I5Q-MC-CGAW Clinical Protocol

A Randomized, Double-Blind, Placebo-Controlled Study of Galcanezumab in Adults with Treatment-Resistant Migraine – the CONQUER Study

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Confidential Information

galcanezumab (LY2951742)

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1. Synopsis

Title of Study:
A Randomized, Double-Blind, Placebo-Controlled Study of Galcanezumab in Adults with Treatment-Resistant Migraine – the CONQUER Study

Rationale:
The purpose of Study I5Q-MC-CGAW (CGAW) is to assess the efficacy and safety of galcanezumab (LY2951742) in a treatment-resistant patient population with episodic or chronic migraine. There is preliminary evidence from the treatment-resistant subpopulation in the Phase 3 migraine studies that galcanezumab may be efficacious and well-tolerated in these patients. Study CGAW will include up to 6 months on galcanezumab (3 months of double-blind treatment and 3 months of open-label treatment).

Objectives/Endpoints:

Objectives	Endpoints
Primary Objective To test the hypothesis that galcanezumab is superior to placebo in the prevention of migraine in patients with treatment-resistant migraine	The overall mean change from baseline in the number of monthly migraine headache days during the 3-month double-blind treatment phase in the total population (episodic and chronic migraine)[a]
Key Secondary Objectives **Note:** All key secondary objectives will be tested in both the total population (episodic and chronic migraine) and the episodic migraine subpopulation unless otherwise specified.	The specific methodology (including testing order and population) for the tests of the following key secondary endpoints will be specified in the statistical analysis plan:
• To compare galcanezumab with placebo with respect to prevention of migraine in the episodic migraine subpopulation	• The overall mean change from baseline in the number of monthly migraine headache days during the 3-month double-blind treatment phase in patients with episodic migraine
• To compare galcanezumab with placebo with respect to 50% response rate	• The percentage of patients with ≥50% reduction from baseline in monthly migraine headache days during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to change in functioning	• The mean change from baseline in the Role Function-Restrictive domain score of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) at Month 3
• To compare galcanezumab with placebo with respect to 75% response rate	• The percentage of patients with ≥75% reduction from baseline in monthly migraine headache days during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to 100% response rate	• The percentage of patients with 100% reduction from baseline in monthly migraine headache days during the 3-month double-blind treatment phase

[a] Episodic migraine is defined as 4 to 14 migraine headache days and <15 headache days per 30-day period in the prospective baseline period. Chronic migraine is defined as at least 15 headache days per 30-day period in the prospective baseline period, of which at least 8 are migraine.

Summary of Study Design:

Study CGAW is a multicenter, randomized, double-blind, parallel, placebo-controlled study of galcanezumab in patients who meet International Classification of Headache Disorders (ICHD) criteria for a diagnosis of migraine with or without aura or chronic migraine, and who have previously failed 2 to 4 standard-of-care treatments for migraine prevention. The study has 4 periods, including a prospective baseline period to determine patient eligibility.

Treatment Arms and Duration:

Two treatment arms: galcanezumab (120 mg/month, with a 240-mg loading dose) and placebo. Following a 1-month prospective baseline period, eligible patients will be randomized in a 1:1 ratio to receive placebo or galcanezumab for up to 3 months of double-blind treatment. Investigational product is administered as 1 or 2 subcutaneous injections per month (2 injections of 120-mg galcanezumab or 2 injections of placebo at randomization; 1 injection of 120-mg galcanezumab or 1 injection of placebo at the subsequent double-blind dosing visits). Patients who complete the double-blind treatment phase may enter a 3-month open-label treatment phase. At the first dosing visit in the open-label treatment phase, patients previously assigned to placebo will receive an initial loading dose of galcanezumab 240 mg (2 injections of 120 mg each), while patients previously assigned to galcanezumab will receive 1 injection of 120-mg galcanezumab and 1 injection of placebo to retain blinding of dose assignment from the double-blind phase. Thereafter, all patients in the open-label treatment phase will receive 120 mg/month galcanezumab.

Number of Patients:

The study will screen an estimated 764 potential study participants to ensure randomization of approximately 420 patients with migraine, of which approximately 250 patients have episodic migraine.

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 one 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/she has a baseline and a 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 migraine headache days during the 3-month double-blind treatment phase. Migraine headache day is defined to include both migraine and probable migraine days. The primary analysis will be performed using a restricted maximum likelihood-based mixed model repeated measures technique.

2. Schedule of Activities

Table CGAW.1. Schedule of Activities

Study Period	SP I Screening	SP II Prospective Baseline	SP III Double-Blind Treatment				SP IV Open-Label Treatment			ET	Notes
(Target) Interval (days) since previous visit			30-45	30	30	30	30	30	30		
Allowable range (days) between visits	3-30	30-40[a]									
Interval allowance (days)				±2	±2	±2	±2	±2	±2		
Visit	1	2	3	4	5	6	7	8	9		
Month			0	1	2	3	4	5	6		
Assessments and Procedures											
Informed consent	X										
Inclusion/exclusion	X	X	X								
Demographics	X										
Physical examination	X										
Neurological examination	X								X	X	
Height	X										
Weight	X		X			X			X	X	
Medical history	X										
Substance use	X										Substances: alcohol, caffeine, nicotine, tobacco
ECG	X		X			X			X	X	Predose and prior to blood draws. See Section 9.4.1.

Schedule of Activities

Study Period	SP I Screening	SP II Prospective Baseline	SP III Double-Blind Treatment				SP IV Open-Label Treatment			ET	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**		
Month			**0**	**1**	**2**	**3**	**4**	**5**	**6**		
Vital signs	X		X	X	X	X	X	X	X	X	Includes body temperature, sitting blood pressure, and pulse. Predose and prior to blood draws. See Section 9.4.2.
Adverse events	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	
ePRO and headache medication log training		X									
ePRO daily patient entries		X	X	X	X	X	X	X	X	X	
Headache medication log		X	X	X	X	X	X	X	X	X	
Patient training video			X								
Clinical Laboratory Tests and Sampling Schedule											
Hematology	X		X			X			X	X	See Appendix 2.
Clinical chemistry[b]	X		X			X			X	X	Fasting is not required. See Appendix 2.
HbA1c			X			X			X	X	Fasting is not required.
Urinalysis	X		X			X			X	X	See Appendix 2. In the event of a positive urine leukocyte esterase result, a repeat urine sample will be collected and shipped to the central laboratory.
Serum Pregnancy (for women of childbearing potential) or FSH (Visit 1 only; all other female patients)	X								X	X	A positive urine test must be followed by a serum pregnancy test for confirmation. Collect serum pregnancy at Visit 6 if patient not continuing into SP IV.

Schedule of Activities

Study Period	SP I Screening	SP II Prospective Baseline	SP III Double-Blind Treatment				SP IV Open-Label Treatment			ET	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**		
Month			**0**	**1**	**2**	**3**	**4**	**5**	**6**		
Urine pregnancy			X	X	X	X	X	X			A positive urine test must be followed by a serum pregnancy test for confirmation. Collect serum pregnancy at Visit 6 if patient not continuing into SP IV.
Urine drug screen	X										
Immunogenicity storage sample[c]			X								Predose
Pharmacogenetic sample (genetic sample/DNA)			X								Predose
RNA			X			X					Predose
Study drug administered			X	X	X	X*	X	X			IP injections are to occur after all other visit procedures are completed. ***Patients not entering SP IV will not receive IP at V6.**
Scales, Questionnaires, and Outcome Measures											
MIDAS			X			X			X	X	
MSQ v2.1			X	X	X	X	X	X	X	X	
HCRU/Employment Status			X	X	X	X	X	X	X	X	
PGI-S			X			X			X	X	
MIBS-4			X	X	X	X	X	X	X	X	
EQ-5D-5L			X			X			X	X	
WPAI			X			X			X	X	
CCI			X			X			X	X	
CCI			X			X			X	X	

Schedule of Activities

Abbreviations: AE = adverse event; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ePRO = electronic patient-reported outcomes; EQ-5D-5L = European Quality of Life 5-Dimensions 5-Levels; ET = early termination; FSH = follicle stimulating hormone; CCI [redacted] CCI [redacted]; HbA1c = hemoglobin A1c; HCRU = Health Care Resource Utilization questionnaire; IP = investigational product; MIBS-4 = 4-item Migraine Interictal Burden Scale; MIDAS = Migraine Disability Assessment; MSQ (v2.1) = Migraine-Specific Quality of Life Questionnaire version 2.1; PGI-S = Patient Global Impression of Severity; CCI [redacted]; RNA = ribonucleic acid; SP = study period; V = visit; WPAI = Work Productivity and Activity Impairment Questionnaire.

[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] 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. 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 use the 800 series as the visit designation.

[c] An immunogenicity sample may also be collected and analyzed in the event of a serious potential systemic hypersensitivity AE. Additional tests may be requested in order to further characterize the event and/or aid interpretation of the anti-drug antibody result. See Section 9.4.3.

3. Introduction

3.1. Study Rationale

The purpose of Study I5Q-MC-CGAW (CGAW) is to assess the efficacy and safety of galcanezumab (LY2951742) in a treatment-resistant patient population with episodic or chronic migraine. Treatment resistance, in this study, will be defined as previous failure to respond to 2 to 4 different standard-of-care migraine preventive medications either due to inadequate efficacy and/or due to safety/tolerability reasons (see Section 6.1 for further details).

The efficacy and safety of galcanezumab have previously been established in three Phase 3 clinical trials (Study I5Q-MC-CGAG [CGAG] and Study I5Q-MC-CGAH [CGAH] for episodic migraine and Study I5Q-MC-CGAI [CGAI] for chronic migraine). Subgroup analyses in those patients with at least 2 prior migraine preventive treatment failures due to efficacy alone (prespecified) or efficacy and/or safety/tolerability reasons (post hoc) have indicated clinically meaningful improvements in multiple outcomes. However, the Phase 3 studies excluded patients who had failed medications from 3 or more classes of migraine preventives due to inadequate efficacy among those medications with Level A or Level B evidence (defined as those listed in Silberstein et al. [2012] or botulinum toxin A or B).

Study CGAW will thus enable a comprehensive clinical assessment of galcanezumab in a broader treatment-resistant patient population, including patients who may potentially have failed up to 4 different classes of standard-of-care migraine preventives. Treatment resistance is more prevalent among patients with chronic migraine than episodic; however, the episodic form of migraine (ie, 4 to 14 migraine headache days and fewer than 15 headache days per month) is the most common, with approximately 7% of the migraine population suffering from the chronic form (ie, at least 15 headache days per month, of which at least 8 are migraine) (Buse et al. 2012; Katsarava et al. 2012; Blumenfeld et al. 2013; ICHD-3 2018). Therefore, there is a need to evaluate the efficacy and safety of galcanezumab in a treatment-resistant population, as well as specifically address for the episodic population. Study CGAW will include up to 6 months on galcanezumab (3 months of double-blind treatment and 3 months of open-label treatment).

3.2. Background

Migraine is a chronic, debilitating neurological disease found to be one of the top 10 causes of disability worldwide (Vos et al. 2012). Despite the availability of preventive medications for migraine, many patients do not respond to these treatments or are unable to tolerate them. Research on treatment patterns indicate that, among all preventive medication users in the United States, Germany, France, and Japan, approximately 43% have a history of previous preventive medication failure or of switching treatments (Pike et al. 2016). Among patients with episodic or chronic migraine who are undergoing oral preventive treatment, side effects and a lack of efficacy are the most common reasons for discontinuation (Blumenfeld et al. 2013). Among patients whose disease is not adequately managed, the negative impact on patient functioning increases, leading to losses in work/school and home productivity, missing or restricting family and social activities, and an overall decrease in quality of life (Blumenfeld et al. 2011; Lantéri-Minet et al. 2011; Bagley et al. 2012; Abu Bakar et al. 2016). Another indicator of the disabling

nature of the inadequate treatment of migraine is health care resource utilization (Shah et al. 2013; Messali et al. 2016). The number of outpatient visits is greater among patients with migraine compared to patients without migraine, and the direct costs associated with health care resource utilization are even greater among patients with a history of switching and discontinuing multiple migraine preventive treatments (Bonafede et al. 2017; Ford et al. 2017; Raval and Shah 2017). Therefore, new treatment options are needed, particularly for those patients who have previously failed multiple preventive medications.

Calcitonin gene-related peptide (CGRP) is a 37-amino acid neuropeptide widely expressed throughout the central and peripheral nervous system. Calcitonin gene-related peptide 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. 1998, 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.

3.3. Benefit/Risk Assessment

Galcanezumab is a humanized monoclonal antibody that potently and selectively binds to CGRP and prevents its biological activity without blocking the CGRP receptor. The efficacy of galcanezumab for the prevention of migraine has been demonstrated in three Phase 3 randomized, double-blind trials which found statistically significant and clinically meaningful mean reduction of monthly migraine headache days and improvement in patient function compared to placebo in patients with episodic and chronic migraine. Across Phase 2 and Phase 3 clinical studies in patients with migraine, galcanezumab exhibited a favorable safety profile at doses up to 300 mg every 4 weeks for 3 months, or 240 mg monthly for up to 1 year. The incidences of serious adverse events (SAEs) and discontinuations due to adverse events (AEs) were low, and treatment-emergent adverse events (TEAEs) were generally of mild to moderate severity. In the Phase 3 studies, the most commonly reported TEAEs were injection site pain and injection site reactions, also generally of mild to moderate severity. There was no evidence of an effect on cardiovascular function. These data provide a favorable benefit-risk profile for galcanezumab for migraine prevention.

More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of galcanezumab are to be found in the Investigator's Brochure (IB).

4. Objectives and Endpoints

Table CGAW.2 shows the objectives and endpoints of the study. Table CGAW.3 provides migraine and headache endpoint definitions.

Table CGAW.2. Objectives and Endpoints

Objectives	Endpoints
Primary Objective To test the hypothesis that galcanezumab is superior to placebo in the prevention of migraine in patients with treatment-resistant migraine	The overall mean change from baseline in the number of monthly migraine headache days during the 3-month double-blind treatment phase in the total population (episodic and chronic migraine)[a]
Key Secondary Objectives **Note:** All key secondary objectives will be tested in both the total population (episodic and chronic migraine) and the episodic migraine subpopulation unless otherwise specified.	The specific methodology (including testing order and population) for the tests of the following key secondary endpoints will be specified in Section 10.3.3.2 and the statistical analysis plan:
• To compare galcanezumab with placebo with respect to prevention of migraine in the episodic migraine subpopulation	• The overall mean change from baseline in the number of monthly migraine headache days during the 3-month double-blind treatment phase in patients with episodic migraine
• To compare galcanezumab with placebo with respect to 50% response rate	• The percentage of patients with ≥50% reduction from baseline in monthly migraine headache days during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to change in functioning	• The mean change from baseline in the Role Function-Restrictive domain score of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) at Month 3
• To compare galcanezumab with placebo with respect to 75% response rate	• The percentage of patients with ≥75% reduction from baseline in monthly migraine headache days during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to 100% response rate	• The percentage of patients with 100% reduction from baseline in monthly migraine headache days during the 3-month double-blind treatment phase

Objectives and Endpoints

Objectives	Endpoints
Other Secondary Objectives **Note:** All other secondary objectives will be tested in both the total population (episodic and chronic migraine) and the episodic migraine subpopulation unless otherwise specified.	
• 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 migraine headache days is demonstrated and maintained at all subsequent months through Month 3 in the double-blind treatment phase • If the initial month of onset is Month 1, then the initial week at which statistical separation in mean change from baseline in the number of weekly migraine headache days is demonstrated and maintained at all subsequent weeks during Month 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 days with acute headache medication use during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to change in monthly 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 International Classification of Headache Disorders (ICHD) migraine headache days	• The overall mean change from baseline in the number of monthly International Classification of Headache Disorders (ICHD) migraine headache days during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to change in monthly migraine headache hours	• The overall mean change from baseline in the number of monthly migraine headache hours during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to change in monthly headache hours	• The overall mean change from baseline in the number of monthly headache hours during the 3-month double-blind treatment phase

Objectives and Endpoints

Objectives	Endpoints
Other Secondary Objectives (continued)	
• To compare galcanezumab with placebo with respect to changes in disability and quality of life	• Changes from baseline to Month 3 on the following measures: • Migraine Disability Assessment test (MIDAS) total score and individual items • MSQ v2.1 total score, and Role Function-Preventive and Emotional Function domain scores • Health Care Resource Utilization (HCRU) and Employment Status • European Quality of Life Questionnaire 5-Dimensions 5-Levels (EQ-5D-5L) • 4-item Migraine Interictal Burden Scale (MIBS-4) • Work Productivity and Activity Impairment Questionnaire (WPAI)
• To compare galcanezumab with placebo with respect to change in patient global impression of the severity of migraine	• 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 migraine attacks (episodic migraine subpopulation only)	• The overall mean change from baseline in the number of monthly migraine attacks during the 3-month double-blind treatment phase in patients with episodic migraine
• To compare galcanezumab with placebo with respect to 30% response rate (chronic migraine subpopulation only)	• The percentage of chronic migraine patients with ≥30% reduction from baseline in monthly migraine headache days during the 3-month double-blind treatment phase
• 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 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 phase o Among patients previously treated with galcanezumab who meet 50% response criteria at Month 3 in the double-blind treatment phase, the proportion of patients who demonstrate 50% response for all 3 months in the open-label treatment phase

Objectives and Endpoints

Objectives	Endpoints
Tertiary Objectives **Note:** All tertiary objectives will be tested in both the total population (episodic and chronic migraine) and the episodic migraine subpopulation.	
• To compare galcanezumab with placebo with respect to changes in symptoms associated with migraine	• Change from baseline in the number of monthly migraine headache days with: o nausea and/or vomiting o photophobia and phonophobia o aura o prodromal symptoms • Change from baseline in the number of monthly symptom-free days and headache-free days
• CCI [redacted]	• CCI [redacted]
• To explore use of comfort measures at the injection site	• Descriptive summary of comfort measures used

[a] Episodic migraine is defined as 4 to 14 migraine headache days and <15 headache days per 30-day period in the prospective baseline period. Chronic migraine is defined as at least 15 headache days per 30-day period in the prospective baseline period, of which at least 8 are migraine.

Table CGAW.3. Migraine and Headache Endpoint Definitions

Diagnosis	Definition/Criteria
Migraine headache	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 • Pulsating 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 definition)*
Probable migraine headache	A headache of ≥30 minutes duration, with or without aura, but missing one of the migraine features in the IHS ICHD-3 definition. To be exact, it meets either at least two A criteria and zero B criteria, or one A criteria and at least one B criteria.
Migraine headache day (primary objective)	A calendar day on which a migraine headache or probable migraine headache occurs.
ICHD migraine headache day	A calendar day on which a migraine headache occurs.
Migraine headache attack	Beginning on any day a migraine headache or probable migraine headache is recorded and ends when a migraine-free day occurs.
Non-migraine headache	All headaches of ≥30 minutes duration not fulfilling the definition of migraine or probable migraine.
Non-migraine headache day	A calendar day on which a non-migraine headache occurs.
Headache day	A calendar day on which any type of headache occurs (including migraine, probable migraine, and non-migraine headache).
Episodic migraine	Four to 14 migraine headache days and <15 headache days per 30-day period in the prospective baseline period.
Chronic migraine	At least 15 headache days per 30-day period in the prospective baseline period, of which at least 8 are migraine.

Abbreviations: ICHD = International Classification of Headache Disorders; IHS = International Headache Society.

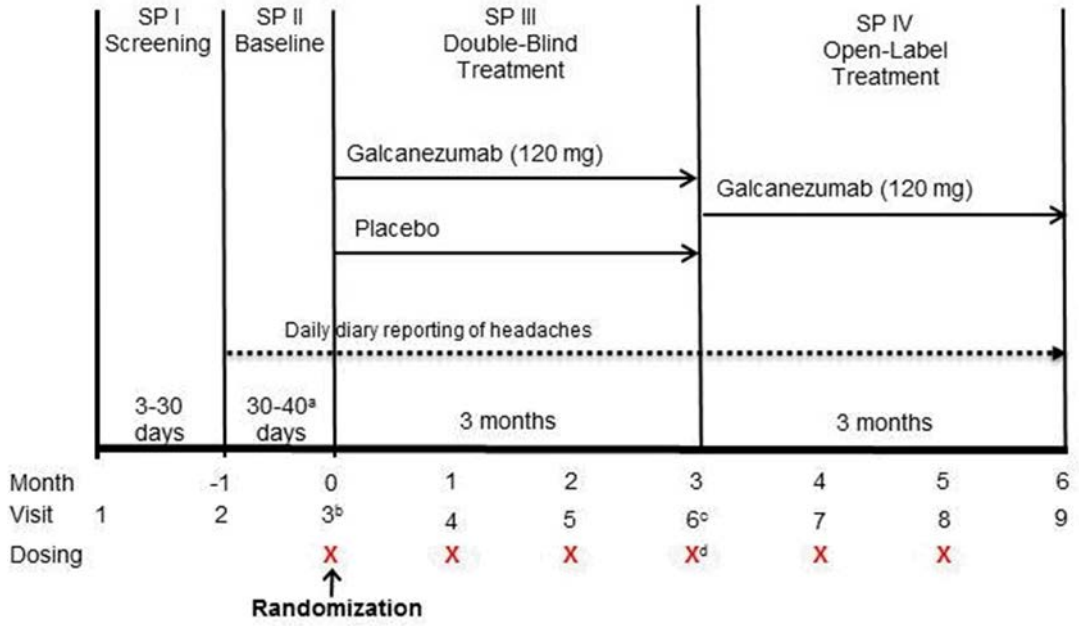
5. Study Design

5.1. Overall Design

Study CGAW is a Phase 3, multicenter, randomized, double-blind, parallel, placebo-controlled study of galcanezumab in patients who meet International Headache Society (IHS) International Classification of Headache Disorders – 3rd edition (ICHD-3) criteria for a diagnosis of migraine with or without aura or chronic migraine, and have a history of 2 to 4 prior migraine preventive treatment failures due to inadequate efficacy or tolerability. The study has 4 periods, including a prospective baseline period to determine patient eligibility.

Study governance considerations are described in detail in Appendix 3.

Figure CGAW.1 illustrates the study design.



Abbreviation: SP = study period.

[a] Eligibility period determined between a minimum of 30 days and a maximum of 40 days, with up to 5 additional days to schedule randomization visit, if necessary.

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

[c] Patients randomized to placebo who enter SP IV will receive a loading dose of galcanezumab 240 mg at the first injection only of SP IV (Visit 6).

[d] First injection of the open-label treatment phase will occur at Visit 6 once all study procedures for the double-blind phase are completed.

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

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 treatments for migraine prevention at least 5 days prior to Visit 2. Botulinum toxin A or B in the head or neck area for therapeutic use must be discontinued at least 3 months prior to Visit 2. Nerve blocks or device use, such as transcranial magnetic stimulation, in the head or neck area or for migraine prevention are not allowed within 30 days before 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 (see Schedule of Activities, Section 2). Visit 1 will be complete when the last scheduled procedure of the screening assessment for the patient 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 double-blind treatment phase. 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 whether any acute headache medication was taken. Also beginning at Visit 2, patients will 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 migraine or headache days 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 120 mg/month galcanezumab (with an initial 240-mg loading dose) or placebo. At Visit 3, if available and where local regulations and ethical review boards (ERBs) allow, patients will also watch a training video designed to address patient expectations with regard to participation in a placebo-controlled trial and the difference between medical treatment and research. To preserve blinding, patients in both treatment groups will receive 2 injections of investigational product at the first dosing visit (2 galcanezumab injections of 120 mg or 2 placebo injections) and then 1 injection of investigational product (120-mg galcanezumab or placebo) for the next 2 dosing visits.

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 investigational product (galcanezumab or placebo) injections during office visits (Figure CGAW.1). For both treatment groups, investigational product will be administered by subcutaneous injection once monthly at the dosing visits. Patients will continue to log in and complete the ePRO diary each day. Patients may continue to take their allowed acute migraine headache medication (with some limitations; see Section 7.7) during the treatment phase and will continue to record this use.

Patients will receive their last double-blind dose of investigational product at Visit 5. Patients who do not opt to continue into Study Period IV will receive no further injections.

Study Period IV: Patients who complete the double-blind treatment phase (Study Period III) can opt to enter an open-label treatment phase (Study Period IV) for 3 months of treatment with galcanezumab. Sites and patients will remain blinded to patients' previous treatment assignments. In order to preserve that blind but to allow for a loading dose to be administered to previous placebo patients, all patients who enter the open-label treatment phase will receive 2 injections at Visit 6, and sites and patients will remain blinded to the dose administered at Visit 6; patients previously assigned to galcanezumab will receive 1 injection of 120 mg and 1 injection of placebo, while those patients previously assigned to placebo will receive an initial loading dose of galcanezumab 240 mg (2 injections of 120 mg each). Injections administered after Visit 6 will be unblinded to dose as all patients will be receiving 120 mg/month galcanezumab at the next 2 dosing visits (Visit 7 and Visit 8). Patients will continue to have efficacy and safety assessed, including daily completion of the ePRO diary and recording of acute headache medication use (see Schedule of Activities, Section 2).

5.2. Number of Participants

The study will screen an estimated 764 potential study participants to ensure randomization of approximately 420 patients with migraine, of which approximately 250 patients have episodic migraine (defined as 4 to 14 migraine headache days and <15 headache days per 30-day period in the prospective baseline period). To ensure an appropriate balance of patients with episodic and chronic migraine, the sponsor will stop enrollment of patients with chronic migraine if the number of patients exceeds approximately 40%. Chronic migraine will be defined as at least 15 headache days per 30-day period in the prospective baseline period, of which at least 8 are migraine. Further details are available in Section 10.1.

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, double-blind treatment phase (3 months) is considered a sufficient duration to demonstrate the efficacy of a migraine preventive medication versus placebo given the mechanism and observed onset of action for CGRP antibodies (Dodick et al. 2014a, 2014b). Furthermore, a placebo-controlled study with a duration longer than 3 months may not be tolerated by patients suffering from chronic migraine. A 3-month open-label extension is included to allow for assessment of maintenance of effect and longer-term safety.

The use of a placebo-controlled study is considered to be appropriate, as major treatment guidelines rely on placebo-controlled data as the gold standard for establishing levels of evidence in support of treatment efficacy (eg, European Federation of Neurological Societies [Evers et al. 2009], American Academy of Neurology [Silberstein et al. 2012]).

5.5. Justification for Dose

In the adult Phase 3 migraine studies, the dose regimen of 120 mg/month with a 240-mg loading dose was found to be efficacious and safe for the prevention of migraine in adult patients. A loading dose of 240 mg resulted in achievement of steady-state concentrations for the 120-mg monthly maintenance dose by Month 1.

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 Sections 6.1 and 6.2. The nature of any comorbid conditions present at the time of the physical examination and any pre-existing 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 (see Section 6.4).

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 75 years of age (inclusive) at the time of screening.

[2] Have a diagnosis of migraine as defined by IHS ICHD-3 guidelines (1.1, 1.2, or 1.3) (ICHD-3 2018), with a history of migraine headaches 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 at least 4 migraine headache days and at least 1 headache-free day per month on average within the past 3 months.

[4] Prior to Visit 1, have documentation (medical or pharmacy record or by physician's confirmation) of previous failure to 2 to 4 migraine preventive medication categories in the past 10 years from the following list due to inadequate efficacy (that is, maximum tolerated dose for at least 2 months) and/or safety/tolerability reasons.

a) propranolol or metoprolol
b) topiramate
c) valproate or divalproex
d) amitriptyline
e) flunarizine
f) candesartan
g) botulinum toxin A or B (if documented that botulinum toxin was taken for chronic migraine)
h) medication locally approved for prevention of migraine

Note: Patients only qualifying under the above criteria with f) and h) should not exceed 20% of the total study population.

[5] From Visit 2 to Visit 3 (prospective baseline period), have a frequency of 4 or more migraine headache days and at least 1 headache-free day per 30-day period (see definitions in Table CGAW.3). **To avoid biased reporting, patients will not be told the number of migraine or headache days on which study qualification is based.**

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

Informed Consent and Patient Agreements

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

[8] Are reliable and willing to follow study procedures.

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

[10] All females 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 with contraceptive foam, or intrauterine devices; or a partner with vasectomy. Birth control is not required if the female is infertile due to surgical sterilization (hysterectomy, or at least 6 weeks after surgical bilateral oophorectomy or 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 6-12 months and a follicle stimulating hormone level >40 mIU/mL.

[11] Agree not to post any personal medical data related to the study or information related to the study on any website or social media site (eg, Facebook, Twitter, LinkedIn, Google+, etc.) until the entire trial has completed.

6.2. Exclusion Criteria

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

Prior/Concomitant Therapy

[12] 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.

[13] 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.

[14] Prior use of galcanezumab or another CGRP antibody or CGRP receptor antibody, including those who have previously completed or withdrawn from this study.

[15] Known hypersensitivity to monoclonal antibodies or other therapeutic proteins, or to galcanezumab.

[16] Are currently receiving medication or other treatments for the prevention of migraine headaches. Patients must have discontinued such treatment at least 5 days prior to Visit 2. Botulinum toxin A and B that has been administered in the head or neck area for therapeutic use must be discontinued at least 3 months prior to Visit 2. Nerve blocks or device use (such as transcranial magnetic stimulation) in the head or neck area or for migraine prevention must be discontinued at least 30 days prior to Visit 2.

[17] Have previously failed more than 4 migraine preventive medication categories from the list in Inclusion Criterion [4] due to inadequate efficacy (that is, maximum tolerated dose for at least 2 months) and/or safety/tolerability reasons. Previous failures to medications not on the above list will not count toward this exclusion.

Diagnostics Assessments

[18] History of cluster headache or migraine subtypes including hemiplegic (sporadic or familial) migraine, ophthalmoplegic migraine, and migraine with brainstem aura (basilar-type migraine) defined by IHS ICHD-3.

[19] In the 3 months prior to randomization, have other types of headache besides migraine, tension type headache, or medication overuse headache (MOH) as defined by IHS ICHD-3. (In other words, patients can have migraine, tension type headache, or MOH in the 3 months prior to randomization, but they cannot have other types of headache in that time.)

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

[21] History of traumatic head injury associated with significant change in the quality or frequency of their headaches.

Medical Conditions

[22] Have centralized reading of ECG at Visit 1 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 stroke within 6 months of screening, or have planned cardiovascular surgery or percutaneous coronary angioplasty. Fridericia-corrected QT interval (QTcF) >450 msec for males or >470 msec for females based on the centralized reading of the ECG at Visit 1 must be discussed and judged not clinically significant by the principal investigator and Lilly Medical prior to enrollment.

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

[24] Evidence of significant active or unstable psychiatric disease by medical history, such as bipolar disorder, schizophrenia, personality disorders, or other serious mood or anxiety disorders. 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.

[25] Patients who, in the clinician's judgment, are actively suicidal and therefore deemed to be at significant risk for suicide, or have had clinically significant suicidal ideation within the past month (eg, includes some plan or intent to act), or have had any suicidal behavior within the past month.

[26] Women who are pregnant or nursing.

[27] Patients who have used opioids or barbiturate containing analgesic >4 days per month for the treatment of pain in more than 2 of the past 3 months.

[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 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 positive urine drug screen for any substances of abuse at Visit 1. Note: A retest is allowed if the urine drug screen is positive for any prescribed substance or if, in the judgment of the investigator, there is an acceptable medical explanation for the positive result. The results of the retest must be negative at or prior to Visit 2.

[30] Have an acute, serious, or unstable medical condition that, in the judgment of the investigator, indicates a medical problem that would preclude study participation.

Other Exclusions

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

[32] 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.

[33] Are Lilly employees.

[34] 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. Fasting is not required prior to collection of laboratory samples.

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

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be considered for rescreen once, with approval from Lilly Medical for only the criteria shown below. If rescreening is performed, the individual must sign a new ICF and will be assigned a new identification number

- Inclusion Criterion [1] (age): 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 [4] (2 to 4 previous treatment failures)
- Inclusion Criterion [9] (negative pregnancy test)
- Exclusion Criterion [13] (washout previous investigational product)
- Exclusion Criterion [16] (washout previous preventives)
- Exclusion Criterion [26] (pregnant or nursing)

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. Treatments

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. Site staff will administer injections of galcanezumab or placebo at 3 office visits during the double-blind treatment phase and administer galcanezumab at 3 office visits during the open-label treatment phase (Section 2).

Possible injection sites include the abdomen, thigh, and upper arm. Buttocks may also be used, if needed. Site staff are encouraged to administer comfort measures (such as cold compress, ice pack, or topical anesthetic cream) to the injection site prior to or after the injection at their clinical discretion or as needed. Injection locations and any comfort measures used will be recorded in the patient's electronic case report form (eCRF).

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

- explaining the correct use of the investigational agent to the site personnel
- verifying that instructions are followed properly
- 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 during the double-blind treatment phase. 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 single syringe cartons, with the appropriate quantity of syringes dispensed specific to the planned dispensing schedule of the investigational product.

Clinical study 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 during the double-blind treatment phase. The IWRS will also be used to assign investigational product during the open-label treatment

phase. 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 migraine frequency from the prospective baseline period (low frequency episodic, high frequency episodic, chronic). Low frequency episodic will be defined as 4 to <8 migraine headache days per 30-day period. High frequency episodic will be defined as 8 to 14 migraine headache days per 30-day period, with <15 headache days (migraine or nonmigraine) per 30-day period. Chronic migraine will be defined as ≥8 migraine headache days per 30-day period, with ≥15 headache days (migraine or nonmigraine) per 30-day period. To ensure an appropriate balance of patients with episodic and chronic migraine, the sponsor will stop enrollment of patients with chronic migraine if the number of patients exceeds approximately 40%.

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

7.3. Blinding

This is a double-blind study. Blinded crossover to an open-label treatment 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 sponsor personnel will be unblinded to complete the study report and prepare for submission. However, any sponsor personnel continuing with the management and oversight of the trial will remain blinded to patients' previous 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 clinical research physician or clinical research scientist 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 for medical management of the event. Patient safety must always be the first consideration in making such a determination. If a patient's treatment assignment is unblinded, Lilly must be notified immediately. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

7.4. Dosage Modification

No dose modification will be allowed during the double-blind or open-label treatment phases.

7.5. Preparation/Handling/Storage/Accountability

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

- confirming appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- ensuring that only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- the investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

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

To administer the galcanezumab injections, the investigational sites are to refer to the pharmacy binder for the preparation and handling instructions of the packaged investigational product.

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, the situation should be discussed with Lilly to determine if the patient may continue.

7.7. Concomitant Therapy

Table CGAW.4 contains the list of medications that are, and are not, allowed in this study. Any changes in the list of allowed/not allowed medications will be communicated to investigators and will not constitute a protocol amendment. The concomitant use of acute medications to treat migraine is allowed, with some limitations. Treatments used for the prevention of migraine, including nutraceuticals and non-pharmacological interventions, are not allowed at any time during Study Periods II, III, or IV. Patients should have washed out all migraine preventive treatments at least 5 days prior to Visit 2. Botulinum toxin A or B in the head or neck area for therapeutic use is not allowed within 3 months prior to Visit 2. Nerve blocks or use of therapeutic devices (such as transcranial magnetic stimulation) in the head or neck area or for migraine prevention are not allowed within 30 days before Visit 2.

Patients will capture whether they took any acute headache medication as part of their daily diary entry during Study Periods II, III, and IV. Acute headache medication name, dose, and date will be recorded by patients during Study Periods II, III, and IV on a headache medication log, which will be returned to site staff at each study visit.

Table CGAW.4. Treatments Allowed and Treatments Not Allowed as Concomitant Therapy

A. Medications allowed for the ACUTE treatment of migraine headaches or other pain or injury:

Acetaminophen (paracetamol), NSAIDs; Triptans; Ergotamine and derivatives; Isometheptene mucate, dichloralphenazone and acetaminophen combination (Midrin); or combinations thereof.

The following medications are allowed with restrictions:

1. Opioid and barbiturates no more than 4 days/month.
2. Single dose of injectable steroids allowed only once during the study, in an emergency setting (SP II, III, IV).

B. Medications, Procedures or Devices not allowed for any reason/indication in SP II, III, or IV:

Acetazolamide
Acupuncture
Anticonvulsants/Antiepileptics
Antipsychotics
Beta-blockers
Botulinum toxin applied to head/neck area for therapeutic use
Cannabis / Cannabinoids
Chiropractic procedures, physiotherapy, TENS or other electric devices on head and neck
Corticosteroids for oral use
Flunarizine
Gabapentin
Herbals with anti-inflammatory effect (feverfew, willow bark, petasites/butterbur)
Iprazochrome
Lomerizine
Monoamine oxidase inhibitors (MAOIs)
Memantine
Methysergide
Neurotropin®
Nerve block in head/neck area
Oxetorone
Pizotifen
Pregabalin
Serotonin 5HT2a/2c antagonists, e.g.: trazodone, nefazodone
Stimulants (prescription strength), e.g.: methylphenidate, dextroamphetamine, mixed amphetamine salts
Tizanidine
Tricyclic antidepressants (TCAs)
Triptans for prophylaxis of menstrual related migraine
Venlafaxine
Verapamil

Treatments Allowed and Treatments Not Allowed as Concomitant Therapy

C. Restricted medication during SP II and III: Use of the following medications for indications other than migraine prevention is allowed providing the dose is stable 2 months prior to Visit 2 and is expected to remain stable during Visit 2 through 6.

ACE inhibitors
Angiotensin receptor blockers (ARBs)
Benzodiazepines
Bupropion
Calcium-channel blockers (except verapamil, flunarizine, and lomerizine)
Clonidine
Guanfacine
Mirtazapine
SSRIs/NRIs/SNRIs (other than venlafaxine)
Use of electric devices (ie, TENS), physiotherapy, chiropractic procedures on low back and extremities

D. During SP IV (Visit 6 through 9):

No medications from List B.
No medications or treatments for the prevention of migraine.
Medications in List C may now be started, stopped, or have dose modification as long as not being used for migraine prevention.

Abbreviations: 5HT = 5-hydroxytryptamine; ACE = angiotensin-converting enzyme; NRI = norepinephrine reuptake inhibitor; NSAID = nonsteroidal anti-inflammatory drug; SNRI = serotonin-norepinephrine reuptake inhibitor; SP = Study Period; SSRI = selective serotonin reuptake inhibitor; TENS = transcutaneous electrical nerve stimulation.

7.8. Treatment after the End of the Study

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

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

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 Lilly Medical:

- ALT or aspartate aminotransferase (AST) >8X ULN
- ALT or AST >5X ULN for more than 2 weeks
- ALT or AST >3X ULN and TBL >2X ULN or international normalized ratio >1.5
- ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP >3X ULN
- ALP >2.5X ULN and TBL >2X ULN
- ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

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.

Patients must be discontinued from investigational product in the event of pregnancy.

Patients must be discontinued from investigational product if the patient requests to discontinue.

Patients discontinuing from the investigational product prematurely for any reason should complete AE and other follow-up/early termination 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 identify 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 Lilly Medical agree it is medically appropriate to continue, the investigator must obtain documented approval from Lilly Medical to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product. Safety follow up/early termination procedures are 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

Patients will be discontinued in the following circumstances:

- Enrollment in any other clinical study 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 a disallowed therapeutic agent that has been demonstrated to be effective for the study indication (prevention of migraine) during Study Periods II, III, or IV, discontinuation from the study occurs prior to introduction of the new agent
- Patient Decision
    - the patient requests to be withdrawn from the study

Patients discontinuing from the study prematurely for any reason should complete AE and other safety follow-up/early termination procedures 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.

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 to record headache information, including reporting headaches, intensity of headache, headache features, and whether any acute headache medication was taken. The system also will be used to collect information about migraine-associated symptoms (eg, photophobia, phonophobia, nausea, and/or vomiting).

9.1.2. Secondary Efficacy Assessments

Secondary efficacy assessments in this study (Table CGAW.2) are intended to facilitate the collection and analysis of information such as response (≥50% reduction from baseline in the number of migraine headache days per month) and changes in medication use for the acute treatment of headache. Much of this information 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 monthly site visits. The scale to be used for secondary efficacy assessment is summarized below.

Patient Global Impression of Severity Scale: The Patient Global Impression of Severity (PGI-S) scale (Guy 1976) is a patient-rated instrument that measures illness severity. For this study, the patient will be instructed as follows: "Considering migraine as a chronic condition, how would you rate your level of illness?" 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

The efficacy and safety assessments used in this study 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, disability, CCI [redacted].

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 and ECG.

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. However, any worsening of the primary study condition should be recorded as an AE.

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

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

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

The investigator will answer yes or no when making this assessment.

The investigator will use AE follow-up forms to record additional details regarding AEs related to injection sites and hypersensitivity events.

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 discontinuation 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 (ie, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- when a condition related to the investigational device (eg, 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.

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria. The SAE reporting to the sponsor 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, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines (see Section 9.2) 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. Patients with a serious hepatic AE should have additional data collected using the eCRF.

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 following 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 disposition 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/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 guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording, and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

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 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

Refer to the IB.

9.4. Safety

9.4.1. Electrocardiograms

For each patient, a single 12-lead digital ECG will be collected according to the Schedule of Activities (Section 2). 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. Electrocardiograms will have a central overread and should be recorded according to the study-specific recommendations included in the ECG manual.

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the patient receives the first dose of the investigational treatment 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 as a single measurement in the sitting position prior to blood draws and dosing, according to the Schedule of Activities (Section 2) and following the study-specific recommendations included in the Manual of Operations for the study.

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

In addition, an immunogenicity blood sample will be collected, when possible, for any patient who experiences a serious potential systemic hypersensitivity event during the study as judged by the investigator. This immunogenicity blood 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.

Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor. Note that any anti-drug antibody result that may unblind a site would not be shared.

9.4.4. Immunogenicity Assessments

Immunogenicity will not be proactively evaluated in this study. However, where local regulations and ERBs allow, a single venous blood sample will be collected prior to the start of treatment as specified in the Schedule of Activities (Section 2) and stored for future immunogenicity assessments, if applicable. Immunogenicity samples may also be collected from a patient in the event of a serious potential systemic hypersensitivity event, as noted in Section 9.4.3.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and ERBs allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to galcanezumab. Any samples remaining after 15 years will be destroyed.

9.4.5. Safety Monitoring

Investigators are responsible for monitoring individual patient safety throughout the trial.

Neurological examinations will be conducted in order to assess for any signs of pre-existing or treatment-emergent neurological abnormalities such as stroke or other cerebrovascular events.

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 ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X 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 Lilly Medical. 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 eCRF if one or more of the following conditions occur:

- elevation of serum ALT to ≥5X ULN on 2 or more consecutive blood tests
- elevated serum TBL to ≥ 2X ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2X 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 an SAE

9.5. Pharmacokinetics

Not applicable.

9.6. Pharmacodynamics

Not applicable.

9.7. Genetics

9.7.1. Whole Blood Sample for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities (Section 2) where local regulations and ERBs allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to galcanezumab and to investigate genetic variants thought to play a role in migraine. Assessment of variable response may include evaluation of AEs or differences in efficacy. These studies may include, but are not limited to, CGRP and molecules that directly and indirectly influence CGRP signaling to evaluate their association with observed response to galcanezumab.

All pharmacogenetic samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel. Samples will be destroyed according to a process consistent with local regulations.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs impose shorter time limits, at a facility selected by the sponsor. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in drug development or when the drug becomes commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome wide association studies, candidate gene studies, and epigenetic analyses. Regardless of technology utilized, genotyping data generated will be used only for the specific research scope described in this section.

9.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics, mechanism of action, variability of patient response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including deoxyribonucleic acid (DNA), ribonucleic acid (RNA), proteins, lipids, and other cellular elements.

Blood samples for nonpharmacogenetic biomarker research will be collected at the times specified in the Schedule of Activities (Section 2) where local regulations and ERBs allow.

Samples will be used for research on the drug target, disease process, variable response to galcanezumab, pathways associated with migraine and/or other pain conditions, mechanism of action of galcanezumab, and/or research method or in validating diagnostic tools or assay(s) related to migraine and/or other pain conditions.

All biomarker samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel. Samples will be destroyed according to a process consistent with local regulations.

Samples will be retained for a maximum 15 years after the last patient visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits, at a facility selected by the sponsor. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in drug development or when the drug is commercially available.

9.9. Health Economics

Health outcome measures of galcanezumab in patients with migraine will be collected as described in the Schedule of Activities (Section 2) based on the following scales:

Migraine-Specific Quality of Life Questionnaire version 2.1: The Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) is a self-administered health status instrument that was developed to address the physical and emotional impact on functioning that is of specific concern to individuals suffering from migraine headaches. 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. 1998b). The restrictive domain specifically measures disability as related to the impact on performance of normal activities, with the preventive domain addressing complete functional impairment and the emotional domain assessing the feelings related to disabling monthly migraine headache days. Responses are given using a

6-point Likert-type scale, ranging from "none of the time" to "all of the time." Raw scores for each domain are computed as a sum of item responses, with the collective sum providing a total raw score that is then converted to a 0 to 100 scale, with higher scores indicating a better health status, and a positive change in scores reflecting functional improvement (Jhingran et al. 1998a; Martin et al. 2000). The instrument was designed with a 4-week recall period and is considered reliable, valid, and sensitive to change in functional impairment due to migraine (Jhingran et al. 1998b; Bagley et al. 2012).

Migraine Disability Assessment: The Migraine Disability Assessment (MIDAS) is a patient-rated scale which 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 missed, or with reduced productivity at work or home and social events. Each question is answered as the number of days during the past 3 months of assessment, ranging from 0 to 90, with the total score being the summation of the 5 numeric responses. A higher value is indicative of more disability (Stewart et al. 1999, 2001). This instrument is considered highly reliable and valid, and is correlated with clinical judgment regarding the need for medical care (Stewart et al. 1999, 2001). For clinical interpretability, 4 categorical grades were developed based on the total score: Grade I (0 to 5) is for little or no disability, Grade II (6 to 10) is for mild disability, Grade III (11 to 20) is for moderate disability, and Grade IV (21+) is for severe disability. The severe disability category has subsequently been subdivided into Grade IV-A (severe [21 to 40]) and Grade IV-B (very severe [41 to 270]) because a high proportion of patients with chronic migraine are in Grade IV (Blumenfeld et al. 2011).

Health Care Resource Utilization and Employment Status: The Health Care Resource Utilization questionnaire (HCRU) will be solicited by study personnel while documenting patient responses. The HCRU consists of 3 questions, asking about the number of hospital emergency room visits, overnight stays in a hospital, and any other visits with a healthcare professional that occurred since the patient's last study visit, outside of visits associated with their participation in the clinical trial. Patients are also specifically asked about the number of healthcare events that are related to migraine headaches. The baseline visit will include the same questions, however with the frame of reference being over the last 6 months. A question on employment status will also be solicited, given the correlation and potential confounding with health outcomes measures.

Migraine Interictal Burden Scale: The 4-item Migraine Interictal Burden Scale (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: 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, 1-2 mild, 3-4 moderate, and $\geq$5 severe (Buse et al. 2007, 2009).

European Quality of Life 5-Dimensions 5-Levels: The European Quality of Life 5-Dimensions 5-Levels (EQ-5D-5L) questionnaire is a widely used, generic patient-rated scale that assesses current health status at the time of questionnaire completion, that is 'today' (EuroQol 1990; Herdman et al. 2011). The questionnaire consists of 2 parts. The first part assesses 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that have 5 possible levels of response (no problems, slight problems, moderate problems, severe problems, extreme problems). This part of the EQ-5D-5L can be used to generate a health state index score, which is often used to compute quality-adjusted life years for utilization in health economic analyses. The health state index score is calculated based on the responses to the 5 dimensions, providing a single value on a scale from less than 0 (where zero is a health state equivalent to death; negative values are valued as worse than dead) to 1 (perfect health), with higher scores indicating better health utility. The second part of the questionnaire consists of a visual analog scale (VAS) on which the patient rates their perceived health state from 0 (the worst health you can imagine) to 100 (the best health you can imagine).

Work Productivity and Activity Impairment Questionnaire: The Work Productivity and Activity Impairment Questionnaire (WPAI) is a patient-reported instrument developed to measure the impact on work productivity and regular activities attributable to a specific health problem (Reilly et al. 1993); for this study, the questions are specific to migraine. Recall period is the past 7 days. The scale contains 6 items that measure: 1) employment status, 2) hours missed from work due to the specific health problem, 3) hours missed from work for other reasons, 4) hours actually worked, 5) degree health affected productivity while working, and 6) degree health affected productivity in regular unpaid activities. Four scores are calculated from the responses to these 6 items: absenteeism, presenteeism, work productivity loss, and activity impairment. Scores are calculated as impairment percentages, with higher numbers indicating greater impairment and less productivity, ie, worse outcomes.

CCI

[redacted]

CCI

10. Statistical Considerations

10.1. Sample Size Determination

The study will enroll approximately 420 patients. Eligible patients will be randomized in blinded fashion in a 1:1 ratio to placebo or galcanezumab 120 mg (with a loading dose of 240 mg). With the assumption of a 10% discontinuation rate and an effect size of 0.39, it is estimated that this sample size will provide approximately 96% power that galcanezumab will separate from placebo at a 2-sided significance level of 0.05 for the intent-to-treat (ITT) population in this study.

The study is also powered for the subpopulation of patients with episodic migraine. The study will seek to enroll approximately 250 patients with episodic migraine as determined during the prospective baseline period. With the assumption of a 10% discontinuation rate and an effect size of 0.46, it is estimated that this will provide approximately 93% power that galcanezumab will separate from placebo at a 2-sided significance level of 0.05 for the episodic migraine subpopulation in this study.

Assumptions in this sample size calculation were based on data from 3 double-blind, placebo-controlled, Phase 3 studies, with an adjustment made to reflect differences in this study and the potential impact of the development phase and the inclusion of an open-label treatment phase on placebo responses.

10.2. Populations for Analyses

Three analysis populations are defined as follows: ITT population, safety population, and open-label treatment population. The ITT and safety populations include all patients who are randomized and receive at least one dose of investigational product. The open-label treatment population includes all patients who enter the open-label treatment phase as indicated by receiving any injection starting from Visit 6.

Unless otherwise stated, all efficacy analyses will be analyzed according to the ITT principle on the ITT population; that is, patients will be analyzed according to the treatment to which they were randomized, regardless of whether they actually received a different treatment. Safety analyses will be conducted on the safety population based on treatment the patient received. Analyses for the open-label treatment phase only will be based on the open-label treatment population.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

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

Unless otherwise specified, analyses will be conducted on the ITT population for efficacy analyses and on the safety population for safety analyses (see Section 10.2). When change from

baseline is assessed, the patient will be included in the analysis only if he/she has a baseline and a postbaseline measurement.

Continuous efficacy variables with repeated measures will be analyzed using mixed model repeated measures (MMRM) methods. The MMRM will include the fixed categorical effects of treatment, baseline migraine headache day frequency category (low episodic migraine, high episodic migraine, chronic migraine), pooled country, month, and treatment-by-month interaction, as well as the continuous fixed covariates of baseline and baseline-by-month interaction. For the model of the primary endpoint, the baseline migraine headache day frequency category will be excluded from the covariates since the continuous baseline monthly migraine headache day value is already in the model.

For continuous efficacy variables without repeated measures, an analysis of covariance (ANCOVA) model with last observation carried forward (LOCF) imputation will be used, which contains the main effects of treatment, baseline migraine headache day frequency category, and pooled country, as well as the continuous fixed covariate of baseline. Type III sum-of-squares for the Least Squares Means (LSMeans) will be used for the statistical comparisons.

Binary efficacy variables with repeated measures will be analyzed using a generalized linear mixed model (GLIMMIX) as pseudo-likelihood-based mixed effects repeated measures analysis. The GLIMMIX model will include the fixed, categorical effects of treatment, month, and treatment-by-month interaction, as well as the continuous, fixed covariate of baseline value.

For binary efficacy variables without repeated measures, comparisons between treatment groups will be performed using logistic regressions with the same model terms as the ANCOVA model. Pooled country may be removed to ensure model convergence.

For continuous safety variables with repeated measures, MMRM methods will be used, as well as an ANCOVA model with LOCF imputation if deemed appropriate. When an ANCOVA model is used for safety measures, the model will contain the main effect of treatment, as well as the continuous fixed covariate of baseline. Type III sum-of-squares for the LSMeans will be used for the statistical comparisons.

For categorical safety variables (such as AEs and other categorical changes of interest), as well as categorical baseline characteristics, comparisons between treatment groups will be performed using Fisher's exact test.

Treatment effects will be evaluated based on a 2-sided significance level of 0.05 for all the efficacy and safety analyses unless otherwise stated. The 95% confidence intervals for the difference in LSMeans between treatment groups will be presented. Type I error due to multiple comparisons for the primary and key secondary objectives will be controlled using sequential gating procedure (see Section 10.3.3.2). There will be no adjustments for multiplicity for analyses of other data (other secondary objectives or tertiary objectives).

Unless otherwise noted, all efficacy and safety analyses will be conducted on the total population and the episodic migraine subpopulation.

Countries will be pooled as deemed necessary for statistical analysis purposes.

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 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. 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 Study Period III and Study Period IV separately. Reasons for discontinuation will be compared between treatment groups for Study Period III with the ITT population. Descriptive statistics only will be presented for the treatment groups in Study Period IV. In addition, subcategories of discontinuation due to patient decision will be summarized.

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, sex, ethnic origin, height, weight, body mass index)
- Migraine and/or headache-related measures from the ePRO diary per 30-day baseline period
- Number of prior migraine preventive treatment failures from the list in Section 6.1 (Inclusion Criterion [4]):
    - Failed 2 medication categories
    - Failed 3 medication categories
    - Failed 4 medication categories
- Alcohol, tobacco, caffeine, and nicotine consumption
- Medical history and pre-existing conditions

Medical history and pre-existing conditions will be summarized by preferred term within system organ class (SOC).

10.3.2.3. Concomitant Therapy

The proportion of patients who received concomitant medication collected from eCRFs and the acute medications collected on the headache medication log will be summarized for all ITT patients for Study Period III and Study Period IV separately.

10.3.2.4. Treatment Compliance

Dosing will occur at monthly study visits. Treatment compliance for each patient in the double-blind treatment phase 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 before the last dosing visit (Visit 5) or early discontinuation visit in the double-blind treatment phase.

10.3.2.5. Electronic Patient-reported Outcome Diary Compliance

Electronic patient-reported outcomes diary compliance at each 1-month period (including baseline, Month 1, Month 2, Month 3, … to Month 6) as well as for Study Period III overall (Month 1 through Month 3) will be calculated. Diary compliance at each period is calculated as:

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

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary efficacy endpoint is the overall mean change from the baseline period in the number of monthly migraine headache days during the 3-month double-blind treatment phase, and the primary analysis will evaluate the efficacy of galcanezumab compared with placebo in the total ITT population.

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

An unstructured covariance structure will be used to model 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

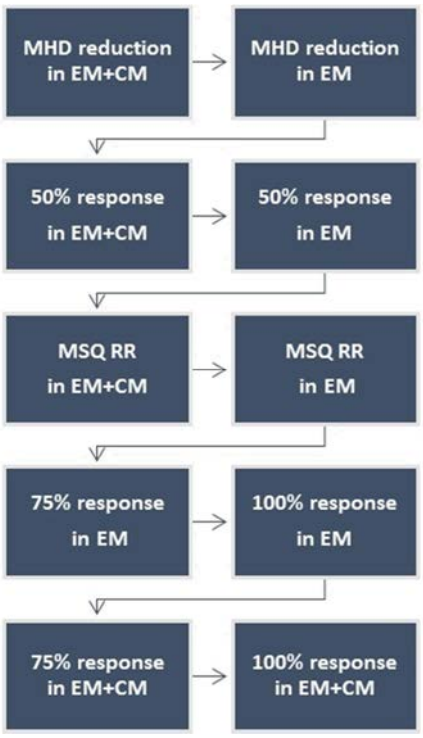
sandwich estimator is utilized, the Kenward-Roger approximation for denominator degrees of freedom cannot be used. Instead, the denominator degrees of freedom will be partitioned into between-subject and within-subject portions by the DDFM=BETWITHIN option in SAS®. SAS® PROC MIXED will be used to perform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

10.3.3.2. Key Secondary Analyses

The key secondary measures (see Table CGAW.2) will be analyzed for the double-blind treatment phase (Study Period III). The analysis models are described in Section 10.3.1. Populations tested will include the total population (episodic and chronic migraine combined) and the episodic migraine subpopulation. Patients will be categorized as episodic or chronic based on their number of migraine and headache days during the prospective baseline period.

In order to control for type I error, the key secondary analyses will be tested using a gated testing approach at a 2-sided alpha level of 0.05. If the null hypothesis is rejected for the primary endpoint, key secondary endpoints will be sequentially tested following the gatekeeping hierarchy depicted in Figure CGAW.2, starting with the comparison of change in migraine headache days between treatment groups based on the episodic migraine subpopulation. If the null hypothesis is rejected for that comparison, then the comparison of 50% response rate between treatment groups will be tested in the total population. If that null hypothesis is rejected, then the next comparison in the sequence will be tested (50% response rate in the episodic subpopulation), following this same pattern until all hypotheses are tested or until the null hypothesis is accepted for an endpoint, at which point, any further testing would stop for the key secondary objectives.

If the multiple testing approach for key secondary measures needs to be changed, the updated approach will be provided in the SAP, and it should not lead to modification of this protocol.



Abbreviations: CM = chronic migraine patients; EM = episodic migraine patients; MHD = the number of monthly migraine headache days (mean change from baseline); MSQ RR = Migraine Specific Quality of Life Questionnaire Role Function-Restrictive domain; response = response rate.
Note: All testing will be conducted at a 2-sided alpha of 0.05.

Figure CGAW.2. Gatekeeping sequence for testing of primary and key secondary endpoints.

10.3.3.3. Other Secondary and Tertiary Analyses

There will be no adjustments for multiplicity for analyses of the other secondary or tertiary endpoints not listed in Figure CGAW.2. The analysis models are described in Section 10.3.1.

10.3.4. Safety Analyses

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

- TEAEs
- SAEs
- AEs leading to discontinuation
- potential hypersensitivity events
- AEs related to injection sites
- vital signs and weight
- ECGs

- laboratory measurements

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 Fisher's exact test for Study Period III with the safety population. Descriptive statistics only will be presented for the analyses in Study Period IV.

Analyses of continuous safety data will be conducted for Study Period III and Study Period III/IV using the safety population. In those analyses, only values collected at scheduled visits will be used.

10.3.4.1. Treatment-Emergent Adverse Events

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

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

10.3.4.2. Vital Signs

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.

The number and percentage of patients meeting criteria for treatment-emergent abnormalities in vital signs and weight at any time during study will be summarized. Treatment group comparisons will be performed using Fisher's exact test.

10.3.4.3. Electrocardiogram Intervals and Heart Rate

The corrected QT interval will be calculated using the Fridericia method (QTcF). The number and percentage of patients meeting criteria for treatment-emergent abnormalities in ECG intervals (pulse, 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.

10.3.4.4. Laboratory Tests

The incidence rates of patients with treatment-emergent abnormal, high, or low laboratory values at any time postbaseline will be assessed using 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. Health Economics

The change from baseline for the double-blind treatment phase and for the open-label treatment phase for MSQ v2.1 (Role Function-Restrictive, Role Function-Preventive, and Emotional Function domains and total score), MIDAS (item scores and total score), EQ-5D-5L, MIBS-4, WPAI questionnaire, CCI [redacted] will be analyzed. In addition, categorical analyses will be performed. Changes in health care resource utilization and employment status will also be evaluated. Details are summarized in the SAP.

10.3.6. Subgroup Analyses

Subgroup analyses for the primary efficacy measure of change from baseline in the number of monthly migraine headache days will include the following subgroup variables:

- sex
- racial origin
- age
- migraine headache day frequency categories (high frequency episodic migraine, low frequency episodic migraine, or chronic migraine)
- number of failed preventive migraine medication categories (2, 3, or 4)
- geographical region

Additional details are available in the SAP.

10.3.7. Interim Analyses

An interim analysis will be conducted after all patients have had the opportunity to complete Study Period III, and thus will be the final analysis of the primary efficacy endpoint.

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.

No other 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.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	anti-drug antibodies
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
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.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
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
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.

enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ePRO	electronic patient-reported outcomes
EQ-5D-5L	European Quality of Life 5-Dimensions 5-Levels
ERB	ethical review board
CCI	[redacted]
CCI	[redacted]
GCP	good clinical practice
HCRU	Health Care Resource Utilization questionnaire
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.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
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
LOCF	last observation carried forward
LSMean	Least Squares Mean
MDD	major depressive disorder

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
CCI	[redacted]
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: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
VAS	visual analog scale
WPAI	Work Productivity and Activity Impairment Questionnaire

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology	**Clinical Chemistry**[c]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume	Total bilirubin (TBL)
Mean cell hemoglobin concentration	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase (ALP)
Neutrophils, segmented	Alanine aminotransferase (ALT)
Lymphocytes	Aspartate aminotransferase (AST)
Monocytes	Blood urea nitrogen (BUN)
Eosinophils	Creatinine
Basophils	Uric acid
Platelets	Calcium
HbA1c	Glucose
	Albumin
Urinalysis	Total cholesterol
Specific gravity	Creatine kinase (CK)
pH	
Protein	**Pregnancy Test** (females only)[b]
Glucose	Serum pregnancy or FSH
Ketones	Urine pregnancy test (local)
Blood	
Urine leukocyte esterase[a]	**Stored Samples**
Urine drug screen[b]	Immunogenicity[d]
	Pharmacogenetic sample (genetic sample/DNA)
	RNA

Abbreviations: DNA = deoxyribonucleic acid; FSH = follicle stimulating hormone; RBC = red blood cells; RNA = ribonucleic acid; WBC = white blood cells.

a A positive urine leukocyte esterase result will require a follow-up sample with microscopic analysis and possibly a urine culture.

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

c Fasting not required.

d An immunogenicity sample may also be collected and analyzed in the event of a serious potential systemic hypersensitivity adverse event. Additional tests may be requested in order to further characterize the event and/or aid interpretation of the anti-drug antibody result.

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. 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 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

Eli Lilly and Company (Lilly) 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 sites. Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative sites. All ICFs must be compliant with the ICH guideline on Good Clinical Practice (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
- ICF
- 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.

An 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
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- make periodic visits to the study site

- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate eCRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

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

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

Appendix 3.2.1. Data Capture System

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

In this study, patient headache data will be collected directly via an electronic patient-reported outcome (ePRO) diary as part of an ePRO/Clinical Outcome Assessment (COA) system. Patient-rated scales/questionnaires will be collected directly via an ePRO tablet device at each visit. Data entered into the ePRO/COA system will serve as the source data.

If ePRO records are stored at a third party site, investigator sites will have continuous access to the source documents during the study and will receive an archival copy at the end of the study for retention.

Any data for which the ePRO instrument record will serve to collect source data will be identified and documented by each site in that site's study file.

Electronic case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data or ECG data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Any data for which paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient in this study will include a headache medication log on which patients will record their acute headache medication use during the study.

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, 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 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-CGAW is described in the Clinical Trial Agreement.

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/clinical research scientist.

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	
GGT	**Alkaline Phosphatase Isoenzymes[a]**
CPK	
	Anti-smooth muscle antibody (or anti-actin antibody)[a]

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

[a] Assayed by Lilly-designated or local laboratory.

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

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