Protocol: I5Q-MC-CGAX(a)

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Galcanezumab in Patients with Episodic Migraine – the PERSIST Study

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Approval Date: 10-Jan-2020

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Galcanezumab (LY2951742)

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Protocol Electronically Signed and Approved by Lilly: 29-Sep-2018 GMT.
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Approval Date: 10-Jan-2020 GMT

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1. Synopsis

Title of Study:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Galcanezumab in Patients with Episodic Migraine (EM) – the PERSIST Study.

Rationale:
Study I5Q-MC-CGAX (CGAX; PERSIST) is designed to evaluate the efficacy and safety of galcanezumab, in the prevention of migraine compared with placebo in patients with EM in multiple regions. Episodic migraine is defined as 4 to 14 migraine headache days (MHDs) (with or without aura) per month.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary To test the hypothesis that galcanezumab (240-mg loading dose followed by 120 mg monthly) is superior to placebo in the prevention of migraine in patients with EM.	The overall mean change from baseline in the number of monthly MHDs during the 3-month double-blind treatment phase.
Secondary Objectives	
• To compare galcanezumab with placebo with respect to a 30% response rate	• The overall proportion of patients with ≥30% reduction from baseline in monthly MHDs during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to 50% response rate	• The overall proportion of patients with ≥50% reduction from baseline in monthly MHDs during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to 75% response rate	• The overall proportion of patients with ≥75% reduction from baseline in monthly MHDs during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to 100% response rate	• The overall proportion of patients with a 100% reduction from baseline in monthly MHDs during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to distribution of response rates	• Cumulative distribution of monthly MHDs response rates during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to change in functioning	• The overall mean change of Months 1 to 3 from baseline in the Role Function-Restrictive domain score of the Migraine-Specific Quality-of-Life Questionnaire version 2.1 (MSQ v2.1)

Objectives (cont.)	Endpoints (cont.)
Secondary Objectives (cont.)	
• To compare galcanezumab with placebo with respect to change in use of acute headache treatment	• The overall mean change from baseline in the number of monthly MHDs taking medication for the acute treatment of headache during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to change in headache days	• The overall mean change from baseline in the number of monthly headache days during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to change in moderate to severe headache days	• The overall mean change from baseline in the number of monthly moderate to severe headache days during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to time to 50% response	• Time to first occurrence of a ≥50% reduction from baseline in the number of monthly MHDs (Kaplan-Meier analysis)
• To compare galcanezumab with placebo with respect to onset of effect	• The initial month at which statistical separation in mean change from baseline in the number of monthly MHDs is demonstrated and maintained at all subsequent months through Month 3
• To compare galcanezumab with placebo with respect to onset of 50% sustained response	• The initial month at which statistical separation in the proportion of patients meeting at least a 50% reduction in monthly MHDs that is maintained at all subsequent months through Month 3
• To compare galcanezumab with placebo with respect to maintenance of 50% response	• The proportion of patients who maintain 50% response criteria for all 3 months of double-blind treatment
• To compare galcanezumab with placebo with respect to changes in other efficacy parameters, specifically: o International Classification of Headache Disorders (ICHD) MHDs o migraine attacks o migraine headache hours o headache hours o severity of remaining migraines	• Overall mean change from baseline (during the 3-month double-blind treatment phase) on the following monthly measures: o ICHD MHDs o migraine attacks o migraine headache hours o headache hours o severity of remaining migraines

Objectives (cont.)	Endpoints (cont.)
Secondary Objectives (cont.)	
• To compare galcanezumab with placebo with respect to change in patients' global impression of migraine severity	• Mean change from baseline in the Patient Global Impression of Severity (PGI-S) at Month 3
• To compare galcanezumab with placebo with respect to changes in disability and quality of life	• Mean change from baseline to Month 3 on the Migraine Disability Assessment test (MIDAS) total score and individual items • Overall mean change from baseline during Months 1 to 3 on MSQ v2.1 total score, and Role Function-Preventive and Emotional Function domain scores
• To compare galcanezumab with placebo with respect to safety and tolerability	• Analysis of: o treatment-emergent adverse events (TEAEs) o serious adverse events (SAEs) o discontinuation due to adverse events (AEs) o discontinuation rates o vital signs and weight o electrocardiograms (ECGs) o laboratory measures
• To evaluate the immunogenicity of galcanezumab	• Incidence and consequences of anti-drug antibodies and neutralizing anti-drug antibodies to galcanezumab
• To evaluate the pharmacokinetics of galcanezumab	• Serum concentrations of galcanezumab

Summary of Study Design:

A multicenter, randomized, double-blind, parallel, placebo-controlled Phase 3 trial comparing 120-mg galcanezumab with placebo given as subcutaneous injection once monthly over 3 months in patients who meet International Classification of Headache Disorders (ICHD) 3 criteria for a diagnosis of migraine with or without aura (1.1 or 1.2), with 4 to 14 MHDs per month.

Treatment Arms and Duration:

Two treatment arms: galcanezumab (120 mg/month with a 240-mg loading dose at the first injection [administered as 2 injections of 120 mg at Visit 3]) and placebo. Following a prospective baseline (30 to 40 days) period, eligible patients will be randomized in a 1:1 ratio to receive placebo or 120 mg/month of galcanezumab, respectively, and will begin a 3-month double-blind treatment phase. Patients who complete the double-blind period may enter a 3-month open-label extension phase during which all patients will receive galcanezumab 120 mg/month. At Visit 7, patients originally assigned to placebo will receive an initial loading dose of 240-mg galcanezumab; patients originally assigned to galcanezumab will continue the

dose of 120 mg but will receive 2 injections (1 injection of 120-mg galcanezumab and 1 injection of placebo) to maintain blinding. At Visit 8 and Visit 9 of the open-label phase, all patients will receive a 120-mg dose of galcanezumab. All patients will be followed for a 4-month, post-treatment phase during which no study medication will be administered.

Number of Patients:

The study will randomize approximately 486 patients with EM. China, Russia, and India intend to participate in the study.

Statistical Analysis:

Unless otherwise specified, analyses will be conducted on an intent-to-treat (ITT) population, which includes all patients who are randomized and receive at least 1 dose of investigational product. Patients in the ITT population will be analyzed according to the treatment group to which they are randomized. When mean change from baseline is assessed, the patient will be included in the analysis only if the patient has a baseline and postbaseline measurement.

The primary analysis will evaluate the efficacy of galcanezumab compared with placebo on the overall mean change from baseline in the number of monthly MHDs during the 3-month double-blind treatment phase. Migraine headache days will be defined to include both migraine and probable migraine (a headache missing 1 of the migraine features in the International Headache Society [IHS] ICHD-3 definition) days. The primary analysis will be performed using a restricted maximum likelihood based mixed models repeated measures (MMRM) technique. The analysis will include the fixed categorical effects of treatment, country, month, and treatment-by-month interaction, as well as the continuous fixed covariates of baseline number of MHDs and baseline number of MHDs-by-visit interaction.

2. Schedule of Activities

Table CGAX.1. Schedule of Activities
Protocol I5Q-MC-CGAX (Double-Blind Treatment Phase)

Study Period (SP)	SP I-Screening	SP II-Prospective Baseline	SP III Double-Blind Treatment				
(Target) Interval (days) since previous visit			30-45	14	16	30	30
Allowable range (days) between visits	3-45	30-40[a]					
Interval allowance (days)				+/- 5	+/- 2	+/- 2	+/- 2
Visit	1	2	3	4[b]	5[l]	6	7
Month			0	0.5	1	2	3
Assessments and Procedures							
Informed consent	X						
Inclusion/exclusion	X	X	X				
Demographics	X						
Physical examination	X						
Neurological examination[c]	X						X
Height	X						
Weight	X						X
Medical history	X						
Prespecified migraine history[d]			X				
ECG[e]	X		X				X
Vital signs[f]	X		X		X	X	X
Adverse events	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
ePRO and headache medication log training		X					
ePRO diary daily patient entries		X	X	X	X	X	X
Headache medication log		X	X	X	X	X	X

Schedule of Activities
Protocol I5Q-MC-CGAX (Double-Blind Treatment Phase)

Study Period (SP)	SP I-Screening	SP II-Prospective Baseline	SP III Double-Blind Treatment				
(Target) Interval (days) since previous visit			30-45	14	16	30	30
Allowable range (days) between visits	3-45	30-40[a]					
Interval allowance (days)				+/- 5	+/- 2	+/- 2	+/- 2
Visit	1	2	3	4[b]	5[l]	6	7
Month			0	0.5	1	2	3
Clinical Laboratory Tests and Sampling Schedules							
Hematology	X		X				X
Clinical chemistry	X		X				X
HbA1c			X				X
Urinalysis	X		X				X
Serum Pregnancy (for women of childbearing potential) or FSH at Visit 1 (all other female patients)[g]	X						
Urine pregnancy[g]			X		X	X	X
Immunogenicity[h]			X		X		X
PK blood sample[h]					X		X
Study drug administered[i]			X		X	X	X[j]
Scales, Questionnaires, and Outcome Measures							
MIDAS			X				X
MSQ v2.1			X		X	X	X
MIBS-4			X		X	X	X
PGI-S			X				X
GAD-7			X				X
PHQ-9			X				X

Schedule of Activities, Protocol I5Q-MC-CGAX (Open-Label and Post-Treatment Phases)

Study Period (SP)	SP IV Open-Label			SP V Post-treatment		
(Target) Interval (days) since previous visit	30	30	30	60	60	ET[K]
Interval allowance (days)	+/- 2	+/- 2	+/- 2	+/- 5	+/- 5	
Visit	8	9	10	11[b]	12	
Month	4	5	6	8	10	
Assessments and Procedures						
Weight			X		X	X
Neurological examination[c]			X		X	X
ECG[e]			X		X	X
Vital signs[f]	X	X	X		X	X
Adverse events	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X
ePRO diary daily patient entries	X	X	X	X	X	X
Headache medication log	X	X	X	X	X	X
Clinical Laboratory Tests and Sampling Schedule						
Hematology			X		X	X
Clinical chemistry			X		X	X
HbA1c			X		X	X
Urinalysis			X		X	X
Serum Pregnancy (for women of childbearing potential)[g]			X		X	X
Urine pregnancy[g]	X	X				
Immunogenicity[h]			X		X	X
PK blood sample[h]			X		X	X
Study drug administered[i]	X	X				
Scales, Questionnaires, and Outcome Measures						
MIDAS			X		X	X
MSQv2.1	X	X	X		X	X
MIBS-4	X	X	X		X	X
PGI-S			X		X	X
GAD-7			X		X	X
PHQ-9			X		X	X

Schedule of Activities, Protocol I5Q-MC-CGAX

Abbreviations: AE = adverse event; ECG = electrocardiogram; ePRO = electronic patient reported outcomes; ET = early termination; FSH = follicle stimulating hormone; GAD-7 = 7-item Generalized Anxiety Disorder Scale; HbA1c = glycosylated hemoglobin; MIBS = Migraine Interictal Burden Scale; MIDAS = Migraine Disability Assessment test; MSQ (v2.1) = Migraine Specific Quality-of-Life Questionnaire; PGI-S = Patient Global Impression of Severity; PHQ-9 = Patient Health Questionnaire-9; PK = pharmacokinetics; SP = study period.

Note: 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 Medical representative. See Appendix 4 for more details regarding specific hepatic monitoring tests. If the patient has discontinued the trial and returns for hepatic follow-up, the site should collect safety data via case report form as the visit designation.

[a] The eligibility period of the prospective baseline assessment will last from 30 to 40 days. Investigators and patients may have up to an additional 5 days to schedule their Visit 3 appointment (beyond the 40 days); however, eligibility will be based on the 30- to 40-day period.

[b] Visit would be a virtual visit through telephone. The main purpose of telephone visits is to check any spontaneously reported AEs, concomitant medications, and performance of electronic patient-reported outcomes (ePRO) diary entries. Telephone visits can also be conducted as office visits at the study site, if more practical.

[c] A neurological exam will be conducted at screening, Month 3, the final visit of the open-label period, as well as at the final visit of the post-treatment follow-up period or early termination visit in order to assess for any signs of preexisting or treatment-emergent neurological abnormalities such as stroke or other cerebrovascular events.

[d] Questions about “menstrually related migraine” and “migraine with or without aura” will be included in case report form (CRF).

[e] Electrocardiograms will be performed at the scheduled visits. Note: Electrocardiograms should be collected prior to blood draws and dosing. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

[f] Vital signs will 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. Blood pressure will be assessed by utilizing a calibrated machine.

[g] A positive urine test must be followed by a serum pregnancy test for confirmation.

[h] Immunogenicity and PK sampling to be performed at the indicated visits and prior to dose administration if the visit is a dosing visit. Samples will be taken in the event of early termination. Immunogenicity samples also may be collected in the event of a systemic allergic/hypersensitivity reaction (see Section 9.4.3). The timing of samples will be recorded.

[i] Patients will receive injections of placebo or galcanezumab after all other visit procedures are completed. Following the injections at Visit 3 and Visit 7, patients will be observed for at least 30 minutes in the office.

[j] Patients will receive the 1st open-label injections of galcanezumab if opt to enter the open-label period (Study Period IV); Patients will not receive any injection if opt not to enter the open-label period (Study Period IV).

[k] Patients who discontinue from the study prior to final scheduled visit for any reason will have an ET Visit performed. All procedures required for the ET Visit should be completed according to the study schedule. The ET visit will be done only once during the trial.

[l] Visit 5 should occur 30 ±2 days from Visit 3 (previous dosing visit).

3. Introduction

3.1. Study Rationale

Study I5Q-MC-CGAX (CGAX; PERSIST) will enable a comprehensive clinical assessment of galcanezumab in China and selected other countries. The evidence of efficacy and safety of galcanezumab in prevention of migraine has already been confirmed in 3 Phase 3 studies conducted mostly in the United States (US) and European Union (EU). The purpose of Study CGAX is to confirm the efficacy of galcanezumab on the episodic migraine (EM) populations of multiple regions that did not participate in the previous Phase 3 studies and to evaluate safety as well. Study CGAX will include up to 6 months on treatment with investigational product (3 months of double-blind treatment and 3 months of open-label treatment) followed by 4 months of post-treatment observation to further evaluate the effects of galcanezumab in preventing migraine.

3.2. Background

Migraine is a common chronic neurological disease. As reported, it is 1 of the 5 leading causes of years lived with disability in the world in 2016 (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators 2017). The prevalence of migraine in China is 9.3%, which is estimated to be approximately 80 million adults (Yu et al. 2012). This is similar to the global average prevalence rate of 11% (Stovner et al. 2007). Despite the high prevalence and association with significant disability, migraine remains undertreated. One study estimated that only a small fraction (3-13%) of patients with migraine in the Western world received preventive treatment, although more than 25% of them needed it (Rizzoli 2014). In China, the corresponding rate for receiving migraine preventive treatment is even lower: only 2.7% of all patients were reported to have received migraine preventive medications (Li et al. 2012). Current pharmacotherapy options for migraine are not ideal due to the safety concern. Most drugs used for migraine prevention were originally developed for other indications (for example, topiramate as an anti-epileptic). Although these drugs (topiramate, propranolol, flunarizine, etc.) have been shown to be effective, not all patients respond to treatment, and patients may experience adverse effects such as paresthesias, memory and concentration problems with topiramate, sleep disturbance with propranolol, etc. (Estemalik and Tepper 2013).

Calcitonin gene-related peptide (CGRP) is a 37-amino acid neuropeptide widely expressed throughout the central and peripheral nervous system. CGRP is implicated in the pathophysiology of migraine and is hypothesized to be involved in the release of inflammatory mediators and the transmission of nociceptive (pain) information from intracranial blood vessels to the nervous system (Villalón and Olesen 2009). In individuals with migraine, serum concentrations of CGRP are significantly elevated during migraine attacks (Goadsby et al. 1990; Goadsby and Edvinsson 1993), and infusion of CGRP to individuals with a history of migraine can trigger migraine attacks (Lassen et al. 2002). The binding of CGRP with antibodies has been shown to prevent its biological activity; thus, these antibodies represent a promising pharmacologic approach for the prevention of migraine (Dodick et al. 2014a, 2014b; Skljarevski et al. 2018).

Galcanezumab is a humanized monoclonal antibody that prevents CGRP-mediated biological effects by binding potently and selectively to CGRP (Investigator's Brochure [IB], Section 3.1). As of 12 May 2017, 3156 clinical trial participants have been exposed to galcanezumab at single doses ranging from 1 to 600 mg and multiple doses up to 300 mg (IB, Section 3.2). Results from all 3 migraine Phase 3 efficacy studies (I5Q-MC-CGAG [CGAG] and I5Q-MC-CGAH [CGAH] in patients with EM, I5Q-MC-CGAI [CGAI] in patients with chronic migraine) provided consistent evidence that galcanezumab treatment significantly reduced migraine headache day (MHD) frequency and alleviated migraine-related disability. Data from all clinical studies conducted so far indicated that galcanezumab has been well-tolerated in both healthy subjects and patients with migraine. The adverse events (AEs) generally have been mild or moderate in severity. During double-blind treatment phase of Studies CGAG, CGAH, and CGAI, galcanezumab treatment (dose groups pooled) was associated with a low incidence of serious adverse events (SAEs) (<2%) and discontinuations due to AEs (<3%) (IB Section 6.2.1.2). Most hypersensitivity events were also mild to moderate in severity, and there was no evidence of an effect on cardiovascular function. No deaths were reported in the migraine clinical studies of galcanezumab.

3.3. Benefit/Risk Assessment

More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of galcanezumab are to be found in the IB.

4. Objectives and Endpoints

Table CGAX.2 shows the objectives and endpoints of the study. Table CGAX.3 provides definitions for the terms referenced below.

Table CGAX.2. Objectives and Endpoints

Objectives	Endpoints
Primary To test the hypothesis that galcanezumab (240-mg loading dose followed by 120 mg monthly) is superior to placebo in the prevention of migraine in patients with EM.	The overall mean change from baseline in the number of monthly MHDs during the 3-month double-blind treatment phase
Secondary Objectives	
• To compare galcanezumab with placebo with respect to a 30% response rate	• The overall proportion of patients with ≥30% reduction from baseline in monthly MHDs during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to 50% response rate	• The overall proportion of patients with ≥50% reduction from baseline in monthly MHDs during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to 75% response rate	• The overall proportion of patients with ≥75% reduction from baseline in monthly MHDs during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to 100% response rate	• The overall proportion of patients with a 100% reduction from baseline in monthly MHDs during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to distribution of response rates	• Cumulative distribution of monthly MHDs response rates during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to change in functioning	• The overall mean change of Months 1 to 3 from baseline in the Role Function-Restrictive domain score of the MSQ v2.1
• To compare galcanezumab with placebo with respect to change in use of acute headache treatment	• The overall mean change from baseline in the number of monthly MHDs taking medication for the acute treatment of headache during the 3-month double-blind treatment phase

Objectives and Endpoints

Objectives (cont.)	Endpoints (cont.)
Secondary Objectives	
• To compare galcanezumab with placebo with respect to change in headache days	• The overall mean change from baseline in the number of monthly headache days during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to change in moderate to severe headache days	• The overall mean change from baseline in the number of monthly moderate to severe headache days during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to time to 50% response	• Time to first occurrence of a ≥50% reduction from baseline in the number of monthly MHDs (Kaplan-Meier analysis)
• To compare galcanezumab with placebo with respect to onset of effect	• The initial month at which statistical separation in mean change from baseline in the number of monthly MHDs is demonstrated and maintained at all subsequent months through Month 3
• To compare galcanezumab with placebo with respect to onset of 50% sustained response	• The initial month at which statistical separation in the proportion of patients meeting at least a 50% reduction in monthly MHDs that is maintained at all subsequent months through Month 3
• To compare galcanezumab with placebo with respect to maintenance of 50% response	• The proportion of patients who maintain 50% response criteria for all 3 months of double-blind treatment

Objectives and Endpoints

Objectives (cont.)	Endpoints (cont.)
Secondary Objectives (cont.)	
• To compare galcanezumab with placebo with respect to changes in other efficacy parameters, specifically: o ICHD MHDs o migraine attacks o migraine headache hours o headache hours o severity of remaining migraines	• Overall mean change from baseline (during the 3-month double-blind treatment phase) on the following monthly measures: o ICHD MHDs o migraine attacks o migraine headache hours o headache hours o severity of remaining migraines
• To compare galcanezumab with placebo with respect to change in patients' global impression of migraine severity	• Mean change from baseline in the PGI-S at Month 3
• To compare galcanezumab with placebo with respect to changes in disability and quality of life	• Mean change from baseline to Month 3 on the MIDAS total score and individual items • Overall mean change from baseline to Months 1 to 3 on MSQ v2.1 total score, and Role Function-Preventive and Emotional Function domain scores
• To compare galcanezumab with placebo with respect to safety and tolerability	• Analysis of: o TEAEs o SAEs o discontinuation due to AEs o discontinuation rates o vital signs and weight o ECGs o laboratory measures
• To evaluate the immunogenicity of galcanezumab	• Incidence and consequences of anti-drug antibodies and neutralizing anti-drug antibodies to galcanezumab
• To evaluate the pharmacokinetics of galcanezumab	• Serum concentrations of galcanezumab

Objectives and Endpoints

Objectives (cont.)	Endpoints (cont.)
Tertiary Objectives	
• To compare galcanezumab with placebo with respect to changes in quality of life	• Percentages of patients with ≥50% improvement in MIDAS total score • The mean change from baseline in the MIBS-4 total score
• To compare galcanezumab with placebo with respect to changes in symptoms that accompany migraine or probable migraine	• Change from baseline in the number of monthly MHDs with: o nausea and/or vomiting o photophobia and phonophobia
• To compare galcanezumab with placebo with respect to changes in symptoms of depression and anxiety	• Changes from baseline to Month 3 on the following measures: o PHQ-9 o GAD-7
• To assess changes in efficacy, safety, and functional outcomes during Study Period IV (open-label treatment)	• In Study Period IV: o Mean changes in all continuous measures of efficacy, safety, and functional outcomes that are also assessed in the double-blind period o Among patients previously treated with galcanezumab who met 50% response criteria at Month 3 in the double-blind treatment period, the proportion of patients who demonstrate response throughout the open-label treatment period
• To assess changes in efficacy outcomes during Study Period V as collected by ePRO diary data	• In Study Period V: o Mean change in monthly MHDs from baseline to the end of the post-treatment follow-up phase o Time to first loss of response among patients who met the 50% response rate criteria at their last injection interval o Time to initiation of treatment with a migraine prevention medication

Abbreviations: AE = adverse event; ECG = electrocardiogram; EM = episodic migraine; ePRO = electronic patient reported outcomes; GAD-7 = 7-item Generalized Anxiety Disorder Scale; ICHD = International Classification of Headache Disorders; MHD = migraine headache day; MIBS-4 = Migraine Interictal Burden Scale; MIDAS = Migraine Disability Assessment test; MSQ (v2.1) = Migraine Specific Quality-of-Life Questionnaire; PGI-S = Patient Global Impression of Severity; PHQ-9 = Patient Health Questionnaire-9; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Table CGAX.3. Migraine and Headache Endpoint Definitions

Diagnosis	Definition/Criteria
Migraine	A headache, with or without aura, of ≥30 minutes duration with both of the following required features (A and B): A. At least 2 of the following headache characteristics: • Unilateral location • Pulsatile quality • Moderate or severe pain intensity • Aggravation by or causing avoidance of routine physical activity AND B. During headache at least one of the following: • Nausea and/or vomiting • Photophobia and phonophobia *(Definition adapted from the standard IHS ICHD-3*
Probable migraine	A headache missing 1 of the migraine features in the IHS ICHD-3 definition such that 1 feature in Criterion A is missing or 1 feature in Criterion B is missing; that is, meet at least 2 A criteria and none of the B criteria or meet 1 of the A criteria and at least 1 of the B criteria.
MHD (primary objective)	A calendar day on which a migraine or probable migraine occurred.
ICHD MHD	A calendar day on which a migraine occurs.
Migraine attack	Beginning on any day a migraine or probable migraine is recorded and ends when a migraine-free day occurs.
Non-migraine headache	All headaches of at least 30 minutes duration not fulfilling the definition of migraine or probable migraine are classified as non-migraine headaches.
Non-migraine headache day	A calendar day on which a non-migraine headache occurred.
Headache day	A calendar day on which any type of headache occurs (including migraine headache, probable migraine headache, and non-migraine headache).
Episodic migraine	4 to 14 migraine headache days and <15 headache days per 30-day period in the prospective baseline period.

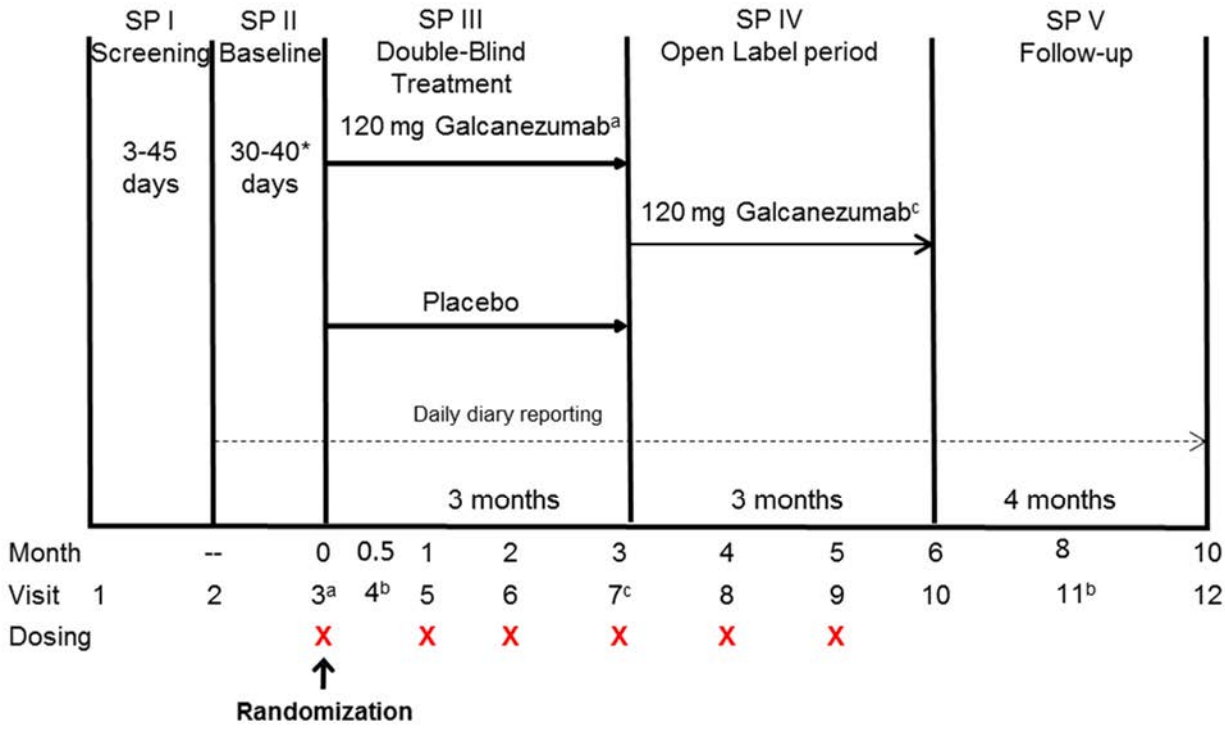
Abbreviations: ICHD = International Classification of Headache Disorders; IHS = International Headache Society; MHD = migraine headache day.

5. Study Design

5.1. Overall Design

Study CGAX is a Phase 3, multicenter, double-blind, randomized, placebo-controlled study of galcanezumab in patients with EM, who have 4 to 14 MHDs (with or without aura) per month. The study has 5 periods, including a prospective baseline phase to determine patient eligibility.

Figure CGAX.1 illustrates the study design.



*Eligibility period determined between a minimum of 30 days and a maximum of 40 days. Investigators may have up to 5 additional days (beyond the 40 days) if needed to schedule patients' Visit 3 appointment.

[a]Patients randomized to galcanezumab will receive a loading dose of 240 mg at the first injection only (Visit 3).

[b] Visit 4 and Visit 11 will be telephone visits.

[c] At Visit 7, patients randomized to placebo who enter the open-label extension will receive galcanezumab at a dose of 240 mg. Patients randomized to galcanezumab will continue the dose of 120 mg.

Abbreviations: SP = study period.

Figure CGAX.1. Illustration of study design for Clinical Protocol I5Q-MC-CGAX.

Study Period I: The study and potential risks will be explained to the patient at Visit 1. The informed consent form (ICF) must be signed before any study procedures are performed. Patients are required to discontinue all excluded medications or migraine prevention treatments at least 28 days prior to Visit 2. Botulinum toxin A or B in the head or neck area must be discontinued at least 4 months prior to Visit 2.

The screening visit (Visit 1) will consist of a full clinical assessment, including a comprehensive medical evaluation documenting medical history, and a physical and neurological examination (Section 2). Visit 1 will be completed when the last scheduled procedure of the screening assessment is completed.

Study Period II: Qualified patients will enter Study Period II (prospective baseline) to determine their eligibility for the study and to establish baseline data for comparison of endpoints during the treatment period. Beginning at Visit 2, patients will log in daily to the electronic patient-reported outcomes (ePRO) system to answer questions about the occurrence of headaches, headache duration, headache features, severity of headache, and use of headache medication, etc. Patients will also record the name, dose, and date of any acute headache medication on a headache medication log which will be returned to site staff at each study visit. At the end of the prospective baseline period, sites will be notified whether their patients met criteria and are eligible to be randomized at Visit 3.

To avoid biased reporting, patients must not be told the number of MHDs on which study qualification is based.

Study Period III: At the start of the 3-month double-blind treatment phase (Visit 3), patients meeting all eligibility requirements will be randomized in a 1:1 ratio to receive placebo or 120-mg/month galcanezumab, respectively.

Patients randomized to the 120-mg dose of galcanezumab will receive an initial loading dose of 240 mg (2 injections of 120 mg each at Visit 3 only). To preserve blinding at Visit 3, each patient in any treatment groups will receive 2 injections of investigational product (2 placebo injections or two 120-mg galcanezumab injections).

The patient will be considered enrolled in the study when randomization occurs. During this phase, study procedures at dosing visits must always occur prior to the patient receiving their assigned treatment.

Patients will be given injections of investigational product during office visits (Figure CGAX.1). For all treatment groups, subcutaneous injections will be administered once monthly at the dosing visits. At Visit 3 (first dose), patients will be required to remain in the office for observation for 30 minutes post injection. Patients will continue to log in and complete the ePRO diary each day. Patients may continue to take their allowed acute migraine or headache medication (with some limitations; see Section 7.7) during the treatment phase and keep recording headache medication log.

Visit 4 (Month 0.5) will be a virtual visit through telephone by site staff and is to include a review of any spontaneously reported AEs, queries on concomitant medications, and performance of ePRO diary entries since last visit.

Patients will receive their last double-blind dose of investigational product at Visit 6 (Month 2). Patients who do not opt to continue into Study Period IV will receive no further injections and will proceed directly to the post-treatment follow-up phase.

Study Period IV: Patients who complete the double-blind period of this study can opt to enter an open-label period (Study Period IV) for up to 3 months of treatment with 120-mg/month galcanezumab. Following completion of the double-blind period Visit 7 (Month 3) assessments and procedures, patients may enroll in the open-label period of the study and receive open-label study drug. Sites and patients will remain blinded to patients' previous treatment assignments. To preserve blinding at Visit 7, each patient in any treatment group will receive 2 injections: patients randomized to placebo will receive an initial loading dose of 240-mg galcanezumab (2 injections of 120-mg galcanezumab at Visit 7 only); patients randomized to galcanezumab will continue the dose of 120 mg but also receive 2 injections (1 placebo injection and 1 120-mg galcanezumab injection at Visit 7 only). All patients will remain at the office for a 30-minute post-injection observation at this visit. At Visit 8 and Visit 9, all patients will receive a dose of 120-mg galcanezumab. Patients will continue to have efficacy and safety assessed, including daily completion of the ePRO diary and headache medication log (see Section 2, Schedule of Activities). Patients may continue to take their allowed acute migraine or headache medication as in Study Period III.

Study Period V: Patients who complete open-label treatment phase or discontinue for any reason during Study Period III or IV must enter into Study Period V for assessment during washout of investigational study drug. During this 4-month phase, sites and patients will remain blinded to patients' treatment assignments. Patients will follow all study procedures during Study Period V but will not receive galcanezumab or placebo. After completion of Visit 10 (Month 6) assessments, if clinically warranted due to a worsening of symptoms, patients may start migraine prevention medications at the discretion of the investigator. The list of allowed preventive medications will be provided separately. At Visit 12 (Month 10), patients will return to the site for their last study visit and be discharged from the study.

Visit 11 (Month 8) will be a virtual visit through telephone by site staff and is to include a review of any spontaneously reported AEs, queries on concomitant medications, and ePRO diary entries since last visit.

5.2. Number of Participants

Approximately 486 participants will be randomized such that approximately 388 evaluable participants complete the double-blind treatment phase. China, Russia, and India intend to participate in the study.

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last patient.

5.4. Scientific Rationale for Study Design

The length of the randomized treatment phase is considered sufficient to assess the safety and efficacy of a migraine prevention medication, given the mechanism and observed onset of action for CGRP antibodies as well as the evidence of efficacy and safety from completed Phase 2 and Phase 3 studies of galcanezumab and from other drugs in the same class (Dodick et al. 2014a,

2014b; Goadsby et al. 2017; Skljarevski et al. 2018). A 3-month open-label phase is included to enlarge study drug exposure. A 4-month post-treatment follow-up phase is included to evaluate patient safety during wash-out of galcanezumab. This allows for a total of 5 months of observation from the time of last injection of galcanezumab. A 5-month post-treatment observation period allows for a wash-out of approximately 5 elimination half-lives of galcanezumab and should decrease galcanezumab serum concentrations by approximately 97% during this time.

5.5. Justification for Dose

The dose regimen planned for this study is a 240-mg loading dose followed by 120 mg once monthly. This dose regimen was demonstrated to be statistically significant and clinically meaningful in reducing MHDs in 3 Phase 3 pivotal efficacy studies of galcanezumab (Studies CGAG, CGAH, and CGAI). A dose of 240 mg once monthly showed a similar efficacy and safety profile as a 240-mg loading dose followed by 120 mg once monthly. As such, only a 240-mg loading dose followed by 120 mg once monthly is proposed for Study CGAX.

6. Study Population

All patients must meet the following selection criteria. Eligibility of patients for study enrollment will be based on the results of a screening medical history, physical examination, neurological examination, clinical laboratory tests, electrocardiograms (ECGs), and migraine history during screening and a prospective baseline period, as described in the Inclusion and Exclusion Criteria sections. The nature of any comorbid conditions present at the time of the physical examination and any preexisting conditions must be documented. Individuals who do not meet the criteria for participation in this study (screen failure) for specific reasons as outlined may be considered for rescreening once, with approval from Eli Lilly and Company (Lilly) Medical (Section 6.4).

Study participants should be instructed not to donate blood or blood products during the study and for 5 months following last administration of investigational product.

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

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria at screening:

Patient and Disease Characteristics

[1] Patients are 18 to 65 years of age (inclusive) at the time of screening.

[2] Have a diagnosis of migraine as defined by International Headache Society (IHS) International Classification of Headache Disorders (ICHD)-3 (1.1 or 1.2) (ICHD-3 2018), with a history of migraine of at least 1 year prior to Visit 1, and migraine onset prior to age 50.

[3] Prior to Visit 1, have a history of 4 to 14 MHDs and at least 2 migraine attacks per month on average within the past 3 months.

[4] From Visit 2 to Visit 3 (prospective baseline period), have a frequency of 4 to 14 MHDs and at least 2 migraine attacks (see definitions, Table CGAX.3). **To avoid biased reporting, patients must not be told the number of MHDs on which study qualification is based.**

[5] From Visit 2 to Visit 3 (prospective baseline period), must demonstrate sufficient compliance with ePRO daily headache entries as documented by completion of at least 80% of daily diary entries.

Informed Consent and Patient Agreements

[6] Are able and willing to give signed informed consent.

[7] Are reliable and willing to follow study procedures, including all follow-up visits.

[8] Women of child-bearing potential must test negative for pregnancy at the time of enrollment based on a serum pregnancy test.

[9] All female patients must agree to use a reliable method of birth control during the study as well as for 5 months after the last dose of investigational product. Acceptable methods of birth control for this study include oral contraceptives; implantable contraceptives; injectable contraceptives; a contraceptive patch; barrier methods such as diaphragms with contraceptive jelly, cervical caps with contraceptive jelly, condoms, or intrauterine devices; a partner with vasectomy. Birth control is not required if the female is infertile due to surgical sterilization (at least 6 weeks after surgical bilateral oophorectomy, hysterectomy, or at least 6 weeks after tubal ligation) confirmed by medical history or menopause. Menopause is defined as spontaneous amenorrhea for at least 12 months not induced by a medical condition, or spontaneous amenorrhea of 6 to 12 months and a follicle stimulating hormone level >40 mIU/mL.

6.2. Exclusion Criteria

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

Prior/Concurrent Clinical Trial Experience

[10] Are currently enrolled in any other clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

[11] Have participated within the last 30 days or within 5 half-lives (whichever is longer) in a clinical trial involving an investigational product. If the investigational product's half-life is not known, 6 months should have passed prior to Visit 1.

[12] Current use or prior exposure to galcanezumab or another CGRP antibody, including those who have previously completed or withdrawn from this study or any other study investigating a CGRP antibody.

Prior/Concomitant Therapy

[13] Patients who are taking, or are expected to take, therapeutic antibodies during the course of the study (for example, adalimumab, infliximab, trastuzumab, bevacizumab, etc.). Prior use of therapeutic antibodies, other than antibodies to CGRP or its receptor, is allowed if that use was more than 12 months prior to Visit 2.

[14] Known hypersensitivity to multiple drugs, monoclonal antibodies or other therapeutic proteins, or to galcanezumab.

[15] Are currently receiving medication or other treatments for the prevention of migraine. Patients must have discontinued such treatment at least 28 days prior to Visit 2. Botulinum toxin A and B that has been administered in the head or neck area must be discontinued at least 4 months prior to Visit 2.

[16] Failure to respond to 3 or more adequately dosed migraine preventive treatments from different classes (that is, maximum tolerated dose for at least 2 months). Failure to respond due to tolerability issues is not considered a treatment failure. Migraine preventive treatments are defined as medications listed in Appendix 5, as well as botulinum toxin A or B and any medications locally approved for prevention of migraine.

Diagnostics Assessments

[17] History of headache meets any diagnosis of 1.2.2 Migraine with brainstem aura, 1.2.3 Hemiplegic migraine, 1.3 Chronic migraine, 1.4 Complications of migraine, 3 Trigeminal autonomic cephalalgias, 4.10 New daily persistent headache, or 13.10 Recurrent painful ophthalmoplegic neuropathy as defined by IHS ICHD-3.

[18] History of headache (for example, cluster headache, Medication Overuse Headache) other than migraine or tension-type headache as defined by IHS ICHD-3 within 3 months prior to Visit 3.

[19] Prior to Visit 1, a history of ≥15 headache days (migraine, probable migraine, or any other headache) per month on average during the past 3 months or are suspected of suffering from chronic migraine as defined per ICHD-3.

[20] History of head or neck injury within 6 months prior to Visit 1.

[21] Patients with a history of traumatic head injury associated with significant change in the quality or frequency of their headaches should be excluded.

Medical Conditions

[22] Have ECGs at screening showing abnormalities compatible with acute cardiovascular events and/or serious cardiovascular risk, or have had myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft, or deep vein thrombosis/pulmonary embolism within 6 months of screening, or have planned cardiovascular surgery or percutaneous coronary angioplasty, or patients with a lifetime history of stroke. The corrected QT (QTcF [Fridericia's]) interval >470 msec for women and >450 msec for men, must be discussed and judged not clinically significant by the principal investigator and Lilly Medical prior to enrollment.

[23] Patients with a body mass index ≥40 kg/m^2.

[24] Any liver tests outside the normal range at Visit 1 that are clinically significant. Alanine aminotransferase (ALT) >2-fold upper limit of normal (ULN), or total bilirubin (TBL) >1.5-fold ULN, or alkaline phosphatase (ALP) >2-fold ULN must be discussed and judged not clinically significant by Lilly prior to enrollment.

[25] Evidence of significant psychiatric disease by medical history, such as bipolar disorder, schizophrenia, personality disorders, or other serious mood or anxiety disorders. Note: Patients with major depressive disorder (MDD) or generalized anxiety disorder (GAD) 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 medications.

[26] Patients who, in the clinician's judgment, are actively suicidal and therefore deemed to be at significant risk for suicide, or those who have had clinically significant suicidal ideation or any suicidal behavior occurred within the past month.

[27] Women who are pregnant or nursing.

[28] History of drug or alcohol abuse/dependence within 1 year prior to Visit 1 (excessive or compulsive use as judged by the investigator), or currently using drugs of potential abuse (including opioids, barbiturates, and marijuana), or any prescribed or over-the-counter medication in a manner that the investigator considers indicative of abuse/dependence.

[29] Have a history or presence of any other medical illness including but not limited to any autoimmune disorder, cardiovascular, hepatic, respiratory, hematological, endocrine, psychiatric or neurological disease, active viral infection (for example, human immunodeficiency virus or viral hepatitis), or any clinically significant laboratory abnormality, that in the judgment of the investigator, indicates a medical problem that would preclude study participation. The screening tests are not required for enrollment.

Other Exclusions

[30] In the opinion of the investigator, have other issues that would interfere with compliance with the study requirements and completion of evaluations required for this study.

[31] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[32] Are Lilly employees or its designee or are employees of third-party organizations (TPOs) involved in the study.

[33] Are unwilling or unable to comply with the use of a data collection device.

6.3. Lifestyle Restrictions

No changes in lifestyle or dietary requirements are required during the study.

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 for only the criteria shown below. The interval between screening and rescreening must be at least 45 days or longer if required for the specified timeframes in the inclusion/exclusion criteria or concomitant medications requirements. If rescreening is performed, the individual must sign a new ICF and will be assigned a new identification number.

- Inclusion Criterion 1. If patients are less than age 18 at time of informed consent, they may be rescreened if they reach age 18 during the study enrollment period.
- Inclusion Criterion 8
- Exclusion Criterion 11
- Exclusion Criterion 13
- Exclusion Criterion 15
- Exclusion Criterion 27

Patients using a concomitant medication that requires a stable dose for a specific duration prior to Visit 2 may be rescreened if additional time is needed to meet the duration requirement.

In addition, after consultation with and approval by a Lilly Medical representative, a patient may be rescreened if there is an unexpected technical difficulty with the electronic diary capture during the prospective baseline period.

7. Treatment

7.1. Treatments Administered

This study involves a comparison of galcanezumab 120 mg (with an initial 240-mg loading dose) administered by subcutaneous injection once monthly with placebo. Sites will administer injections of investigational product (galcanezumab or placebo) at 3 office visits during the double-blind treatment phase and galcanezumab at 3 office visits during the open-label treatment phase (Section 2).

Possible injection sites include the abdomen, thigh, and upper arm. The buttocks may also be used, if needed.

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

- maintaining accurate records of investigational product dispensing
- at the end of the study, returning all unused medication to Lilly, or its designee, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law

7.1.1. Packaging and Labelling

Galcanezumab and matching placebo (excipients only) will be supplied as an injectable solution in 1-mL, single-dose, prefilled, disposable manual syringes with study-specific labels. Each syringe of galcanezumab is designed to deliver galcanezumab 120 mg. The syringes (and contents) containing either galcanezumab or placebo will be visibly indistinguishable from each other. Syringes will be supplied in cartons, with the appropriate quantity of syringes specific to the planned dispensing schedule of investigational product.

Clinical trial materials will be labeled according to the country's regulatory requirements.

7.1.2. Medical Devices

The manufactured medical devices provided for use in the study are prefilled syringes.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized to double-blind treatment at Visit 3. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign double-blind investigational product to each patient. Site personnel will confirm that they have located the correctly assigned package by entering the confirmation number found on the package into the IWRS.

To achieve between-group comparability, the randomization will be stratified by country and baseline migraine frequency (<8 MHDs versus ≥8 MHDs). To ensure an appropriate balance of patients with low- and high-frequency MHDs, the sponsor will stop enrollment of low-frequency patients if the number exceeds an estimated 292.

7.2.1. Selection and Timing of Doses

This is a fixed-dose study. The actual time of all dose administrations will be recorded in the patient's electronic case report form (eCRF).

7.3. Blinding

This is a double-blind study. Blinded transition to open-label treatment phase and/or post-treatment follow-up phase is included in this study.

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete. After the reporting database is locked for statistical analysis of the double-blind treatment phase, a limited number of Lilly personnel will be unblinded to complete the study report and prepare for submission. However, study sites, patients and all Lilly personnel directly involved in the ongoing open-label and post-treatment follow-up phases will remain blinded to patients' double-blind treatment assignment.

Emergency unblinding for AEs may be performed through the IWRS. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All unblinding events are recorded and reported by the IWRS.

If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study. In cases where there are ethical reasons to have the patient remain in the study, the investigator must obtain specific approval from a Lilly Medical representative for the patient to continue in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If an emergency unblinding occurs, Lilly must be notified as soon as possible.

7.4. Dose Modification

Dose modifications are not permitted in this study.

7.4.1. Special Treatment Considerations

During the post-treatment follow-up period, patients will not receive galcanezumab or placebo. After completion of Visit 10 (Month 6) assessments, if clinically warranted due to a worsening of symptoms, patients may start migraine prevention medications at the discretion of the investigator. The list of allowed preventive medications is provided separately.

7.5. Preparation/Handling/Storage/Accountability

The packaged investigational product must be stored according to the storage requirements printed onto the packaging label.

To administer the galcanezumab injections, sites are to refer to the pharmacy binder for the preparation and handling instructions of the packaged pre-filled syringes.

7.6. Treatment Compliance

Investigators will be required to document the administration of investigational product in the eCRF.

Investigational product must be administered as indicated in the Schedule of Activities (Section 2). If the investigator is unable to administer the investigational product in the allowed window, then the situation should be discussed with Lilly to determine if the patient may continue.

7.7. Concomitant Therapy

Acute treatment of migraine or headache is allowed throughout the study but with some limitations. Patient will be asked to capture usage of any acute migraine or headache medication or not via ePRO device during Study Periods II, III, IV, and V. Acute migraine or headache medication name, dose, and date will be recorded by patients during Study Periods II, III, IV, and V on a headache medication log, which will be returned to site staff at each office visit in the study.

Treatments used for the prevention of migraine, including migraine preventive treatments as defined in Exclusion Criterion [16], or any other medications as well as non-pharmacological interventions aiming to prevent migraine, are not allowed at any time during Study Periods II through IV. Patients should have discontinued all migraine preventive treatments at least 28 days prior to Visit 2. Botulinum toxin A or B in the head or neck area for therapeutic use should be discontinued within 4 months prior to Visit 2.

The list of medications allowed or not allowed will be provided separately in the operation manual. Any changes in the list will be communicated to investigators and will not constitute a protocol amendment.

7.8. Treatment after the End of the Study

7.8.1. Study Extensions

Not applicable.

7.8.2. Continued Access

Investigational product will not be made available to patients after conclusion of the study.

8. Discontinuation Criteria

Patients who discontinue the investigational product during the double-blind treatment phase (Study Period III) or open-label treatment phase (Study Period IV) will proceed immediately to Study Period V.

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

Discontinuation of the investigational product is required in cases of pregnancy.

Possible reasons leading to permanent discontinuation of investigational product are as follows:

- **Subject Decision**
  - the patient requests to discontinue investigational product.

- **Discontinuation due to a hepatic event or liver test abnormality.** Patients who are discontinued from investigational product due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via eCRF.

  Discontinuation of the investigational product for abnormal liver tests **should be** considered by the investigator when a patient meets one of the following conditions after consultation with the Lilly-designated medical monitor:
  - ALT or aspartate aminotransferase (AST) >8-fold ULN
  - ALT or AST >5-fold ULN for more than 2 weeks
  - ALT or AST >3-fold ULN and TBL >2-fold ULN or international normalized ratio (INR) >1.5
  - ALT or AST >3-fold ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
  - ALP >3-fold ULN
  - ALP >2.5-fold ULN and TBL >2-fold ULN
  - ALP >2.5-fold ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Patients discontinuing from the investigational product prematurely for any reason should complete AE and other follow-up procedures per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.1.2. Temporary Discontinuation from Study Treatment

Not applicable.

8.1.3. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from study treatment unless there

are extenuating circumstances that make it medically necessary for the patient to continue on study treatment. If the investigator and the sponsor Medical representative agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor Medical representative to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product. Safety follow up is as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of the protocol.

8.2. Discontinuation from the Study

Some possible reasons that may lead to permanent discontinuation include the following:

- 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)
- Investigator Decision
    - the investigator decides that the patient should be discontinued from the study
    - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for the study indication (prevention of migraine) during Study Period III, discontinuation from the study occurs prior to introduction of the new agent
- Subject Decision
    - the patient asks to be withdrawn from the study

Patients discontinuing from the study prematurely for any reason should complete AE and other safety follow-up per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.3. Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly 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.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, with the study procedures and their timing (including tolerance limits for timing).

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

Appendix 4 lists the tests that may be obtained in the event of a treatment-emergent hepatic abnormality.

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

9.1.1. Primary Efficacy Assessments

ePRO Diary: Patients will be asked to use an ePRO device (starting at Visit 2) to record headache information, including but not limited to reporting headaches, features and intensity of headache, usage of any acute headache medication or not, and other information such as migraine-associated symptoms (for example, nausea, vomiting, photophobia, and/or phonophobia).

9.1.2. Secondary Efficacy Assessments

Most of secondary efficacy assessments in this study (Table CGAX.2) will be provided by the ePRO diary; however, details of acute headache medication use will be captured by a headache medication log and reported at site visits.

9.1.2.1. Patient Global Impression of Severity

The Patient Global Impression of Severity (PGI-S) scale (Guy 1976) is a patient-rated instrument that measures baseline illness severity. The PGI-S includes a range of possible responses, from 1 (“normal, not at all ill”) to 7 (“extremely ill”).

9.1.3. 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. This includes health outcomes measures considered to be appropriate for evaluating changes in quality of life, global functioning, and disability (Section 9.9).

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 ICF is signed, study site personnel will record via eCRF the occurrence and nature of each patient's preexisting condition(s), including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record via eCRF any change in the condition(s) and any new condition(s) as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure or investigational product via eCRF.

The investigator will decide whether he or she interprets the observed AEs as reasonably possibly related to migraine, to the investigational product, study device, study procedure, or other concomitant treatment or pathologies. The investigator will answer 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 one 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 investigational device (for example, 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 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 that occurs during the study, including those in which conception occurred within 5 months after last administration of investigational product, should be reported using the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in patients 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 patient has been discharged from the study, and he or 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 Union Clinical Trial Directive 2001/20/EC and the associated detailed guidance 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 guidance.

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.

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 (or drug delivery system such as a prefilled syringe) so that the situation can be assessed.

9.3. Treatment of Overdose

No data are available at this stage of development.

9.4. Safety

9.4.1. Electrocardiograms

For each patient, a single, 12-lead digital ECG will be collected at the visits shown in the Schedule of Activities (Section 2). Electrocardiograms should be recorded according to the study-specific recommendations.

Any clinically significant findings from ECGs that result in a diagnosis should be reported to Lilly or its designee as an AE via eCRF.

9.4.2. Vital Signs

Vital signs will include body temperature, blood pressure, and pulse. Blood pressure and pulse will be measured in triplicate in the sitting position prior to blood draws and study drug administration (see Study Schedule [Section 2]).

Any clinically significant findings from vital signs measurement that result in a diagnosis should be reported to Lilly or its designee as an AE via eCRF.

9.4.3. Laboratory Tests

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

Any clinically significant findings from laboratory tests that result in a diagnosis should be reported to Lilly or its designee as an AE via eCRF.

In addition, an immunogenicity sample will be collected, when possible, for any patient who experiences a potential systemic allergic/hypersensitivity reaction during the study as judged by the investigator. This immunogenicity sample should be collected immediately or as soon as possible, taking into consideration the availability and well-being of the patient. Exact date and time of the sample should be recorded on the laboratory requisition form.

9.4.4. Samples for Immunogenicity Research

Where local regulations and ethical review boards (ERBs) allow, blood samples for immunogenicity testing will be collected to determine antibody production against galcanezumab as specified in the Schedule of Activities (Section 2). Immunogenicity will be assessed by a validated assay designed to detect anti-drug antibodies (ADAs) in the presence of the investigational product. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity 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 the sponsor. The duration allows the sponsor to respond to future regulatory requests related to galcanezumab.

9.4.5. Safety Monitoring

Investigators are responsible for monitoring individual patient safety throughout the trial. If a study patient/subject experiences elevated ALT ≥3-fold ULN, ALP ≥2-fold ULN, or elevated TBL ≥2-fold 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 Medical representative regarding collection of specific recommended clinical information and follow-up laboratory tests. See Appendix 4.

Neurological examinations will be conducted at screening, Month 3, and Month 6 of treatment, as well as at the final visit of the post-treatment follow-up period or early termination visit in order to assess for any signs of preexisting or treatment-emergent neurological abnormalities such as stroke or other cerebrovascular events. If a study patient experiences signs of a cerebrovascular event, appropriate follow-up and clinical management should be conducted by the investigator, and the Lilly Medical representative should be consulted regarding collection of further clinical information and follow-up testing.

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

9.4.5.1. Hepatic Safety Monitoring

If a study patient experiences elevated ALT ≥3-fold ULN, ALP ≥2-fold ULN, or elevated TBL ≥2-fold ULN, liver testing (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Hepatic Safety Data Collection

Additional safety data should be collected via the CRF if 1 or more of the following conditions occur:

- elevation of serum ALT to ≥5-fold ULN on 2 or more consecutive blood tests
- elevated serum TBL to ≥2-fold ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2-fold ULN on 2 or more consecutive blood tests
- patient discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be a SAE

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 2.5 mL each will be collected to determine the serum concentrations of galcanezumab. A maximum of 3 samples 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.

When a blood sample is collected, the time and date of last dose administration prior to blood sampling should be recorded. The actual date and time (24-hour clock time) of each sampling will be recorded. Galcanezumab concentration information that may/would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded. 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 serum galcanezumab concentrations. Samples will be analyzed at a laboratory approved by the sponsor.

It is intended that blood samples collected from patients who received placebo should not be analyzed for determination of serum concentrations of galcanezumab.

9.6. Pharmacodynamics

Not applicable.

9.7. Genetics

Not applicable.

9.8. Biomarkers

Not applicable.

9.9. Health Economics

Health economic, disability, and quality-of-life assessments of galcanezumab in patients with migraine will be based on the following scales:

Migraine Disability Assessment test (MIDAS): The MIDAS was designed to quantify headache-related disability over a 3-month period. This instrument consists of 5 items that reflect the number of days reported as missing, or with reduced productivity at work or home and social events; a higher value is indicative of more disability (Stewart et al. 1999, 2001). This instrument is considered reliable and valid and is correlated with clinical judgment regarding the need for medical care (Stewart et al. 1999, 2001).

Migraine Specific Quality-of-Life questionnaire (MSQ v2.1): The MSQ v2.1 is a self-administered health status instrument that was developed to address physical and emotional limitations of specific concern to individuals suffering from migraine. The instrument consists of 14 items that address 3 domains: (1) Role Function-Restrictive; (2) Role Function-Preventive; and, (3) Emotional Function (Jhingran et al. 1998). The instrument was designed with a 4-week recall period, and is considered reliable, valid, and sensitive to change in migraine (Jhingran et al. 1998; Rendas-Baum et al. 2013).

Migraine Interictal Burden Scale (MIBS-4): The MIBS-4 measures the burden related to headache in the time between attacks. The self-administered instrument consists of 4 items that

address disruption at work and school, diminished family and social life, difficulty planning, and emotional difficulty. The questionnaire specifically asks about the effect of the disease over the past 4 weeks on days without a headache attack. Response options include the following: don't know/not applicable, never, rarely, some of the time, much of the time, or most or all of the time. Each response has an associated numerical score, with the summation across all 4 items resulting in a total score ranging from 0 to 12, and the level of interictal burden being categorized into the following: 0 for none, 1 or 2 mild, 3 or 4 moderate, and >5 severe (Buse et al. 2009).

Patient Health Questionnaire-9: The Patient Health Questionnaire-9 (PHQ-9) is a 9-item patient-completed instrument that was designed for detecting MDD and for measuring the severity of depressive symptoms (Kroenke et al. 2001). The 9 items pertain to the diagnostic criteria for MDD from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and are still applicable for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5): anhedonia; depressed mood; trouble sleeping; feeling tired; change in appetite; guilt, self-blame, or worthlessness; trouble concentrating; feeling slowed down or restless; and thoughts of being better off dead or hurting oneself. Each item is rated on a 4-point scale (0 = never, 1 = several days, 2 = more than half the time, 3 = nearly every day) based on symptoms over the past 2 weeks. The overall score ranges from 0 to 27, with the levels of depression severity defined as follows: 0 to 4 minimal, 5 to 9 mild, 10 to 14 moderate, 15 to 19 moderately severe, and 20 to 27 severe. The instrument is considered reliable and valid for use in research and clinical settings (Kroenke et al. 2001), including in patients with migraine (Seo and Park 2015a).

7-Item Generalized Anxiety Disorder Scale: The 7-item Generalized Anxiety Disorder Scale (GAD-7) is a 7-item patient-completed questionnaire that was designed to screen for GAD and for measuring the severity of anxiety symptoms (Spitzer et al. 2006). The tool was developed based on symptom criteria for GAD in the DSM-IV (still applicable for DSM-5) as well as review of existing anxiety scales, with items addressing the following: feelings of nervousness, uncontrollable worrying, excessive worrying, trouble relaxing, restlessness, irritability, and fearfulness. The patient identifies how much they have been bothered by these symptoms over the past 2 weeks. Each of the 7 items is rated on a 4-point scale (0 = not at all, 1 = several days, 2 = more than half the days, 3 = nearly every day), with total score ranging from 0 to 21. The levels of anxiety severity are defined as follows: 0 to 4 minimal, 5 to 9 mild, 10 to 14 moderate, and 15 to 21 severe. The instrument is considered reliable and valid for use in research and clinical settings (Spitzer et al. 2006), including in patients with migraine (Seo and Park 2015b).

10. Statistical Considerations

10.1. Sample Size Determination

Approximately 486 patients will be randomized in a 1:1 ratio to the galcanezumab 120-mg/month or placebo treatment groups. With 243 patients per treatment group, this study will have approximately 90% power to detect an effect size of 0.33 between galcanezumab 120-mg/month and placebo treatment groups. Within the framework of a MMRM, the sample size is determined using a between-treatment group t-test, 2-sided with a type I error of 0.05, assuming a discontinuation rate of 20% during the double-blind phase. Parameters used in the sample size calculations are based on results from 2 double-blind, placebo-controlled Phase 3 studies (Studies CGAG and CGAH) and clinical justification.

10.2. Populations for Analyses

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

The detailed definitions of populations for analyses will be described in the statistical analysis plan (SAP).

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 SAP.

The primary analysis will be performed using a restricted maximum likelihood-based MMRM technique with prespecified model terms (Section 10.3.3.1).

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

In addition to the MMRM approach, analysis of covariance (ANCOVA) model or analysis of variance (ANOVA) may also be implemented. When an ANCOVA model is used to analyze a continuous variable, the model will contain the main effects of treatment and country as well as the continuous fixed covariates of baseline. The ANOVA model will use the same terms except the continuous fixed covariate of baseline. Type III sum-of-squares for the least-squares means will be used for the statistical comparisons, unless otherwise specified.

Continuous efficacy and health outcome endpoints will be analyzed using MMRM methods, as well as an ANCOVA model if deemed appropriate.

Categorical comparisons between treatment groups will be performed using Cochran-Mantel-Haenszel controlling for country or using the Fisher's exact test, where appropriate.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated.

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 clinical study report or SAP. Changes may only be made in the SAP prior to unblinding. Additional exploratory analyses of the data will be conducted as deemed appropriate.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

The number and percentage of ITT patients who complete the study or discontinue early will be tabulated for all treatment groups for double-blind treatment (Study Period III), open-label treatment (Study Period IV), and post-treatment follow-up (Study Period V) both overall and by visit.

Patient allocation by investigator will be summarized for Study Period III for all ITT patients. Patient allocation by investigator will also be listed for all study periods.

10.3.2.2. Patient Characteristics

The following patient characteristics at baseline will be summarized by treatment group for all ITT patients:

- Demographic (age, gender, ethnic origin, height, weight, body mass index)
- Migraine headache, headache, variation of migraine/headache measures per 30-day baseline period
- Medical history and preexisting condition

Medical history and preexisting conditions will be summarized by preferred term (PT) within system organ class (SOC).

10.3.2.3. Concomitant Therapy

The proportion of patients who received concomitant medication (as recorded via eCRF) will be summarized for all ITT patients for the double-blind, open-label, and post-treatment phases separately. Details will be included in the SAP.

10.3.2.4. Treatment Compliance

Dosing will occur at monthly study visits. Treatment compliance for each patient will be calculated as the number of completed scheduled dosing visits in which the patient receives an injection, divided by the number of completed scheduled dosing visits, including any skipped dosing visits at or before the last dosing visit (Visit 9) or early discontinuation visit.

Treatment compliance for each period will be summarized overall and by treatment group, and treatment comparisons for the double-blind treatment phase will be performed using an ANOVA with treatment and country in the model.

10.3.2.5. Electronic Patient-Reported Outcome Diary Compliance

Electronic patient-reported outcome diary compliance at each 1-month period (including baseline, Month 1, 2, 3, … till Month 10) will be calculated. Diary compliance at each period is calculated as follows:

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

Actual number of diary days is calculated as the total number of days with nonmissing answers.

Diary compliance for each period will be summarized overall and by treatment group, and treatment comparisons for the double-blind treatment phase will be performed using an ANOVA with treatment and country in the model.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary efficacy measure is the overall mean change from the baseline period in the number of monthly MHDs during the 3-month double-blind treatment phase, and the primary analysis will evaluate the efficacy of galcanezumab (120 mg/month) compared with placebo.

The primary analysis will be performed using a restricted maximum likelihood-based MMRM technique. The analysis will include the fixed categorical effects of treatment, country, month, and treatment-by-month interaction, as well as the continuous fixed covariates of baseline number of MHDs and baseline number of MHDs-by-month interaction.

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

- heterogeneous Toeplitz
- heterogeneous first-order autoregressive
- Toeplitz
- first-order autoregressive

When the unstructured covariance matrix is not utilized, the sandwich estimator (Diggle and Kenward 1994) will be used to estimate the standard errors of the fixed effects parameters. The sandwich estimator is implemented by specifying the EMPIRICAL option in SAS®. When the

sandwich estimator is utilized, the Kenward-Roger approximation for denominator degrees of freedom cannot be used. Instead, the denominator degrees of freedom will be partitioned into between-subject and within-subject portions by the DDFM=BETWITHIN option in SAS®. SAS® PROC MIXED will be used to perform the analysis.

10.3.3.2. Secondary Analyses

The secondary analyses will be conducted for the double-blind treatment phase. For the continuous secondary efficacy and health outcomes, the change from baseline to each scheduled postbaseline measure will be analyzed from repeated measures analyses with similar models as described in Section 10.3.3.1, with baseline number of migraine headache days category (<8 versus ≥8) included as a covariate. Further details will be provided in the SAP.

For the analysis of 30%, 50%, 75%, and 100% response, the percentage of patients meeting response criteria during the 3-month double-blind treatment phase will be estimated for each treatment from a categorical, pseudo-likelihood-based repeated measures analysis of longitudinal binary outcomes indicating whether patients meet response criteria. This analysis will be implemented using the GLIMMIX procedure in SAS. Further details regarding secondary analyses will be summarized and described in the SAP.

Among these secondary objectives, some may be chosen as the key secondary objectives, and the key secondary objectives will be tested using an appropriate multiple testing approach providing strong control of the familywise error rate (for the primary and key secondary tests) at a 1-sided 0.025 alpha level (or, equivalently, 2-sided 0.05 alpha level). Details of the key secondary objectives and the specific testing methodology (including testing order, relationship, and type I error allocation and propagation) will be specified in the SAP.

10.3.3.3. Tertiary Efficacy Analyses

The exploratory efficacy analyses will be conducted for the double-blind treatment, open-label treatment, and post-treatment phases. Further details regarding tertiary efficacy analyses are summarized in the SAP.

10.3.4. Safety Analyses

The safety analyses will be conducted for the double-blind treatment, open-label treatment, and post-treatment follow-up phases.

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

- AEs
  - treatment-emergent adverse events (TEAEs)
    - by preferred term
    - by SOC
    - by maximum severity
  - SAEs
  - AEs leading to discontinuation
- vital signs and weight
- ECGs

- laboratory measurements

10.3.4.1. Categorical Safety Variables

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

Comparisons between treatment groups for all categorical safety measures will be made using the Fisher's exact test for Study Period III (double-blind treatment). Descriptive statistics only will be presented for the treatment groups in the open-label phase (Study Period IV) and in the post-treatment follow-up phase (Study Period V) with the post-treatment population.

10.3.4.2. Adverse Events

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

10.3.4.3. Vital Signs and Weight

Vital signs collected during the study include systolic and diastolic blood pressure, pulse, and temperature. Blood pressure and pulse measurements will be taken when the patient is in a sitting position. Three measurements of sitting blood pressure and pulse will be collected at every visit (except for Visit 2 and phone visits); the 3 sitting blood pressure and pulse measurements will be averaged and used as the value for that visit for analysis.

The incidence rates of patients with treatment-emergent vital sign and weight changes based at any time postbaseline will be assessed using the Fisher's exact test. Specific criteria for treatment-emergent definition will be documented in the SAP.

10.3.4.4. Electrocardiogram Intervals and Heart Rate

The corrected QT interval will be calculated using the Fridericia method (QTcF). The number and percent of patients meeting criteria for treatment-emergent abnormalities in ECG intervals (pulse rate, QRS, and QTcF) and heart rate at any time during study will be summarized. Treatment group comparisons will be performed using the Fisher's exact test.

10.3.4.5. Laboratory Tests

The incidence rates of patients with treatment-emergent abnormal, high, or low laboratory values at any time postbaseline will be assessed using the Fisher's exact test for each laboratory test.

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

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

10.3.5. Pharmacokinetic Analyses

Galcanezumab concentrations will be illustrated graphically and summarized descriptively. If warranted and based on availability of data, the relationship of serum galcanezumab concentrations to efficacy endpoints, safety endpoints, or ADA may be explored. Patient and healthy subject data, including but not limited to serum galcanezumab concentrations, 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. Evaluation of Immunogenicity

The frequency and percentage of patients with preexisting ADA and with treatment-emergent ADA-positive to galcanezumab will be tabulated. Treatment-emergent ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA). For the treatment-emergent ADA-positive patients, the distribution of maximum titers will be described. The frequency of neutralizing antibodies will also be tabulated in treatment-emergent ADA-positive patients.

The relationship between ADA and safety and efficacy endpoints may be assessed.

10.3.7. Other Analyses

10.3.7.1. Health Economics

The change from baseline for the double-blind treatment phase and for the double-blind treatment, open-label treatment, and post-treatment follow-up phases combined for MSQ v2.1 (Role Function-Restrictive, Role Function-Preventive, Emotional Function, and total score),

MIDAS (item scores and total score), MIBS-4 (total score), GAD-7, and PHQ-9 will be analyzed. In addition, analysis for the categorical measures will be performed.

10.3.7.2. Subgroup Analyses

Subgroup analyses will be performed for the primary efficacy measure (change from baseline in the number of MHDs) separately for each of the subgroup populations listed in Table CGAX.4. Subgroup analyses will be conducted only for the ITT patients in Study Period III.

Each of the subgroup analyses for the primary measure of change from baseline in the number of MHDs will be conducted using MMRM. The same MMRM model described in Section 10.3.3.1 will be used, with terms of subgroup, subgroup-by-treatment, subgroup-by-month, and subgroup-by-treatment-by-month interactions added as additional covariates.

Table CGAX.4. Definition of Subgroup Variables

Subgroup Variable	Categories
Sex	Male, female
Country	Defined in the statistical analysis plan
Baseline number of MHDs	2 levels of baseline migraine frequency : • <8 MHDs • ≥8 MHDs
CCI [redacted]	
Having aura or not (during baseline period)	Yes or No

Abbreviation: MHD = migraine headache day.

10.3.8. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the appropriate Lilly medical director, or designee, will be consulted to determine whether it is necessary to amend the protocol.

This study will include two database locks. The first is to occur after all patients have had the opportunity to complete the 3-month double-blind treatment phase (Study Period III). The purpose of this analysis is the final analysis of the primary efficacy endpoint, as well as efficacy and safety analyses of the double-blind phase. Study sites, patients, and all Lilly personnel directly involved in the continuing trial will remain blinded to patients' double-blind treatment assignment. Unblinding details are specified in the unblinding plan section of the SAP or a separate unblinding plan document. This analysis will not be considered an interim analysis because the double-blind phase is of primary interest.

The second database lock will occur at the post-treatment follow-up phase once all patients have had the opportunity to complete the entire study. This reporting database will include all data for all patients enrolled into the study, including all open-label and post-treatment phase data.

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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 adverse event 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.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
blinding/masking	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received.
CGRP	calcitonin gene-related peptide
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.
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ECG	electrocardiogram
eCRF	electronic case report form
EM	episodic migraine
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 informed consent form directly or through their legally acceptable representatives.

ePRO	electronic patient-reported outcomes
ERB	ethical review board
EU	European Union
GAD	generalized anxiety disorder
GAD-7	7-item Generalized Anxiety Disorder Scale
GCP	good clinical practice
IB	Investigator's Brochure
ICF	informed consent form
ICHD-3	International Classification of Headache Disorders – 3rd edition
IHS	International Headache Society
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
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.
ITT	intent to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MHDs	migraine headache days
MIBS-4	4-item Migraine Interictal Burden Scale
MIDAS	Migraine Disability Assessment
MMRM	mixed model repeated measures
MSQ (v2.1)	Migraine-Specific Quality-of-Life Questionnaire version 2.1

PGI-S	Patient Global Impression of Severity
PHQ-9	Patient Health Questionnaire-9
QTcF	Fridericia's corrected QT interval
SAE	serious adverse event
SAP	statistical analysis plan
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.
SOC	system organ class
SUSARs	suspected unexpected serious adverse reactions
TBL	total bilirubin
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
US	United States

Appendix 2. Clinical Laboratory Tests

Hematology[a]:
Hemoglobin
Hematocrit
Erythrocyte count (RBC)
Mean cell volume
Mean cell hemoglobin concentration
Leukocytes (WBC)
Neutrophils, segmented
Lymphocytes
Monocytes
Eosinophils
Basophils
Platelets
HbA_{1c}

Urinalysis[a]:
Specific gravity
pH
Protein
Glucose
Ketones
Blood
Microscopic analysis

Clinical Chemistry[a]:
Serum Concentrations of:
Sodium
Potassium
Total bilirubin
Direct bilirubin
Alkaline phosphatase
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Blood urea nitrogen (BUN)
Creatinine
Uric acid
Calcium
Glucose
Albumin
Creatine kinase (CK)
Triglycerides
Total cholesterol
HDL

Other
PK Sample (galcanezumab serum concentration determination)
Immunogenicity

Pregnancy Test (females only)[b]
Serum pregnancy or FSH
Urine pregnancy test (local)

Abbreviations: FSH = follicle-stimulating hormone; HbA_{1c} = glycosylated hemoglobin; HDL = high density lipoprotein; PK = pharmacokinetic; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated laboratory.

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

Appendix 3. Study Governance Considerations

Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 3.1.1. Informed Consent

The investigator is responsible for:

- ensuring that the patient understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (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 study.
- ensuring that a copy of the ICF is provided to the participant or the participant's legal representative and is kept on file.
- ensuring that the medical record includes a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Appendix 3.1.2. Recruitment

Lilly or its designee is responsible for the central recruitment strategy for patients. Individual investigators may have additional local requirements or processes.

Appendix 3.1.3. Ethical Review

The investigator must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Council 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 protocol and related amendments and addenda, current Investigator Brochure (IB) and updates during the course of the study
- informed consent form
- other relevant documents (for example, curricula vitae, advertisements)

Appendix 3.1.4. Regulatory Considerations

This study will be conducted in accordance with the protocol and with the:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) 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 3.1.5. Investigator Information

Investigators in this clinical trial should be neurologists, headache specialists, or other specialists with experience in headache clinical trials and treating migraine patients.

Appendix 3.1.6. 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 3.1.7. Final Report Signature

The clinical study report (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.

The investigator selected by the study team will serve as the CSR coordinating investigator. 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 3.2. 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

- provide sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, 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 verify data reported to detect potential errors

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 3.2.1. Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture system (EDC) will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Additionally, concomitant therapy for acute treatment of migraine or headache will be collected by the subject via a paper source document and will be transcribed by the investigator site personnel into the EDC system.

Electronic Clinical Outcome Assessment (eCOA) data (Patient-rated scales/questionnaires and patient migraine data other than paper source document) will be directly recorded by the subject into an instrument. The eCOA data will serve as the source documentation and the investigator does not maintain a separate, written or electronic record of these data.

Data collected via the sponsor-provided data capture system(s) will be stored at third-party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports/electronic transfers will be provided to the investigator for review and retention. 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 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, 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 3.3.2. Discontinuation of the Study

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

Appendix 3.4. Publication Policy

The publication policy for Study I5Q-MC-CGAX is described in site contracts.

Appendix 4. 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 laboratory.

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

Appendix 5. Medications Defined as Migraine Preventive Treatments per Study CGAX Exclusion Criterion [16]

Medications Defined as Migraine Preventive Treatments per Study CGAX Exclusion Criterion [16]

Anti-depressants	Anti-epileptic drugs	ß blockers	Calcium channel blocker	Triptans (Menstruation Related Migraine)	Traditional Chinese Medicine/Herbal*	Others Locally approved medications of preventive migraine
TCAs: Amitriptyline	Valproic acid	Metoprolol	Flunarizine	Frovatriptan	petasites/butterbur	
SNRIs: Venlafaxine	Topiramate	Propranolol		Naratriptan	Toutongling, Duliang	
		Timolol, Atenolol, Nadolol		Zolmitriptan		

Abbreviations: SNRIs = serotonin–norepinephrine reuptake inhibitors; TCAs = tricyclic antidepressants.

* Medications may not be exhausted and more details refer to the medication list.

Appendix 6. Protocol Amendment I5Q-MC-CGAX(a) Summary: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Galcanezumab in Patients with Episodic Migraine – the PERSIST Study

Overview

Protocol I5Q-MC-CGAX (A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Galcanezumab in Patients with Episodic Migraine – the PERSIST Study) 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 described in the following table:

Amendment Summary for Protocol I5Q-MC-CGAX Amendment (a)

Section # and Name	Description of Change	Brief Rationale
Cover page 1. Synopsis 3.1 Study Rationale	Added the study name PERSIST.	To provide an identifier for this study in future scientific communication.
Header Cover page	Added amendment identifier (a).	To indicate that this is a new protocol.
1. Synopsis	Revised wording to provide additional details of visit number in treatment arms and duration.	To improve clarity.
2. Schedule of Activities	Added a footnote for Visit 5.	To clarify target interval between Visit 5 and previous dosing visit aiming to avoid injection out of standard schedule.
4. Objectives and Endpoints	Removed aura and prodromal symptoms from a tertiary endpoint "Change from baseline in the number of monthly MHDs with:"	Assessing aura and prodromal symptoms cannot be achieved by current electronic patient-reported outcome diary. Removing these symptoms from the tertiary endpoint will not affect the interpretation of galcanezumab efficacy and safety assessment, as deemed by study team.
5.2 Number of Participants	Revised wording regarding estimated number of evaluable participants.	To be consistent with sample size determination.
7.3 Blinding	Added statement of unblinding specifications after primary database lock.	To clarify unblinding requirement for the added primary database lock.
8. Discontinuation Criteria	Revised wording of general statement of discontinuation.	To improve clarity.
10.3.8 Interim Analyses	Added entire section back.	This is a required section of Lilly clinical protocols. Based on previous development strategy and study team assessment, most efficacy and safety endpoints needed for regulatory submission can be achieved during double-blind placebo-controlled treatment phase, thus a primary database lock was added in addition to the final database lock.

Revised Protocol Sections

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

Header

I5Q-MC-CGAX(a) Clinical Protocol

Title

Protocol I5Q-MC-CGAX(a)
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Galcanezumab in Patients with Episodic Migraine – the PERSIST Study

1. Synopsis

Title of Study:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Galcanezumab in Patients with Episodic Migraine (EM) – the PERSIST Study.

Rationale:
Study I5Q-MC-CGAX (CGAX; PERSIST) is designed to evaluate the efficacy and safety of galcanezumab, in the prevention of migraine compared with placebo in patients with EM in multiple regions.

Treatment Arms and Duration:

Patients who complete the double-blind period may enter a 3-month open-label extension phase during which all patients will receive galcanezumab 120 mg/month. At Visit 7, ~~P~~patients originally assigned to placebo will receive an initial loading dose of 240-mg galcanezumab; patients originally assigned to galcanezumab will continue the dose of 120 mg but will receive 2 injections (1 injection of 120-mg galcanezumab and 1 injection of placebo) to maintain blinding. At ~~the~~ Visit 8 and Visit 9~~second and third (last) visits~~ of the open-label phase, all patients will receive a 120-mg dose of galcanezumab. All patients will be followed for a 4-month, post-treatment phase during which no study medication will be administered.

2. Schedule of Activities

Visit	1	2	3	4[b]	5[l]	6	7

[l] Visit 5 should occur 30 ±2 days from Visit 3 (previous dosing visit).

3.1 Study Rationale

Study I5Q-MC-CGAX (CGAX; PERSIST) will enable a comprehensive clinical assessment of galcanezumab in China and selected other countries.

4. Objectives and Endpoints

Objectives (cont.)	Endpoints (cont.)
Tertiary Objectives • To compare galcanezumab with placebo with respect to changes in symptoms that accompany migraine or probable migraine	• Change from baseline in the number of monthly MHDs with: o nausea and/or vomiting o photophobia and phonophobia ~~o aura~~ ~~o prodromal symptoms~~

5.2. Number of Participants

Approximately 486 participants will be randomized such that approximately 388 evaluable participants complete the double-blind treatment phase~~study~~. China, Russia, and India intend to participate in the study.

7.3. Blinding

This is a double-blind study. Blinded transition to ~~an~~ open-label treatment phase and/or post-treatment follow-up phase is included in this study.

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete. After the reporting database is locked for statistical analysis of the double-blind treatment phase, a limited number of Lilly personnel will be unblinded to complete the study report and prepare for submission. However, study sites, patients and all Lilly personnel directly involved in the ongoing open-label and post-treatment follow-up phases will remain blinded to patients' double-blind treatment assignment.

8. Discontinuation Criteria

Patients who discontinue the ~~study or~~ investigational product during the double-blind treatment phase (Study Period III) or open-label treatment phase (Study Period IV) will proceed immediately to Study Period V.

10.3.8. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the appropriate Lilly medical director, or designee, will be consulted to determine whether it is necessary to amend the protocol.

This study will include two database locks. The first is to occur after all patients have had the opportunity to complete the 3-month double-blind treatment phase (Study Period III). The purpose of this analysis is the final analysis of the primary efficacy endpoint, as well as efficacy and safety analyses of the double-blind phase. Study sites, patients, and all Lilly personnel directly involved in the continuing trial will remain blinded to patients' double-blind treatment assignment. Unblinding details are specified in the unblinding plan section of the SAP or a separate unblinding plan document. This analysis will not be considered an interim analysis because the double-blind phase is of primary interest.

The second database lock will occur at the post-treatment follow-up phase once all patients have had the opportunity to complete the entire study. This reporting database will include all data for all patients enrolled into the study, including all open-label and post-treatment phase data.

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