ADAs) in the presence of the investigational product. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the investigational product.

Anti-drug antibody sampling will be initiated immediately prior to first patient dosing with galcanezumab (baseline). Immunogenicity samples must be collected prior to dose administration if the visit is a dosing visit, and the timing of all samples will be recorded.

Samples will also be drawn in the event of early termination or as needed given any safety concerns judged to potentially immunologically mediated.

Samples

Samples will be drawn at Month 0 (first dose), Month 1, Month 6, and then every 6 months, thereafter; prior to dosing unless dosing is temporarily halted due to a clinical efficacy response. When dosing is temporarily halted due to a clinical efficacy response, an immunogenicity sample is scheduled for 1 month after the last dose of galcanezumab. When dosing is resumed, an immunogenicity sample is drawn prior to dosing (Section 2, Schedule of Activities). Additionally, at study termination samples will be drawn approximately 1 month after the last dose of galcanezumab.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if regulations and ERBs impose shorter time limits, at a facility selected by Lilly. The duration allows the sponsor to respond to future regulatory requests related to the investigational product.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities Table 2.1), venous blood samples of approximately 3 mL each will be collected to determine the serum concentrations of galcanezumab.

A maximum of 3 samples per patient may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time of each sampling will be recorded.

Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 1 year following last patient visit for the study.

A validated assay will be used to determine galcanezumab concentrations. Samples will be analyzed at a laboratory approved by the sponsor.

9.6. Pharmacodynamics

Not applicable.

9.7. Pharmacogenomics and Genetics

Not applicable.

9.8. Biomarkers

There are no biomarkers to be collected.

9.9. Health Economics

The self-reported questionnaires will be administered according to the Schedule of Activities (Table 2.1) in countries where the questionnaires have been translated into the native language of the region and linguistically validated.

European Quality of Life Questionnaire 5-Dimensions 5-Levels (EQ-5D-5L) (EuroQoL Group): A generic, multidimensional, health-related, quality-of-life instrument that contains 2 parts: a health status profile and a VAS to rate global health-related quality of life. The profile allows patients to rate their health state on that day within 5 domains, including: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Brooks 1996; Herdman et al. 2011; Stafford et al. 2012). A single score between 1 and 5 is generated for each domain with all 5 domains being mapped to a single index through an algorithm (Van Reenen and Janssen 2015). The index ranges between 0 and 1 with the higher score indicating a better health state perceived by the patient. The VAS provides an overall patient rating of health status on that day, with a range from 0 (i.e., "worst imaginable health state") to 100 (i.e., "best imaginable health state") serving as anchors for the patient's numeric rating on the hash-marked, vertical VAS.

The EQ-5D-5L and cluster headache status data (Section 9.10) will be used to characterize changes in the health status of patient groups. The PGI-I, and other patient characteristics or clinical information may also be used to define specific patient groups associated with EQ-5D-5L outcomes.

9.10. Cluster Headache Attack Assessments

The cluster headache status questions will collect information on the following: if a patient is currently in a bout, the duration of the current bout or time since the last bout; and questions related to attacks that occurred over a 24-hour period (i.e., yesterday from midnight to midnight). Patients will be asked to record the number of cluster headache attacks during that time period, information regarding abortive medication use, cluster headache attack duration, and cluster headache attack pain severity will also be recorded. Pain severity will be rated using a 5-point pain scale, where 0=no pain, 1=mild pain, 2=moderate pain, 3=severe pain, and 4=very severe pain. Patients should record all cluster attacks regardless of attack duration.

10. Statistical Considerations

10.1. Sample Size Determination

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 Study CGAL or Study CGAM. Therefore, the sample size is determined by the number of patients completing Studies CGAL and CGAM who choose to enroll in this study.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Evaluable	All enrolled patients who take at least 1 dose of investigational product.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. Details of statistical analysis methods will be described in the statistical analysis plan (SAP) document.

Efficacy and safety analyses will be conducted on the evaluable analysis set. The evaluable analysis set includes all enrolled patients receiving at least 1 dose of the investigational product.

Baseline will be the time prior to receiving the first dose in this study. Additional baselines may be further outlined in the SAP along with details related to missing data.

Safety and efficacy analyses will be evaluated based on a 2-sided significance level of 0.05 unless otherwise stated. The 95% confidence intervals (CI) for the change from baseline will be presented. There will be no adjustments for multiplicity.

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.

10.3.2. Treatment Analyses

10.3.2.1. Patient Disposition

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

10.3.2.2. Patient Characteristics

The following information will be recorded at baseline and will be summarized for all enrolled patients.

- Demographics (age, gender, race, ethnicity, height, weight, body mass index [BMI]); Note: Age, gender, race, and ethnicity will be based upon the information from the parent trial.
- Baseline disease characteristic.
    - 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
- Medical history and pre-existing conditions

10.3.2.3. Concomitant Therapy

The proportion of patients who receive concomitant medication will be summarized.

10.3.3. Efficacy Analyses

The proportion and exact 95% CI 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.

Additional analysis of the PGI-I will be included in the SAP.

10.3.4. Safety Analyses

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

- AEs
    - TEAEs
        - By preferred term (PT)
        - By system organ class (SOC)
        - By maximum severity
        - By outcome
        - Considered to be related to treatment by investigator
    - SAEs
    - AEs leading to discontinuation
- Suicidal ideation and behaviors assessed by solicited questioning using the C-SSRS
- Vital signs and weight
- ECGs
- Laboratory measurements

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

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. 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 the specific post-baseline phase. For each patient and TEAE, the maximum severity for the MedDRA level being displayed (PT, High level Term, or SOC) is the maximum post-baseline severity observed from all associated LLTs mapping to that MedDRA level.

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

Suicidal ideation, suicidal behavior, and non-suicidal self-injurious behavior based on the C-SSRS will be summarized. For each of the following events, the number and percentage of patients with the event will be enumerated: completed suicide, non-fatal 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 (not planned) without intent to act, nonspecific active suicidal thoughts, wish to be dead, and non-suicidal self-injurious behavior. In addition, the number and percentage of patients who experienced at least 1 of the composite measures during SP II will be presented. These include suicidal acts (completed suicide and nonfatal suicidal attempts), suicidal behavior (suicidal acts, interrupted attempts, aborted attempts, and preparatory acts or behavior), treatment-emergent suicidal ideation or treatment-emergent suicidal behavior.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Galcanezumab concentrations will be illustrated graphically and summarized descriptively. If warranted and based on availability of data, the exposure-response relationship of serum galcanezumab concentrations to efficacy endpoints and/or safety endpoints may be explored.

Patient and healthy subject data from other clinical studies evaluating galcanezumab may be combined with data from this study to support additional analyses. Such analyses may be reported separately.

10.3.6. Other Analyses

10.3.6.1. Health Economics

Each time point where the EQ-5D-5L survey is administered per the Schedule of Activities (Table 2.1), the 5 domain items (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) will be summarized as follows:

- The sample size (n), mean, standard deviation, median, minimum, and maximum values will be reported.
- Proportions within each of the categorical outcomes for the 5 domains

- In addition, the percentage of patients with 'problems' (combined levels 2 through 5) and the percentage with 'no problems' (level 1) with be reported.

Each time point where the EQ-5D-5L survey is administered per the Schedule of Activities (Table 2.1), the single index score (computed using the algorithm) and the VAS score will be summarized as follows:

The sample size (n), mean, standard deviation, median, minimum, and maximum values will be reported. Changes from the start of treatment (first dose) to the stopping of treatment, and other time points when the EQ-5D-5L are collected, will also be analyzed; clinical variables and country effects will be considered.

10.3.7. Immunogenicity Analyses

Refer to the SAP for details.

10.3.8. Interim Analyses

Interim analyses may occur during the course of the study because of regulatory submission and as required for the evidence dossier for healthcare technology assessment bodies. Any interim analysis will be documented including timing and data included.

11. References

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	anti-drug antibody
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ART-01	I5Q-MC-ART1
AST	aspartate aminotransferase
AV	atrioventricular
BMI	body mass index
BUN	blood urea nitrogen
C-SSRS	Columbia-Suicide Severity Rating Scale
CGAB	I5Q-MC-CGAB
CGAL	I5Q-MC-CGAL
CGAM	I5Q-MC-CGAM
CGAR	I5Q-MC-CGAR
cGMP	current good manufacturing practice
CGRP	calcitonin gene-related peptide
CI	confidence interval
CIDBF	capsaicin-induced dermal blood flow
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.

CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRS	clinical research scientist
CSR	clinical study report
ECG	electrocardiogram
eCRF	electronic case report form
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the ICF directly or through their legally acceptable representatives.
EQ-VAS	European Quality Visual Analogue Scale
EQ-5D-5L	European quality 5-dimensions 5-levels
ERB	Ethical Review Board
EuroQoL	European quality of life
FSH	follicle stimulating hormone
GCP	good clinical practice
HbA_{1c}	hemoglobin A1C
IB	Investigator's Brochure
ICF	informed consent form
ICHD-3	International Classification of Headache Disorders, Third edition, beta version
ICH	International Conference on Harmonisation
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
Lilly	Eli Lilly and Company
LLT	lowest level term
LSD	Lysergic acid diethylamide

MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
PGI-I	Patient Global Impression of Improvement
PK/PD	pharmacokinetics/pharmacodynamics
PT	preferred term
Q2W	every two weeks
QT	QT interval
QTc	corrected QT interval
QTcB	Corrected QT interval (Bazett's Formula)
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SHSF	Self-Harm Supplement Form
SHFU	Self-Harm Follow-up Form
SOC	system organ class
SP	study phase
SP I	screening phase
SP II	open-label treatment phase
SUSARs	suspected unexpected serious adverse reactions
TBL	total bilirubin
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, which and does not necessarily have to have a causal relationship with this treatment.
UA	unstable angina
ULN	upper limit of normal
UDS	urine drug screen

V	visit
VAS	visual analogue scale

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology:	**Clinical Chemistry:**
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume	Total bilirubin
Mean cell hemoglobin concentration	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase
Neutrophils, segmented	Alanine aminotransferase (ALT)
Lymphocytes	Aspartate aminotransferase (AST)
Monocytes	Blood urea nitrogen (BUN)
Eosinophils	Creatinine
Basophils	Uric acid
Platelets	Calcium
HbA_{1C}	
	Glucose
Urinalysis:	Albumin
Specific gravity	Creatine kinase (CK)
pH	Total Cholesterol
Protein	
Glucose	
Ketones	**Other**
Blood	PK Sample (galcanezumab serum concentration
Urine leukocyte esterase	determination)
	Immunogenicity
	Urine Drug Screen[a]
	Pregnancy Test[a] (females only)
	Serum pregnancy or FSH
	Urine pregnancy testing

Abbreviations: FSH = follicle-stimulating hormone; PK = pharmacokinetic; RBC = red blood cells; WBC = white blood cells.

[a] May be repeated during the study at the discretion of the investigator.

Appendix 3. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly, or its designee, clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	**Alkaline phosphatase isoenzymes[a]**
GGT	**Anti-Actin antibody[a]**
CPK	**Anti-smooth muscle antibody[a]**

Abbreviations: ALT = alanine aminotransferase; AST = aspirate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

a Assayed by Lilly-designated or local laboratory.

b Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Appendix 4. Study Governance Considerations

Appendix 4.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 4.1.1. Informed Consent

The investigator is responsible for ensuring:

- that the patient understands the potential risks and benefits of participating in the study.
- that informed consent is given by each patient. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

Appendix 4.1.2. Ethical Review

The investigator must give assurance that the ERB was properly constituted and convened as required by International Conference for Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP.

The study site's ERB(s) should be provided with the following:

- the current IB and updates during the course of the study
- ICF
- relevant curricula vitae

Appendix 4.1.3. Regulatory Considerations

This study will be conducted in accordance with:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- applicable ICH GCP Guidelines
- applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third-party.

Appendix 4.1.4. Investigator Information

Licensed physicians with a specialty including, but not limited to, neurology and headache specialists will participate as investigators in this clinical trial.

Appendix 4.1.5. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Appendix 4.1.6. Final Report Signature

The CSR coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

The sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Appendix 4.2. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate eCRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Appendix 4.2.1. Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Electronic case report form data will be encoded and stored in a clinical trial database.

Data managed by a central vendor, such as laboratory test data or ECG data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

Appendix 4.3. Study and Site Closure

Appendix 4.3.1. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 4.3.2. Discontinuation of the Study

The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 5. Protocol Amendment Summary: I5Q-MC-CGAR(a)

Overview

Protocol I5Q-MC-CGAR(a), a Phase 3b Multicenter, Single-Arm, Open Label Safety Study of LY2951742 (galcanezumab) in Patients with Episodic or Chronic Cluster Headache, has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- Revised Exclusion Criterion 14a to allow for medical judgment in determining exclusion from Study CGAR based on abnormal ECG findings in Study CGAL or Study CGAM.
- Revised Exclusion Criterion 14e because intracranial or carotid aneurysm, intracranial hemorrhage, and stroke are cardiovascular-related conditions, whereas intracranial tumor and significant head trauma are not cardiovascular related. Patients with either of the non-cardiovascular-related conditions mentioned here may be enrolled in the clinical trial if upon discussion with Lilly Medical it is judged not to indicate a medical problem that would preclude study participation (see Exclusion Criterion 15d). This revision aligns Study CGAR with Study CGAL and Study CGAM.
- Revised Exclusion Criterion 14f to allow for medical judgment in determining exclusion from CGAR based on blood pressure readings in Study CGAL or Study CGAM. This revision provides study investigators with the flexibility to employ medical judgment in determining exclusion of patients with inconsistent blood pressure readings during participation in Study CGAL and Study CGAM.
- Revised Exclusion Criterion 15c to allow patients who fail eligibility due to an elevation of ≥2X ULN for ALT, or ≥1.5X ULN TBL or ALP to be retested. The patient's results must be discussed and judged not clinically significant by Lilly Medical prior to enrollment. This revision aligns Study CGAR with Study CGAL and Study CGAM.
- Added Exclusion Criterion 15d to allow for patients with a history of intracranial tumor or head trauma to be enrolled in Study CGAR based on medical discretion. This addition aligns Study CGAR with Study CGAL and Study CGAM.
- Section 6.4 was revised to allow for rescreening of patients who fail eligibility due to a positive UDS.
- Revised protocol text in Section 3.1, Section 5.1, and Section 8.1 to clarify study discontinuation for those patients whose dosing is temporarily interrupted for potential safety concerns. For these patients, the site investigator in consultation with Lilly Medical will determine if dosing can resume for the patient whose potential safety concern is either ruled out, resolved, or otherwise treated. This revision will allow patients who experience a temporary or unconfirmed medical condition and would otherwise be discontinued from Study CGAR to continue to receive treatment as long as

the site investigator, in consultation with Lilly Medical, determines that it is appropriate to do so.

- Minor editorial changes to correct errors or clarify content were made throughout the protocol.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

3.1 Study Rationale

Study CGAR is a Phase 3b study to assess the long-term safety and tolerability of galcanezumab 300 mg in patients with episodic or chronic cluster headache who have completed one of the Phase 3 double-blind, placebo-controlled studies, CGAL or CGAM.

Study CGAR will implement a dosing strategy to more closely approximate what may occur in clinical practice. For each patient, the study investigator will determine whether or not to dose galcanezumab 300 mg at each monthly interval based on clinical symptoms and response. Dosing will be no more frequent than once per month, and the investigator may choose to not dose galcanezumab for 1 or more months at their clinical discretion based on clinical efficacy. As such, some patients may receive monthly long-term treatment with galcanezumab for a period of months or years during the study, while others may have 1 or more months of galcanezumab dose-free intervals based on the investigator's judgment of clinical efficacy. ~~If, however, the investigator stops monthly dosing due to safety concerns, dosing with galcanezumab should not be resumed.~~

5.1 Overall Design

Study Phase II: SP II is the single-arm open-label treatment phase during which patients can receive galcanezumab 300 mg administered SC up to once a month. If a patient meets all eligibility requirements, a urine pregnancy screen will be conducted at the first dosing visit, prior to dosing to confirm that a female patient is not pregnant before administering investigational product. Following the first dose of galcanezumab, the patient should remain in the office for 30 minutes of observation. The site will have a scheduled telephone visit (V~~2~~3) with the patient approximately 1 week after the first investigational product administration to collect spontaneously reported AEs.

Every month, the decision whether to administer a monthly dose will be based upon the study investigator's judgment, which is not limited to, but includes assessment of the patient's clinical symptoms and response as follows:

- Dosing is up to once monthly; more frequent dosing is not allowed. The full 300 mg dose is to be administered, changing the dose amount is not allowed.
- If the patient remits and dosing is halted, the patient may remain in the study, but they should have an office visit 1 month after the last dose to complete the procedures listed in Event List F (Table 2.1).–Dosing in this scenario may be re-initiated at the study investigator's discretion.

- Monthly telephone visits should be completed for patients who are not being dosed, but remain in the study (e.g., in remission).
- ~~Dosing may be re-initiated at the study investigator's discretion, as long as dosing was not halted due to a safety concern, and should be based upon the patient experiencing a cluster headache attack or the anticipated onset of a cluster headache period/bout, based on the patient's history (for example, the anticipated onset of a new cluster period in the spring based on a patient's history of spring-onset cluster periods).~~ If dosing is temporarily interrupted due to a potential safety concern, dosing may be re-initiated at the study investigator's discretion following a discussion and agreement between the study investigator and Lilly Medical that re-initiation of dosing is appropriate.
    - At the office visit **prior to re-initiation of dosing** the following procedures: ECG, immunogenicity, pharmacokinetics (PK), hematology, clinical chemistry, HbA1c and urine pregnancy are to be collected. The urine pregnancy must be negative and the ECG should be evaluated for safety prior to dosing.
- ~~**If dosing is halted for a safety reason, the patient should be discontinued (Section 8.2).**~~

6.1 Inclusion Criteria

1. Patients who **participated in and completed** either Study CGAL or Study CGAM. A study completer is defined as follows:
    a. Study CGAL: a patient who has completed the double-blind treatment and post-treatment follow-up phases.
    b. Study CGAM: a patient who has completed the double-blind treatment, open-label extension and post-treatment follow-up phases. However, if a patient entered Study CGAM prior to Study CGAR being open for enrollment, they will be considered a completer if they completed the double-blind treatment and post-treatment follow-up phases (e.g., opted not to participate in the open-label extension).

6.2 Exclusion Criteria

8. Use of therapeutic antibodies (except galcanezumab) during the course of the study (~~for example,~~ adalimumab, infliximab, trastuzumab, bevacizumab, etc.). Prior use of other therapeutic antibodies is allowed if an adequate washout has occurred (≥5 half-lives) prior to V2.

14. Any of the following cardiovascular-related conditions are exclusionary:
    a. Since enrolling in Study CGAL or Study CGAM or prior to V2 (enrollment), have ECGs showing acute abnormalities of:
        i. evidence of delayed ventricular repolarization including but not limited to a corrected QT (Fridericia's QT interval [QTcF]) interval >470 msec for women and >450 for men, **and/or**

ii. evidence of atrioventricular (AV) depolarization of PR>220, or conduction delay of QRS>120, **and/or**

iii. evidence of ischemia or any of the qualitative findings indicative of ST or J-point elevation, excluding those findings consistent with early repolarization (non-ischemic).

NOTE: Patients who meet 1 of the 14(a) ECG criteria during Study CGAL or Study CGAM may enroll in Study CGAR if the study investigator deems the finding not clinically significant.

b. History of myocardial infarction (MI), unstable angina (UA), percutaneous coronary intervention, coronary artery bypass graft, deep vein thrombosis/pulmonary embolism since enrolling in Study CGAL or Study CGAM and prior to V2 of Study CGAR, or have planned cardiovascular surgery or percutaneous coronary angioplasty or surgery for peripheral arterial disease.

c. Any lifetime history of vasospastic angina or stroke, or history of emergency room visit for chest pain in which an ischemic or cardiac event was not ruled out since enrolling in Study CGAL or Study CGAM and prior to V2 of Study CGAR.

d. Clinical evidence of peripheral vascular disease (e.g., Buerger's Disease) or a diagnosis of Raynaud's Disease or Raynaud's Phenomenon.

e. Have any history of intracranial or carotid aneurysm, intracranial hemorrhage, or stroke. ~~, intracranial tumors or significant head trauma.~~

f. Have uncontrolled high blood pressure characterized by systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg on 2 or more blood pressure assessments prior to V2 of Study CGAR.

NOTE: Patients who meet the 14(f) blood pressure criteria during Study CGAL or Study CGAM may enroll in Study CGAR if the study investigator deems the finding not clinically significant.

15. Any of the following medical conditions are exclusionary:

a. Have a lifetime history of seizures (except for childhood febrile seizures).

b. Have a history or presence of any other medical illness including but not limited to any cardiovascular, hepatic, respiratory, hematological, endocrine, psychiatric or neurological disease, or any clinically significant laboratory abnormality, that in the judgment of the investigator indicates a medical problem that would preclude study participation.

c. Prior to V2, patients who have an elevation of ≥2× the upper limit of normal (ULN) for alanine aminotransferase (ALT), or ≥1.5× ULN for total bilirubin (TBL) or alkaline phosphatase (ALP) may be retested. The patient's results must be discussed with Lilly Medical and judged not clinically significant prior to enrollment.

NOTE: Patients with TBL ≥1.5× ULN are not excluded if they meet all of the following criteria for Gilbert syndrome:

1. Bilirubin is predominantly indirect (unconjugated) at screening (direct bilirubin within normal limits)
2. Absence of liver disease
3. ALT, aspartate aminotransferase (AST), and ALP ≤1× ULN at screening
4. Hemoglobin not significantly decreased at screening

d. Patients with a history of an intracranial tumor or head trauma must be discussed and judged not to indicate a medical problem that would preclude study participation by Lilly Medical prior to enrollment.

6.4 Screen Failures

Exclusion Criteria 16(b): If a patient fails eligibility due to a positive UDS, the patient may be considered for rescreen.

8.1.1 Temporary Discontinuation from Study Treatment

This protocol allows for temporary interruption of treatment, based on clinical symptoms of efficacy and response as judged by the investigator (Section 5.1). Dosing in this scenario may be re-initiated at the study investigator's discretion. ~~Temporary discontinuation of treatment due to safety concerns or AEs is not allowed; discontinuation of treatment due to safety concerns or AEs will be considered permanent discontinuation of treatment and the patient must not be subsequently re-started on investigational product (Section 8.2).~~ If dosing is temporarily interrupted due to a potential safety concern, dosing may be re-initiated at the study investigator's discretion following a discussion and agreement between the study investigator and Lilly Medical that re-initiation of dosing is appropriate.

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