Protocol I5Q-JE-CGAP

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

NCT02959190

Approval Date: 2-Sep-2016

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LY2951742 (galcanezumab)

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

Eli Lilly Japan K.K.
Kobe, Hyogo, Japan

Protocol Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 02-Sep-2016 GMT

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1. Synopsis

Title of Study:
A Phase 3, Long-Term, Open-Label Safety Study of Galcanezumab in Japanese Patients with Migraine

Rationale:
Study I5Q-JE-CGAP (CGAP) is intended to assess the long term safety of galcanezumab (120 mg/month or 240 mg/month) in Japanese patients with migraine.

Objective(s)/Endpoints:

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

Objectives	Endpoints
• To evaluate the long-term effect of galcanezumab on quality of life	PGI-Improvement • Mean change from baseline in the number of monthly migraine headache days or headache days requiring medication for the acute treatment of migraine headache or headache • Mean change from baseline in the number of monthly migraine headache days requiring medication for the acute treatment of migraine headache • Mean change from baseline to endpoint in the evaluation of the MIDAS total score and individual items • Mean change from baseline to endpoint in the MSQ (v2.1) total score and individual domains • Change from baseline in HCRU and employment status
• To evaluate patient satisfaction with medication	• Satisfaction with medication using the PSMQ-M
• To evaluate safety and residual treatment effect during the post-treatment follow-up period	• Analysis of safety parameters • Time to first loss of response (when patient no longer meets 50% response criteria and/or starts treatment using migraine prevention medication) during the post-treatment follow-up phase

Abbreviations: ADA = anti-drug antibodies; CGRP = calcitonin gene-related peptide; C-SSRS = Columbia Suicide Severity Rating Scale; HCRU = health care resource utilization; ECGs = electrocardiograms; MIDAS = Migraine Disability Assessment test; MSQ (v2.1) = Migraine Specific Quality of Life Questionnaire version 2.1; PGI = Patient Global Impression Questionnaire; PSMQ-M = Patient Satisfaction with Medication Questionnaire-Modified; TEAE = treatment-emergent adverse event.

Summary of Study Design:

Study CGAP is a multisite, randomized, open-label trial of Japanese patients with episodic migraine (EM), with the addendum for patients with chronic migraine (CM). The definitions of EM and CM are dependent on the frequency of migraine headache with referring International Classification of Headache Disorders- (ICHD-) 3beta criteria [see details in Section 6 of this protocol and in the CGAP protocol addendum (1), respectively]. A major part of this study is an open-label extension study for patients with EM who complete the treatment period in Study I5Q-JE-CGAN (CGAN) and are willing to continue the study.

Patients with CM

The descriptions relevant for patients with CM are involved in both this protocol and the CGAP protocol addendum (1).

To align the study schedule for patients with both EM and CM, the beginning of Study CGAP for patients with EM is set as Visit 3, not Visit 1; Visit 3 is the first injection visit for patient with

both EM and CM in Study CGAP. Sites for patients with CM and sites for patients with EM are separated.

Treatment Arms and Duration:

There will be 2 treatment arms: galcanezumab 120 mg/month; and galcanezumab 240 mg/month. The detail is shown in Table CGAP.7.1. The patients will be randomized in a 1:1 ratio to receive 120 mg/month of galcanezumab, or 240 mg/month of galcanezumab at Visit 3 of Study CGAN for the patients who roll over from Study CGAN (see Section 7.2). Patients who were in the galcanezumab treatment arms for Study CGAN continue with the same dose in Study CGAP, while patients who were in the placebo arm in Study CGAN are randomized to 120 mg or 240 mg at Visit 3 of Study CGAN (randomization ratio = 1:1). If patients who roll over from Study CGAN are confirmed eligible, the patients will begin a 12-month treatment period (Study Period III). This will be followed by a 4-month follow-up period during which patients will no longer receive any study drug (Study Period IV).

Number of Patients:

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

Approximately 240 EM patients will be rolled-over from Study CGAN (120 patients for the Study CGAP 120 mg arm, 120 patients for the Study CGAP 240 mg arm). Approximately 60 CM patients will be enrolled (30 patients for Study CGAP 120 mg arm, 30 patients for Study CGAP 240 mg arm).

Statistical Analysis:

Effectiveness and safety analyses will be conducted using an intent-to-treat (ITT) population, which is to include all patients who receive at least 1 dose of investigational product.

Statistical summary will be presented by each treatment arm.

In the summary of categorical variables (binary variables), the frequency and percentage will be presented.

In the summary of continuous variables, the mean, standard deviation, minimum, median, and maximum will be reported.

An interim analysis will be conducted in support of regulatory submissions.

2. Schedule of Activities

This is for the EM patients who roll over from Study CGAN.

Study Period (SP)	**SP III – Treatment**														**SP IV – Follow-up**	
(Target) Interval (days) since previous visit	**0**	**14**	**16**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**60**	**60**
Interval allowance (days) compared from previous visit		±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Visit	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16/ ET**	**17**	**18/ ET**
Month	**0**	**(D 14)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**14**	**16**
Assessments and Procedures																
Informed consent	X															
Inclusion/exclusion	X															
Demographics	X															
Physical examination[b]	X															
Height	k															
Weight	X							X						X		X
Waist and hip circumference	k															
Medical History	k															
Pre-specified migraine history	k															
Substance use	k															
Prior Therapy (Migraine Medication)	k															
ECG[c]	X							X						X		X
Vital signs[d]	X		X	X	X	X	X	X			X			X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of migraine and headache days[e]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Paper-diary training	X															
Clinical Laboratory Tests and Sampling Schedules																
Hematology	X				X			X			X			X		X
Clinical chemistry	X				X			X			X			X		X
HbA1c	X							X						X		X
Urinalysis[f]	X							X						X		X

Study Period (SP)	SP III – Treatment														SP IV – Follow-up	
(Target) Interval (days) since previous visit	0	14	16	30	30	30	30	30	30	30	30	30	30	30	60	60
Interval allowance (days) compared from previous visit		±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Visit	3[a]	4	5	6	7	8	9	10	11	12	13	14	15	16/ ET	17	18/ ET
Month	0	(D 14)	1	2	3	4	5	6	7	8	9	10	11	12	14	16
Serum Pregnancy (for women of childbearing potential)[g] or FSH at Visit 3 (for women who have evidence of cessation of menses for at least 12 months)	X													X		X
Urine pregnancy[g]	X		X	X	X	X	X	X	X	X	X	X	X			
Immunogenicity[h]	X	X	X	X	X			X			X			X		X
Biomarker storage sample[h]	X		X		X			X			X			X		X
[redacted] CCI	X	X	X	X	X			X			X			X		X
PK blood sample[h]	X	X	X	X	X			X			X			X		X
CCI [redacted][h]	X							X						X		X
Study drug administered[i]	X		X	X	X	X	X	X	X	X	X	X	X			
Scales, Questionnaires, and Outcome Measures																
MIDAS	X				X			X			X			X		X
MSQ (v2.1)	X		X	X	X	X	X	X			X			X	X	X
HCRU and Employment Status	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
PSMQ-M			X					X						X		X
PGI-S	X		X	X	X	X	X	X						X		X
PGI-I			X	X	X	X	X	X			X			X		X
C-SSRS/SHSF, SHFU[j]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: CGRP = calcitonin gene-related peptide; C-SSRS = Columbia Suicide Severity Rating Scale; D = Day; ECG = electrocardiogram; EM = episodic migraine; ET = early termination; FSH = follicle stimulating hormone; HbA1c = glycated hemoglobin; HCRU = Health Care Resource Utilization; MIDAS = Migraine Disability Assessment test; MSQ (v2.1) = Migraine Specific Quality of Life Questionnaire version 2.1; PGI-I = Patient Global Impression of Improvement; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetic(s); PSMQ-M = Participant Satisfaction with Medication Questionnaire-Modified; RNA=Ribonucleic acid; SP = Study Period. SHSF = Self-harm supplement form; SHFU = Self-harm follow-up form.

a Visit 3 is the same as Visit 12 of Study CGAN. Patients will receive injections of galcanezumab after all other visit procedures at Visit 12 of Study CGAN are completed and confirmation of eligibility. The data of weight, ECG, Vital signs, Assessment of migraine and headache days, Hematology, Clinical chemistry, HbA1c, Urinalysis, Serum Pregnancy (for women of childbearing potential) or FSH (for women who have evidence of cessation of menses for at least 12 months), Urine pregnancy, Immunogenicity, Biomarker storage sample, CGRP plasma

sample, PK blood sample, Whole blood RNA/epigenetic sample, MIDAS, MSQ, HCRU and Employment Status, PGI-S, and C-SSRS/SHSF, SHFU at Visit 3 of study CGAP will utilize the data at Visit 12 of Study CGAN.

b Physical examinations at screening must include a neurological exam.

c ECG as single, 12-lead digital will be performed at Visit 3, Visit 10, Visit 16, and Visit 18 or early termination. Note: the Visit 3 ECG 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.

d Vital signs taken at every office visit will include body temperature, blood pressure, and pulse. Blood pressure and pulse will be measured in triplicate in the sitting position, and should be measured prior to blood draws. Blood pressure will be assessed by utilizing a calibrated machine that will be provided to the sites (see Section 9.4.1 for guidance on vital signs).

e Patients will use a paper-based headache diary (paper diary) provided by sponsor, which can take information of the frequency of headaches, migraine headaches, and medication for migraine or headache. Investigators are responsible for data integrity of paper diary.

f In the event of a positive urine leukocyte esterase result, a repeat urine sample will be collected and shipped to the central laboratory.

g Urine pregnancy tests to be performed every month during SPIII after baseline and as indicated based on the investigator's judgment. A positive urine pregnancy test must be followed by a serum pregnancy test for confirmation.

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

i Patients will receive injections of galcanezumab after all other visit procedures are completed. Following the dose at Visit 3, patients will be observed for at least 30 minutes at the site. Following subsequent doses, patients will be observed for at least 30 minutes post-injection if they have a significant adverse event following any previous injection and/or they are judged by the investigator to have risk of a significant adverse event after injection.

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

k The baseline assessment of Study CGAN will be used.

Note: Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly, 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.

3. Introduction

3.1. Study Rationale

Study I5Q-JE-CGAP (CGAP) is a Phase 3 study conducted in Japan intended to assess the safety of galcanezumab (120 mg/month or 240 mg/month) in Japanese patients with migraine.

3.2. Background

Migraine is a chronic, debilitating condition that impacts the quality of patients' lives. In Japan, the prevalence of migraine is estimated to range from 6.0% to 8.4% (Sakai and Igarashi 1997; Takeshima et al. 2004), which is not different from that in the United States (US). More than 25% of Japanese patients with migraine suffer more than 3 headache days per month, which lead to loss of working days. On the other hand, less than 10% of migraine patients have continuous visits to the hospital (Takeshima et al. 2004). These data suggest that Japanese migraineurs have a considerable amount of socioeconomic burden, and they are not satisfied with the value of medical services, compared to the loss of payment from missing working days.

Migraine has 2 major subtypes: migraine with aura; and migraine without aura. The recurrent episodes of headache is a characteristic of both subtypes; therefore, they are collectively called episodic migraine (EM). A subgroup of migraine patients can gradually worsen into a more severe condition with very frequent episodes of headache, and this condition is categorized as chronic migraine (CM). The International Criteria of Headache Disorders- (ICHD-) 3beta defines CM as a headache occurring on 15 or more days per month for more than 3 months, and which has the features of a migraine headache on at least 8 days per month. Although the prevalence of CM in Japan is still uncertain, it can be estimated to be approximately 7.0% of the total population with migraine (Takeshima 2004), which is consistent with the prevalence in the US (Buse 2012).

Calcitonin gene-related peptide (CGRP) is implicated in the pathophysiology of migraine. Infusion of CGRP to individuals with a history of migraine can trigger migraine attacks (Lassen et al. 2002). The efficacy of small-molecule CGRP antagonists was demonstrated in the acute treatment of migraine (Peroutka 2014) and in the prevention of migraine (Ho et al. 2014). Increased serum CGRP levels are reported in EM patients, as well as in those with CM (Cernuda-Morollón et al. 2013). This evidence suggests that the neutralization of the CGRP signal may represent a promising therapeutic approach for the prevention of EM and CM.

Galcanezumab is a humanized monoclonal antibody that potently and selectively binds to CGRP, preventing CGRP-mediated biological effects. In studies of patients with migraine (Studies I5Q-MC-ART1 [ART-01] and I5Q-MC-CGAB [CGAB]), the efficacy data have demonstrated that galcanezumab had significantly greater mean reductions than placebo in the number of migraine headache days and other efficacy parameters. In these 2 studies, the most frequently reported adverse events (AEs) included: injection site pain, upper respiratory tract infection, abdominal pain, dizziness, injection site erythema, rash, hypertension, and nasopharyngitis.

3.3. Benefit/Risk Assessment

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

4. Objectives and Endpoints

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

Table CGAP.4.1. Objectives and Endpoints

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

Objectives	Endpoints
	headache
• To evaluate the long-term effect of galcanezumab on quality of life	• Mean change from baseline to endpoint in the evaluation of the MIDAS total score and individual items • Mean change from baseline to endpoint in the MSQ (v2.1) total score and individual domains • Change from baseline in HCRU and employment status
• To evaluate patient satisfaction with medication	• Satisfaction with medication using the PSMQ-M
• To evaluate safety and residual treatment effect during the post-treatment follow-up period	• Analysis of safety parameters • Time to first loss of response (when patient no longer meets 50% response criteria and/or starts treatment using migraine prevention medication) during the post-treatment follow-up phase

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

Table CGAP.4.2. Migraine and Headache Endpoint Definitions

Diagnosis	Definition/Criteria
Migraine headache (patients with EM only)	A headache, with or without aura, of ≥30 minutes duration with both of the following required features (A and B): A. At least 2 of the following headache characteristics: • Unilateral location • Pulsatile quality • Moderate or severe pain intensity • Aggravation by or causing avoidance of routine physical activity AND B. During headache at least one of the following: • Nausea and/or vomiting • Photophobia and phonophobia *(Definition adapted from the IHS ICHD-3 beta)*
Probable migraine headache (patients with EM only)	A headache missing 1 of the migraine features in the IHS ICHD-3 beta definition such that 1 feature in criteria A is missing or 1 feature in criteria B is missing; ie, meet at least 2 A criteria and none of the B criteria, or meet 1 of the A criteria and at least 1 of the B criteria.
Migraine headache day	A calendar day on which a **migraine headache or probable migraine headache** occurred.
Migraine headache attack	Beginning on any day a migraine headache and/or a probable migraine headache is recorded, and ends when a migraine-free day occurs.
Non-migraine headache	All headaches of at least 30 minutes' duration not fulfilling the definition of migraine or probable migraine are classified as non-migraine headaches.
Non-migraine headache day	A calendar day on which a non-migraine headache occurred.
Headache day	A calendar day on which any type of headache occurs, (including migraine headache, probable migraine headache, and non-migraine headache).
Migraine headache days with abortive (acute) medication use	Calendar days on which migraine or probable migraine occurs requiring abortive (acute) medication.
Migraine headache days or headache days with abortive (acute) medication use	Calendar days on which any types of headache occurs requiring abortive (acute) medication.

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

5. Study Design

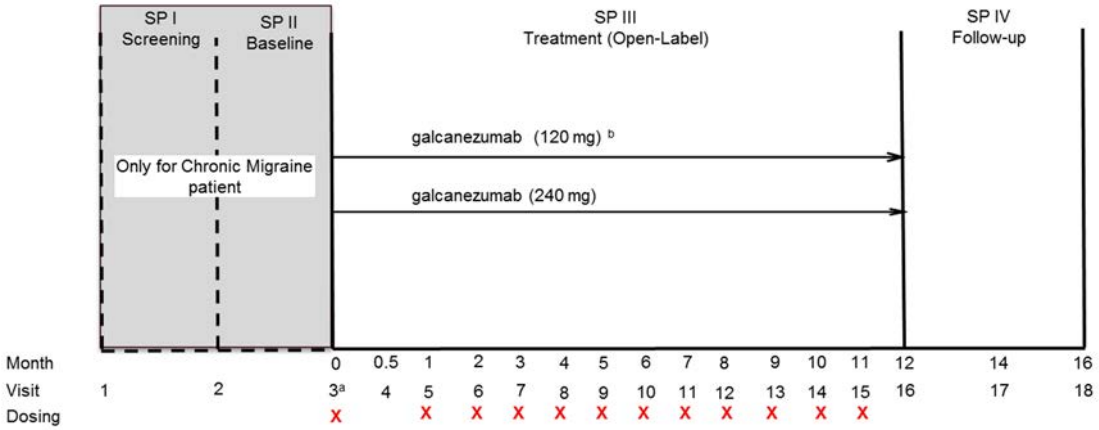
5.1. Overall Design

Study CGAP is a multisite, randomized, open-label, trial with 4 study periods. A major part of this study is a roll over study from parental Study I5Q-JE-CGAN (CGAN) for EM patients who complete Study Period III in Study CGAN, and are willing to continue the study.

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

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

Figure CGAP.5.1 illustrates the study design.



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

Figure CGAP.5.1. Illustration of study design for Clinical Protocol I5Q-JE-CGAP.

At Visit 3 of Study CGAP (Visit 12 of Study CGAN), the study and potential risks will be explained to patients. At this time, the patient will sign and date the informed consent form (ICF).

Study Period III (SPIII): This is a 12-month treatment period. If a patient meets all requirements for study eligibility, the patient will receive galcanezumab at 120 mg/month or 240 mg/month. Patients that were in the 120-mg arm in Study CGAN will continue in the

120-mg arm in Study CGAP. Patients that were in the 240-mg arm in Study CGAN will continue in the 240-mg arm in study CGAP. And patients that were in the placebo arm in Study CGAN will be assigned to either the 120-mg or the 240-mg arm in Study CGAP. The dosing at Visit 3 is blinded for all patients (see Section 7.3).

Patients will be trained to keep track of their migraine and headache days, as well as their medication use days using a paper-based headache diary (paper diary) by the site staff. Retraining will be conducted, as necessary, based upon review of paper diary data.

After study drug is administered at Visit 3, the patient must remain at the site for observation for at least 30 minutes post-injection. Following subsequent doses, patients will be observed for at least 30 minutes post-injection if they have a significant adverse event following any previous injection and/or they are judged by the investigator to have risk of a significant adverse event after injection.

Safety assessments will include treatment-emergent adverse events (TEAEs), vital signs, weight, electrocardiograms (ECGs), and laboratory tests.

If a patient discontinues early for any reason during SPIII, the patient will be expected to take the measurement for Early Termination (ET) and to enter the post-treatment follow-up period (SPIV) to assess safety.

Study Period IV (SPIV): This is a 4-month follow-up period. Patients will no longer receive investigational product. However, patients will continue to track their headache information. Site visits are every 2 months.

Patients who discontinue for any reason during SPIV will be expected to take the measurement for ET.

5.2. Number of Participants

Approximately 300 patients (approximately 150 patients per arm) will be enrolled for the purposes of regulatory registration to ensure at least 100 patients per arm with 1 year of exposure.

Approximately 240 patients with EM will be rolled-over from Study CGAN. Approximately 60 patients with CM will be enrolled.

5.3. End of Study Definition

End of the trial 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 12-month treatment period is considered sufficient to assess the safety of a migraine prevention medication, and is consistent with regulatory requirements. A 4-month post-treatment follow-up period is included to evaluate patient safety during wash-out of galcanezumab. This allows for a total of 5 months of observation from the time of the last injection of galcanezumab. A 5-month, post-treatment, observation period allows for a wash-out

of approximately 5 elimination half-lives of galcanezumab, and should decrease galcanezumab serum concentrations by approximately 97% during this time.

5.5. Justification for Dose

Because a major part of Study CGAP is an extension of Study CGAN, the doses selected for Study CGAP were the same doses used in Study CGAN. A loading dose of galcanezumab 240 mg at Visit 3 will be used for patients who roll over from the placebo arm of Study CGAN to the 120 mg arm of Study CGAP. It will not be used for patients who roll over from the galcanezumab 120 mg arm of Study CGAN to the 120 mg arm of Study CGAP. A loading dose of galcanezumab 240 mg will help patients achieve target serum concentrations of galcanezumab to be consistent with the other treatment groups. In order to maintain the blinding of treatment groups in Study CGAN, 2 injections (galcanezumab and placebo) at Visit 3 of Study CGAP will be used for patients who roll over from the 120 mg arm of Study CGAN.

6. Study Population

Patients who complete the treatment period in Study CGAN will have an opportunity to roll over to study CGAP. Because the diagnosis is already confirmed at the enrollment of Study CGAN, the patients are not needed to meet the definition of patients with EM used in Study CGAN to enter Study CGAP.

The definition of patients with EM which is used in Study CGAN is as follows:

[1] Patients are 18 to 65 years of age (inclusive) at the time of screening.
[2] Have a diagnosis of migraine as defined by International Headache Society (IHS) International Classification of Headache Disorders (ICHD)-3 beta guidelines (1.1 or 1.2) (HCCIHS 2013), 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 4 to 14 migraine headache days and at least 2 migraine attacks per month, on average, within the past 3 months.
[4] From Visit 2 to Visit 3 (prospective baseline period), have a frequency of 4 to 14 migraine headache days and at least 2 migraine attacks per month.

Eligibility of patients for study enrollment will be based on the results of clinical laboratory tests, and ECGs, as shown below. Study participants should be instructed not to donate blood or blood products during the study or for 5 months following last administration of investigational product.

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

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet **all** of the following criteria prior to enrollment:

Patient and Disease Characteristics

[1] Patients completed the treatment period of Study CGAN

Informed Consent and Patient Agreements

[2] Patients are able and willing to give signed informed consent, and in the case of patients under 20 years old, informed consent signed by a parent or guardian.

[3] Patients are reliable and willing to follow study procedures, including all follow-up visits.

[4] Women of child-bearing potential must test negative for pregnancy based on urine pregnancy test kit. Women of non-childbearing potential are defined as follows:

1) Confirmed spontaneous amenorrhea with evidence of cessation of menses for at least 12 months and a follicle-stimulating hormone (FSH) level >40 mIU/mL at Visit 3

Or

2) Confirmed from medical record to be infertile due to congenital or acquired condition (i.e. hysterectomy or bilateral oophorectomy),

Or

3) Confirmed that all partners have had a vasectomy or tubal ligation AND have no fertile sperm based on multiple semen examinations, as shown by their medical record.

Note: the urine pregnancy test result at Visit 3 should be used for the confirmation of eligibility at Visit 3; the serum pregnancy test result at Visit 3 should be used for the confirmation of continuation of the study, and must be negative.

[5] All patients must agree to use a reliable method of birth control during the study, as well as for 5 months after the last dose of investigational product. Acceptable methods of birth control for this study are 1) combination of condom and oral contraceptives, 2) combination of condom and hormonal releasing intrauterine system (IUS), or 3) combination of condom and copper intrauterine device (IUD). These contraception methods are not required for female patients of non-childbearing potential, defined in inclusion criterion [4], or for male patients who meet the criterion defined in definition 3) of inclusion criterion [4].

[6] 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, LINE, Mixi, 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 prior to enrollment:

Prior/Concomitant Therapy

[7] Patients who are taking, or are expected to take, therapeutic antibodies (including chimeric antibodies; eg, adalimumab, infliximab, trastuzumab, bevacizumab, etc.) other than galcanezumab.

Diagnostics Assessments

[8] Patients with a history of head or neck injury during study CGAN.

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

Medical Conditions

[10] Patient who have ECGs showing abnormalities compatible with acute cardiovascular events and/or serious cardiovascular risk, including, but not limited to, a Fridericia's corrected QT interval(QTcF) > 470 msec for women and >450 for men, or have had myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft, stroke, or deep vein thrombosis/pulmonary embolism during Study CGAN, or have planned cardiovascular surgery or percutaneous coronary angioplasty.

[11] Any liver tests outside the normal range during Study CGAN that are clinically significant. Alanine aminotransferase (ALT) >2X the 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 Lilly Medical prior to enrollment.

[12] Patients who, in the clinician's judgment, are actively suicidal and, therefore, deemed to be at significant risk for suicide, or those who have answered "yes" to either Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) or Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the Columbia–Suicide Severity Rating Scale (C-SSRS), or answer "yes" to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act or behavior) on the "Suicidal Behavior" portion of the C-SSRS; and the ideation or behavior occurred within the past month.

[13] Women who are pregnant or nursing.

[14] Patients with a history of drug or alcohol abuse/dependence during Study CGAN (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.

[15] Patients who have a history or presence of any other medical illness including, but not limited to, any autoimmune disorder, cardiovascular, hepatic, respiratory, hematological, endocrine, psychiatric, or neurological disease, or any clinically significant laboratory abnormality that, in the judgment of the investigator, indicates a medical problem that would preclude study participation during Study CGAN.

Other Exclusions

[16] Patients who, 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.

[17] Patients who 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.

[18] Patients who are Lilly employees.

[19] Patients who are unwilling or unable to comply with the use of a paper diary and a data collection device.

[20] Patients who did not meet enrollment criteria and were inadvertently enrolled in Study CGAN

6.3. Lifestyle Restrictions

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

6.4. Screen Failures

The patients with EM who do not meet the criteria for participation in this study (screen failure) will not be rescreened.

7. Treatments

7.1. Treatments Administered

This study involves galcanezumab (120 and 240 mg) administered once monthly. The study drug (galcanezumab) will be administered by subcutaneous injections at 12 office visits during the treatment period (Section 2). Table CGAP.7.1. shows the treatment regimens.

Table CGAP.7.1. Treatment Regimen

Assignment		Regimen	
CGAN Treatment	**CGAP Treatment**	**Dose at Visit 3**	**Dose at Visits 5-15**
Galcanezumab 120 mg	Galcanezumab 120 mg	Galcanezumab 120 mg, subcutaneous (1 injection of 120 mg and 1 injection of placebo using prefilled syringes)	Galcanezumab 120 mg monthly, subcutaneous (1 injection of 120 mg using prefilled syringes)
Galcanezumab 240 mg	Galcanezumab 240 mg	Galcanezumab 240 mg monthly, subcutaneous (2 injections of 120 mg using prefilled syringes)	
Galcanezumab placebo	Galcanezumab 120 mg	Galcanezumab 240 mg, subcutaneous (2 injections of 120 mg using prefilled syringes)	Galcanezumab 120 mg monthly, subcutaneous (1 injection of 120 mg using prefilled syringes
	Galcanezumab 240 mg	Galcanezumab 240 mg monthly, subcutaneous (2 injections of 120 mg using prefilled syringes)	

Injections will be administered by the investigator or patient. If the patient is able to perform the injection, injection should be self-administered by the patient under the supervision of the investigator.

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

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

- Maintaining accurate records of investigational product dispensing and collection.
- At the end of the study, returning all unused medication to Lilly, or its designee, unless the sponsor and sites have agreed that all unused medication is to be destroyed by the site, as allowed by local law.
- Explaining the correct use of the investigational agent(s) to the patient, site personnel, and/or legal representative.
- Verifying that instructions are followed properly.

7.1.1. Packaging and Labeling

Galcanezumab and placebo will be supplied as an injectable solution in 1-mL, single-dose, prefilled, disposable manual syringes with study-specific labels. Each syringe of galcanezumab

is designed to deliver 120 mg of galcanezumab. In order to maintain the blind at Visit 3, the syringes (and contents) containing galcanezumab or placebo will be visibly indistinguishable from each other. Syringes will be supplied in cartons, with the appropriate quantity of syringes specific to the planned dispensing schedule of investigational product.

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

7.1.2. Medical Devices

The medical devices provided for use in the study are prefilled syringes, which are not certified devices in Japan.

7.2. Method of Treatment Assignment

Approximately 240 EM patients are planned to be rolled over from Study CGAN. If a patient meets all requirements for study eligibility, the patient will be administered 120 mg/month or 240 mg/month.

Patients who are in the galcanezumab treatment arms for Study CGAN continue with the same dose in Study CGAP, while patients who are in the placebo arm in Study CGAN are randomized to 120 mg or 240 mg at Visit 3 of Study CGAN (randomization ratio = 1:1). After the randomization, patients are assigned to 1 of the 4 arms:

- LY120/LY120: Study CGAN 120 mg galcanezumab with a loading dose/Study CGAP 120 mg galcanezumab with placebo injection for a loading dose
- LY240/LY240: Study CGAN 240 mg galcanezumab/Study CGAP 240 mg galcanezumab
- PLA/LY120: Study CGAN placebo/Study CGAP 120 mg galcanezumab with a loading dose
- PLA/LY240: Study CGAN placebo/Study CGAP 240 mg galcanezumab

Treatment assignments of CGAP (120 mg or 240 mg) will be disclosed to patients at Visit 5 of Study CGAP.

7.2.1. Selection and Timing of Doses

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

7.3. Blinding

This is an open-label study. However, dosing at Visit 3 is blinded for all patients.

To preserve blinding, information regarding the treatment arm in Study CGAN and a loading dose at Visit 3 in Study CGAP will not be disclosed to investigators or patients until the CGAN/CGAP database locks (including follow-up periods).

7.4. Dosage Modification

Dose modifications are not permitted in this study.

7.5. Preparation/Handling/Storage/Accountability

Investigational product will be shipped (as prefilled syringes) to sites using cold chain transportation. Investigational product must be stable, and stored in a refrigerator at 2ºC to 8ºC (35.6ºF to 46.4ºF).

Approximately 30 minutes prior to administration, the syringes should be removed from the storage area and allowed to equilibrate at ambient conditions. The drug product should be kept away from direct exposure to bright light (such as sunlight) and hot surfaces until administration.

7.6. Treatment Compliance

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

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

7.7. Concomitant Therapy

The list of medications allowed or not allowed for the acute treatment of migraine, as well as those prohibited for the prevention of migraine, is provided in the concomitant medication list in the concomitant medications study tool, along with all concomitant therapies allowed or not allowed during the study. Note that there are some limitations regarding concomitant medications for the acute treatment of migraines during the study. Any changes in the list of allowed/not allowed medications will be communicated to investigators, and will not constitute a protocol amendment.

7.8. Treatment after the End of the Study

7.8.1. Continued Access

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

8. Discontinuation Criteria

Patients who discontinue the study or investigational product during the treatment period (SPIII) should be scheduled for an early discontinuation visit, and encouraged to complete the follow-up period (SPIV).

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 the Lilly designated medical monitor:

- 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 prothrombin time >1.5X ULN
- ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP >3X ULN
- ALP >2.5X ULN and TBL >2X ULN
- ALP >2.5 ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

8.1.2. Discontinuation of Inadvertently Enrolled Patients

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

8.2. Discontinuation from the Study

Some possible reasons that may lead to permanent discontinuation include:

- Enrollment in any other clinical trial involving an investigational product, or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- Investigator decision:

  - The investigator decides that the patient should be discontinued from the study
  - If the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent

- Subject Decision:
  - The patient requests to be withdrawn from the study
- Sponsor Decision:
  - If Lilly judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP

Patients who discontinue the study early (SP III) will have end-of-study (ET) procedures performed, as shown in the Schedule of Activities (Section 2) and are requested to proceed into the post-treatment phase.

Patients who discontinue the study early (SP IV) will have end-of-study (ET) procedures performed, as shown in the Schedule of Activities (Section 2).

8.3. Lost to Follow-Up

A patient will be considered lost to follow-up if he/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.

8.4 Discontinuation of Study Sites

Study site participation may be discontinued if the sponsor, the investigator, or the ethical review board/institutional review board (ERB/IRB) of the study site judges it necessary for any reason.

8.5 Discontinuation of the Study

The study may be discontinued if the sponsor judges it necessary, for any reason.

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. Effectiveness Assessments

9.1.1. Primary Effectiveness Assessments

Not applicable.

9.1.2. Secondary Effectiveness Assessments

As this is an uncontrolled study, all efficacy measures represent measures of treatment effectiveness or health outcomes. Migraine headache day will be defined to include both migraine and probable migraine days. Patients will be asked to use a paper diary to record headache symptoms, duration, and severity. The use of the diary and of the electronic clinical outcome assessment (eCOA) system is described in the Data Capture System section of Appendix 3.

In addition, the following scales will be used for secondary effectiveness assessments, as summarized below.

9.1.2.1. Patient Global Impression of Severity

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

9.1.2.2. Patient Global Impression of Improvement

The Patient Global Impression of Improvement (PGI-I) scale (Guy 1976) is a patient-rated instrument that measures improvement of the patient's symptoms. It is a 7-point scale in which a score of 1 indicates the patient is "very much better," a score of 4 indicates the patient has experienced "no change," and a score of 7 indicates the patient is "very much worse."

9.1.3. Appropriateness of Assessments

All safety and effectiveness assessments have been well documented, and are generally regarded as reliable, accurate, and relevant in this patient population. This includes health outcomes measures considered to be appropriate for evaluating changes in quality of life, global functioning, and disability (Section 9.9).

9.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

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

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

After the ICF is signed, study site personnel will record, via eCRF, the occurrence and nature of each patient's preexisting condition(s), including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record 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 an AE has a reasonable possibility of being related to study treatment, or a study procedure, taking into account the disease, concomitant treatment, or pathologies.

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 any dosage modifications, or discontinuations of treatment.

9.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (ie, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason: important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious, based upon appropriate medical judgment.

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

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

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

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

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. US 21 Code of Federal Regulations 312.32, European Union (EU) 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 recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.1.2. Adverse Event Monitoring with a Systematic Questionnaire

The C-SSRS (Posner et al. 2011) captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior occurred. The tool was developed by the Columbia group (Posner et al. 2011) to prospectively categorize suicide-related events.

Before administering the C-SSRS, study site personnel will question the patient about any change in the preexisting condition(s) and the occurrence and nature of any AEs. Non-serious AEs obtained through the questionnaire are recorded and analyzed separately. Only serious AEs and AEs leading to discontinuation elicited through the C-SSRS are to be recorded as AEs via eCRF. Serious adverse events must be reported to Lilly or its designee within 24 hours as SAEs. Any suicidal behavior, or suicidal ideation per Items 4 or 5 (active suicidal ideation with some intent to act, either without specific plan or with specific plan and intent) would prompt referral of the patient to a mental health professional.

9.2.2. Complaint Handling

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

Patients will be instructed to contact the investigator as soon as possible if he/she has a complaint or problem with the investigational product (or drug delivery system such as a prefilled syringe) so that the situation can be assessed.

9.3. Treatment of Overdose

No data are available at this stage of development.

9.4. Safety

The primary objective of this study is to evaluate the long-term safety and tolerability of galcanezumab 120 mg/month or 240 mg/month in patients with migraine for 1 year of treatment. Safety assessments include the occurrence of AEs, and changes from baseline in vital signs, ECGs, and laboratory tests.

9.4.1. Vital Signs and Weight

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

9.4.2. Electrocardiograms

For each patient, a single 12-lead digital ECG will be collected according to the Schedule of Activities (Section 2). 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 should be reported to Lilly or its designee as an AE via eCRF.

9.4.3. Laboratory Tests

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

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

In addition, an immunogenicity and pharmacokinetic (PK) serum sample will be collected, when possible, for any patient who experiences a potential systemic allergic/hypersensitivity reaction during the study as judged by the investigator. This immunogenicity and PK serum sample

should be collected immediately or as soon as possible, taking into consideration the availability and well-being of the patient. Exact date and time of the sample should be recorded on the laboratory requisition form.

9.4.4. Safety Monitoring

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

Investigators are responsible for monitoring individual patient safety throughout the trial. If a study patient/subject experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, clinical and laboratory monitoring should be initiated by the investigator. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient/subject safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP/CRS regarding collection of specific recommended clinical information and follow-up laboratory tests. See Appendix 4.

9.5. Pharmacokinetics

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

A maximum of 3 samples may be collected at additional time points during the study, if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor.

When a blood sample is collected, the time and date of last-dose administration prior to blood sampling should be recorded. The actual date and time (24-hour clock time) of each sampling will be recorded. To maintain the blinding in study CGAN, galcanezumab concentration information will not be disclosed to either the investigators or the patients until the CGAN/CGAP database locks, including follow-up periods.

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

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

9.6. Pharmacodynamics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine the plasma concentrations of CGRP. A maximum of 3 samples may be collected at additional time points during the study, if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. When a blood sample is collected, the time and date of last dose administration prior to blood sampling should be recorded. The actual date and time (24-hour clock time) of each sampling will be recorded.

A validated galcanezumab-tolerant assay will be used to determine plasma CGRP concentrations. Samples will be analyzed at a laboratory approved by the sponsor. To maintain the blinding in Study CGAN, CGRP concentration information will not be disclosed to either the investigators or the patients until the CGAN/CGAP database locks, including follow-up periods.

Bioanalytical samples collected to measure CGRP will be identified by the patient number (coded) and retained for a maximum of 1 year following last patient visit for the study at a facility selected by the sponsor.

CCI

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9.8. Biomarkers

Plasma and whole blood RNA and epigenetic samples for 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 headache 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 headache 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.

9.8.1. Samples for Immunogenicity Research

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

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

9.9. Medical Resource Utilization and Health Economics

Health economic, disability, and quality-of-life assessments of galcanezumab in patients with migraine, except for Health Care Resource Utilization (HCRU), will be collected through the use of an eCOA system, as described in the Data Capture System section of Appendix 3. The assessments will be based on the following scales:

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

Migraine Specific Quality of Life questionnaire version 2.1 (MSQ v2.1): The MSQ v2.1 is a self-administered health status instrument, and was developed to address physical and emotional limitations 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. 1998). The instrument was designed with a 4-week recall period, and is considered reliable, valid, and sensitive to change in migraine

(Jhingran et al. 1998; Rendas-Baum et al. 2013). Clinically meaningful differences for each domain have been established, and are widely used in the literature.

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

Participant Satisfaction with Medication Questionnaire-Modified (PSMQ-M): The PSMQ-M is a self-rated scale which measures patients' levels of satisfaction with study medication (Kalali 1999). The scale has been modified for use in this study, assessing 3 items related to the clinical trial treatment over the past 4 weeks: satisfaction, preference, and side effects. Satisfaction responses range from "very unsatisfied" to "very satisfied" with the current treatment. Preference compares the current study medication to previous medications, with responses from "much rather prefer my previous medication" to "much rather prefer the medication administered to me during the study."

10. Statistical Considerations

10.1. Sample Size Determination

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

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

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All Randomized Patients (ARP)	All patients who are randomized
Intent-to-Treat (ITT) Population	All patients who are assigned to a treatment and received at least 1 dose of study drug. Patients in the ITT population will be analyzed according to the treatment to which they were assigned. Unless otherwise specified, the ITT population will be the primary population on which statistical analysis will be performed.
Post-treatment Population	All patients who entered the follow-up period (SPIV) as indicated by entering any post-treatment visit.
Per Protocol Set (PPS) Population	All patients in the ITT population who have no important protocol deviation which impact effectiveness analysis. Details will be specified in SAP.

Abbreviations: SPIV = Study Period IV.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

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

Unless otherwise specified, safety and effectiveness analyses will be conducted on an intent-to-treat (ITT) basis, which is to include all patients who receive at least 1 dose of study drug. When change from baseline is assessed, the patient will be included in the analysis only if he/she has a baseline and a post-baseline measurement.

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

Unless specified otherwise, data for the patients with EM in Study CGAP will be reported by the treatment groups described in Section 7.2.

For EM patients' analysis, baseline is Study CGAP Visit 3 (Study CGAN Visit 12) assessment, unless otherwise specified with some exception (eg, immunogenicity analysis).

If baseline data is not available at Study CGAP Visit 3 (eg, height), then baseline assessment of CGAN will be used.

Continuous safety and effectiveness variables will be summarized at each visit for observed measures (no imputation), and for change from baseline by each treatment group. If change from baseline is analyzed, then t-test may be used for each treatment group separately.

Categorical safety and effectiveness variables will be summarized at each visit for observed case.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report (CSR). 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 summarized for the open-label treatment phase (Study Period III) and post-treatment follow-up phase (Study Period IV), both overall and by visit.

10.3.2.2. Patient Characteristics

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

- Demographic (age, gender, ethnic origin, height, weight, waist/hip circumference)
- Migraine headache, headache days
- Alcohol, tobacco, caffeine, and nicotine consumption
- Medical history and preexisting conditions

Medical history and preexisting 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 (as recorded via eCRF), as well as abortive medications (recorded through paper diary), will be summarized for all ITT patients for Study Periods III and IV, separately.

10.3.2.4. Treatment Compliance

Not applicable.

10.3.3. Primary and Secondary Analyses

10.3.3.1. Primary Analyses

The primary objective of this study is to evaluate the long-term safety and tolerability of galcanezumab (120 or 240 mg/month) in patients suffering from migraine, for up to 1 year of treatment.

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

- adverse events
  - treatment-emergent adverse events (TEAEs)
    - by preferred term
    - by SOC
    - by maximum severity
    - considered to be related to investigational product by investigator
  - serious adverse events (SAEs)
  - adverse events leading to discontinuation
  - Follow-up-emergent adverse events (FEAEs)
- suicidal ideation and behaviors assessed by solicited questioning using the C-SSRS
- vital signs and weight
- electrocardiograms (ECGs)
- laboratory measurements
- anti-galcanezumab antibodies

10.3.3.2. Secondary Analyses

10.3.3.2.1. Effectiveness Analyses

The effectiveness objective is to evaluate the effectiveness of galcanezumab in the prevention of migraine, using the following measures:

- mean change from baseline in the number of migraine headache days
- mean change from baseline in the number of headache days
- the proportion of patients meeting criteria for reductions of at least 30%, 50%, 75%, or 100% in the number of migraine headache days
- mean change from baseline in the frequency of medication use for the acute treatment of migraines or headaches
- mean change from baseline in patient's global impression of illness as measured by PGI-Severity

- patient's global impression of improvement as measured by PGI-Improvement postbaseline
- mean change from baseline in the number of monthly migraine headache days or headache days requiring medication for the acute treatment of migraine headache or headache
- mean change from baseline in the number of monthly migraine headache days requiring medication for the acute treatment of migraine headache
- time to first loss of response (when patient no longer meets 50% response criteria and/or starts treatment using migraine prevention medication) during the follow-up phase

10.3.4. Tertiary/Exploratory Analyses

Not applicable.

10.3.5. Other Safety Analyses

10.3.5.1. Immunogenicity Analyses

To evaluate the changes in immunogenicity data (ADA, neutralizing ADA) after treatment, the following statistical analyses are planned:

- To summarize the proportions of positive results at each sample collection time point.
- To summarize the incidence of treatment-emergent immunogenicity for the open-label treatment phase. Treatment-emergent immunogenicity will be defined as any of the following:
  - A negative baseline result and a positive postbaseline ADA result with a titer ≥20. This is also called treatment-induced ADA.
  - A positive baseline result and a positive postbaseline ADA result with a ≥4-fold increase in titers (eg, baseline titer of 10 increasing to ≥40 postbaseline). This is called treatment-boosted ADA.
- To summarize the onset of treatment-induced ADA. Anti-drug antibody onset is defined as the time period between the initial administration of the study drug and the first instance of treatment-induced ADA.

CCI [redacted]

10.3.7. Other Analyses

10.3.7.1. Medical Resource Utilization and Health Economics

Change from baseline to each postbaseline visit for open-label treatment phase for MSQ v2.1 (including Role Function-Restrictive, Role Function-Preventive, Emotional Function, and total score) and MIDAS (item scores and total score) (Section 9.9) will be summarized.

The HCRU and PSMQ-M will be analyzed with details documented in the SAP.

10.3.8. Interim Analyses

A data monitoring committee (DMC) is not planned for this study.

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

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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
AST	aspartate aminotransferase
CGRP	calcitonin gene-related peptide
CIOMS	Council for International Organizations of Medical Sciences
CM	chronic migraine
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
CRP/CRS	Lilly Clinical Research Physician/Clinical Research Scientist: Individual responsible for the medical conduct of the study. Responsibilities of the CRP/CRS may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
eCRF	electronic case report form
EM	episodic migraine
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.

Term	Definition
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ePRO	electronic patient-reported outcomes
ERB	ethical review board
ET	early termination
EU	European Union
FEAE	follow-up-emergent adverse event
FSH	follicle-stimulating hormone
GCP	good clinical practice
HCRU	Health Care Resource Utilization
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
ICHD	International Classification of Headache Disorders
IHS	International Headache Society
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.
IRB	institutional review board
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 (ie, 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.
IUD	intrauterine device
IUS	intrauterine system
MIDAS	Migraine Disability Assessment Test
MSQ v2.1	Migraine Specific Quality of Life Questionnaire version 2.1

Term	Definition
PGI-I	Patient Global Impression of Improvement
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PPS	per protocol set: The set of data generated by the subset of patients who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model.
PSMQ-M	Patient Satisfaction with Medication Questionnaire-Modified
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
SP	study period
SUSARs	suspected unexpected serious adverse reactions
TBL	total bilirubin
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, which and does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
US	United States

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology	**Clinical Chemistry**
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume	Total bilirubin
Mean cell hemoglobin concentration	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase
Neutrophils, segmented	Alanine aminotransferase (ALT)
Lymphocytes	Aspartate aminotransferase (AST)
Monocytes	Blood urea nitrogen (BUN)
Eosinophils	Creatinine
Basophils	Uric acid
Platelets	Calcium
	Glucose
	Albumin
Urinalysis	Creatine kinase (CK)
Specific gravity	Triglycerides
pH	Total cholesterol
Protein	HDL
Glucose	
Ketones	
Blood	HbA1c
Urine leukocyte esterase[a]	
Microscopic analysis[a]	**Other**
Urine culture[a]	CCI
	PK sample (galcanezumab serum concentration determination)
	Immunogenicity
	Pregnancy Test (females only)[b]
	Serum pregnancy or FSH
	Urine pregnancy test (performed by site)
	Stored Samples
	Biomarker storage
	CCI
	(CM patients only)
	RNA/Epigenetic

Abbreviations: CGRP = calcitonin gene-related peptide; CM = chronic migraine; DNA = deoxyribonucleic acid; FSH = follicle-stimulating hormone; HbA1c = glycated hemoglobin; HDL = high density lipoprotein; PK = pharmacokinetic; RBC = red blood cells; RNA = ribonucleic acid; WBC = white blood cell.

[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.

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

Appendix 3.1.2. Ethical Review

The investigator must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Conference on Harmonization (ICH) guidelines and other applicable laws and regulations.

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

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

- the current Investigator's Brochure (IB) and updates during the course of the study
- informed consent form (ICF)
- relevant curricula vitae

Appendix 3.1.3. Regulatory Considerations

This study will be conducted in accordance with:

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

Appendix 3.1.4. Investigator Information

General practitioners, neurologists, and physicians who are pain specialists will participate as investigators in this clinical trial.

Appendix 3.1.5. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his/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 3.1.6. 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/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/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 case report forms (CRFs), and study procedures.
- Make periodic visits to the study site.
- Be available for consultation, and stay in contact with the study site personnel by mail, telephone, and/or fax.
- Review and evaluate CRF 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

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.

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.

Some or all of a patient's data will be directly entered into the electronic case report form (eCRF) at the time the information is obtained. In instances where direct data entry is not used, the site will maintain source documentation in the trial files, and the patient's data will be transcribed into the eCRF. Any data for which the eCRF will serve as the source document, or any other data not entered directly into the eCRF, will be identified and documented by the site in the site's trial file. For data handled by a data management TPO, eCRF data, and some or all data that are related will be managed and stored electronically in the TPO system. Subsequent to the final database lock, validated data will be transferred to the sponsor. For data handled internally, eCRF data and some or all data that are related will be managed by the sponsor and stored electronically in the sponsor's system.

In this study, patient migraine headache data will be collected using a paper-based headache diary (patient diary). Patient migraine headache data will be collected directly via electronic patient-reported outcome (ePRO) diary during CGAN from Visit 11 to Visit 12 and these ePRO diary data will be utilized as CGAP Visit 3 data. Patient-rated scales/questionnaires will be collected directly via an ePRO tablet device at each visit. Data entered into the electronic clinical outcome assessment (eCOA) system will serve as the source data.

If eCOA 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 eCOA instrument record will serve to collect source data will be identified and documented by each site in that site's study file.

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 electrocardiogram (ECG) data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

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

Appendix 4. 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 Lilly or its designee (CRP/CRS).

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 = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

a Assayed by Lilly-designated or local laboratory.

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

Leo Document ID = 6bcbb402-def7-4f18-848a-7ef70981c456

Approver: PPD
Approval Date & Time: 02-Sep-2016 15:12:28 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 02-Sep-2016 15:40:37 GMT
Signature meaning: Approved