Protocol: I5Q-JE-CGAN(a)

A Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 (Galcanezumab) in Japanese Patients With Episodic Migraine

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A Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 (Galcanezumab) in Japanese Patients with Episodic Migraine

Confidential Information

LY2951742 (galcanezumab)

Study CGAN is a, multisite, randomized, double-blind, placebo-controlled, bridging study of galcanezumab in Japanese outpatients suffering from episodic migraine.

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Protocol Electronically Signed and Approved by Lilly: 14 June 2016
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1. Synopsis

Title of Study:

A Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 (galcanezumab) in Japanese Patients with Episodic Migraine

Rationale:

Study I5Q-JE-CGAN (CGAN) is intended to assess the efficacy and safety of galcanezumab compared to placebo in the prevention of migraine headache in Japanese patients suffering from episodic migraine (defined as 4 to14 migraine headache days per month), with or without aura, during 6 months of treatment.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary To test the hypothesis that at least 1 dose of galcanezumab (120 or 240 mg/month) is superior to placebo in the prevention of migraine headache in patients with episodic migraine.	The overall mean change from baseline in the number of monthly migraine headache days during the 6-month, double-blind treatment phase
Key Secondary Objectives Regardless of primary objective results, all comparisons in secondary objectives are galcanezumab 120 mg versus placebo and galcanezumab 240 mg versus placebo.	
• To compare galcanezumab with placebo with respect to 50% response rate	• The proportion of patients with a reduction from baseline ≥50% in monthly migraine headache days during the 6-month, double-blind treatment phase
• To compare galcanezumab with placebo with respect to 75% response rate	• The proportion of patients with a reduction from baseline ≥75% in monthly migraine headache days during the 6-month, double-blind treatment phase
• To compare galcanezumab with placebo with respect to 100% response rate.	• The proportion of patients with a reduction from baseline equal to 100% in monthly migraine headache days during the 6-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 MSQ v2.1 (average of Months 4, 5, and 6)
• To compare galcanezumab with placebo with respect to change in use of acute (abortive) migraine treatment	• The overall 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 during the 6-month, double-blind treatment phase
• To compare galcanezumab with placebo with respect to change in global severity of the migraine condition	• The mean change from baseline in the PGI-S score (average of Months 4, 5, and 6)

Abbreviation: MSQ v2.1 = Migraine-Specific Quality of Life Questionnaire version 2.1; PGI-S = Patient Global Impression of Severity.

Summary of Study Design:

A multisite, randomized, double-blind, placebo-controlled bridging trial with 4 study periods in patients who meet International Classification of Headache Disorders- (ICHD-) 3beta criteria for a diagnosis of migraine, with or without aura, at Visit 1, and fulfill the criteria of episodic frequency (4 to 14 migraine headache days per month) during the baseline period. Patients who complete Study Period III of study CGAN may have an option to roll-over to the open-label extension study, I5Q-JE-CGAP (CGAP).

Treatment Arms and Duration:

Three treatment arms: galcanezumab 120 mg/month with a 240 mg loading dose at the first injection; galcanezumab 240 mg/month; and placebo. Following a prospective baseline (30-40 days) period, eligible patients will be randomized in a 2:1:1 ratio to receive placebo, galcanezumab 120 mg/month with a 240 mg loading dose, and galcanezumab 240 mg/month, respectively, and will begin a 6-month treatment phase. This phase will be followed by a 4-month, post-treatment phase during which patients will no longer receive any study drug.

Number of Patients:

The study will screen an estimated 902 potential study participants to ensure randomization of approximately 451 (225, 113, 113) patients with episodic migraine.

Statistical Analysis:

Unless otherwise specified, the primary analyses will be conducted on an intent to treat (ITT) population, which includes all patients who are randomized and receive at least 1 dose of study product. Patients in the ITT population will be analyzed according to the treatment arm to which they are randomized. When mean change from baseline is assessed, the patient will be included in the analysis only if the patient has a baseline and post-baseline measurement. The primary analysis will evaluate the efficacy of 2 doses of galcanezumab compared with placebo on the overall mean change from baseline in the number of monthly migraine headache days during the 6-month, double-blind treatment phase. The primary analysis will be performed using a restricted-maximum, likelihood-based mixed models repeated measures (MMRM) technique. The analysis will include the fixed categorical effects of treatment, 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.

2. Schedule of Activities

Study Period (SP)	SP I-Screening	SP II-Prospective Baseline	SP III – Treatment										SP IV – Follow-up	
(Target) Interval (days) since previous visit			**30-45**	**14**	**16**	**30**	**30**	**30**	**15**	**15**	**15**	**15**	**60**	**60**
Allowable range (days) between visits	**3-45**	**30-40[a]**												
Interval allowance (days) compared from previous visit				**± 1**	**± 3**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 5**	**± 5**
Visit	**1**	**2**	**3**	**4[b]**	**5**	**6**	**7**	**8**	**9[c]**	**10**	**11[c]**	**12/ET**	**13**	**14/ET**
Month			**0**	**0.5**	**1**	**2**	**3**	**4**	**4.5**	**5**	**5.5**	**6**	**8**	**10**
Informed consent	X													
Inclusion/exclusion	X	X	X											
Demographics	X													
Physical examination[d]	X													
Height	X													
Weight	X											X		X
Waist and hip circumference	X													
Medical history	X													
Pre-specified migraine history		X												
Substance use	X													
Prior Therapy (Migraine Medication)	X													
ECG[e]	X		X									X		X
Vital signs[f]	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
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ePRO training		X												
ePRO daily patient entries[g]		X	X	X	X	X	X	X	X	X	X	X	X	X
Patient training video			X											
Hematology	X		X				X					X		X
Clinical chemistry	X		X				X					X		X

Study Period (SP)	SP I-Screening	SP II-Prospective Baseline	SP III – Treatment										SP IV – Follow-up	
(Target) Interval (days) since previous visit			30-45	14	16	30	30	30	15	15	15	15	60	60
Allowable range (days) between visits	3-45	30-40[a]												
Interval allowance (days) compared from previous visit				± 1	± 3	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 5	± 5
Visit	1	2	3	4[b]	5	6	7	8	9[c]	10	11[c]	12/ET	13	14/ET
Month			0	0.5	1	2	3	4	4.5	5	5.5	6	8	10
HbA1c			X									X		X
Urinalysis[h]	X		X									X		X
Serum Pregnancy (for women of childbearing potential)[i] or FSH at Visit 1 (for women who have evidence of cessation of menses for at least 12 months)	X											X		X
Urine pregnancy[i]			X		X	X	X	X		X		X[m]		
Urine drug screen	X													
Immunogenicity[j]			X	X	X	X	X					X		X
Biomarker storage sample[j]			X		X		X			X		X[m]		X
CCI		X	X	X	X	X	X	X	X	X	X	X	X	X
PK blood sample[j]				X	X	X	X	X	X	X	X	X	X	X
CCI			X											
Whole blood RNA/epigenetic sample[j]			X									X		X
Study drug administered[k]			X		X	X	X	X		X				
MIDAS			X				X					X		X
MSQ v2.1			X		X	X	X	X		X		X		X
PGI-S			X		X	X	X	X		X		X		X
PGI-I					X	X	X	X		X		X		X

Study Period (SP)	SP I-Screening	SP II-Prospective Baseline	SP III – Treatment										SP IV – Follow-up	
(Target) Interval (days) since previous visit			**30-45**	**14**	**16**	**30**	**30**	**30**	**15**	**15**	**15**	**15**	**60**	**60**
Allowable range (days) between visits	**3-45**	**30-40[a]**												
Interval allowance (days) compared from previous visit				**± 1**	**± 3**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 5**	**± 5**
Visit	**1**	**2**	**3**	**4[b]**	**5**	**6**	**7**	**8**	**9[c]**	**10**	**11[c]**	**12/ET**	**13**	**14/ET**
Month			**0**	**0.5**	**1**	**2**	**3**	**4**	**4.5**	**5**	**5.5**	**6**	**8**	**10**
PSMQ-M					X							X		
HCRU and Employment status			X		X	X	X	X		X		X	X	X
C-SSRS/SHSF, SHFU[l]	X	X	X		X	X	X	X		X		X	X	X

Abbreviations: AE = adverse event; CGRP = Calcitonin-gene related peptide; CRP = Lilly Clinical Research Physician; CRS = Lilly Clinical Research Scientist; C-SSRS = Columbia Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ePRO = electronic patient-reported outcomes; 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; PGI-I = Patient Global Impression of Improvement; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetics; PSMQ-M = Patient Satisfaction with Medication Questionnaire-Modified; RNA = ribonucleic acid; SP = Study Period; SHSF = Self-harm supplement form; SHFU = Self-harm follow-up form.

Note: Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality, and follow-up may be required with patients, in consultation with the Lilly, or its designee (CRP/CRS). 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.

[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 30-40 day period.

[b] Visit is to include a review of any spontaneously reported AE, concomitant medications and collection of blood samples for immunogenicity, PK, and CGRP plasma.

[c] Visit is to include a review of any spontaneously reported AE, concomitant medications and collection of blood samples for PK, and CGRP plasma.

[d] Physical examinations at screening must include a neurological exam.

[e] Electrocardiograms as single, 12-lead digital will be performed at Visit 1, Visit 3, Visit 12, and Visit 14 or ET. 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. For screening only, ECG results will be read locally.

[f] Vital signs will include body temperature, blood pressure, and pulse. Blood pressure and pulse will be measured in triplicate, in the sitting position, and should be measured prior to blood draws. Blood pressure will be assessed by utilizing a calibrated machine.

[g] Patient enter into the ePRO diary the occurrence of headaches, headache duration, headache features, severity of headache, and use of headache medication

[h] In the event of a positive urine leukocyte esterase result, a repeat urine sample will be collected at the next visit and shipped to the central laboratory.

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

[j] Biomarker storage samples, immunogenicity, CCI 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 ET. Immunogenicity and PK samples also may be collected in the event of a systemic allergic/hypersensitivity reaction (see Section 9.4.3). The timing of samples will be recorded.

[k] Patients will receive injections of placebo or galcanezumab after all other visit procedures are completed. Following the first 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 after the first injection and/or they are judged by the investigator to have risk of a significant adverse event after injection.

[l] The C-SSRS and SHSF (and SHSU, when applicable) will be completed at scheduled and unscheduled office visits.

[m] Urine pregnancy and biomarker storage sample are collected only for patients rolling over to Study CGAP.

3. Introduction

3.1. Study Rationale

Study I5Q-JE-CGAN (CGAN) is intended to assess the efficacy and safety of galcanezumab compared to placebo in the prevention of migraine headache in Japanese patients suffering from episodic migraine (defined as 4 to14 migraine headache days per month), with or without aura, during 6 months of treatment.

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). Migraine is one of the most common diseases in Japanese middle-aged women (Nagai et al. 2015). More than 25% of Japanese patients with migraine suffer more than 3 headache days per month, which leads to a significant work disability. In addition, about 5.3% to 7.3% of those patients are continuously visiting doctors (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 when compared to loss of earnings from lost work days.

Migraine has 2 major subtypes: migraine with aura; and migraine without aura. Recurrent episodes of headache are a characteristic symptom shared by both migraine subtypes; therefore, they are collectively called as episodic migraine (EM). The frequency of headache episodes may worsen in the clinical course of EM. In addition to the acute treatment, preventive treatment options should be considered for severe and frequent EM. Currently, there are only 4 Food and Drug Administration- (FDA-) approved medications for migraine prevention. These are topiramate, divalproex sodium, timolol, and propranolol. In Japan, sodium valproate, propranolol, and lomerizine (a calcium channel blocker originally developed in Japan) are approved for the prevention of migraine. While these drugs have been shown to be fairly effective in some cases, not all patients respond to them. Moreover, the established adverse effect of valproate on fetuses has made clinicians reluctant to prescribe it for young female patients (Meador et al. 2012). New treatment options with improved efficacy and tolerability are needed for patients suffering from migraine headaches.

Calcitonin gene-related peptide (CGRP), a 37-amino acid neuropeptide, is widely expressed throughout the central and peripheral nervous systems, and acts as a local facilitator of inflammatory processes. Numerous lines of evidence implicate CGRP in the pathophysiology of migraine. These include increased levels of CGRP in the peripheral and cranial circulation during a migraine attack (Goadsby and Edvinsson 1990; Goadsby and Edvinsson 1993), normalization of increased CGRP levels following effective migraine treatment (Buzzi et al. 1995; Fanciullacci et al. 1995), and efficacy of small-molecule CGRP antagonists in the acute treatment of migraine (Peroutka 2014) and the prevention of migraine (Ho et al. 2014). Correspondingly, the neutralization of the CGRP signal with neutralizing antibodies has been shown to modulate neurogenic inflammation; thus, these antibodies may represent a promising therapeutic approach for the prevention of migraine.

Galcanezumab is a humanized monoclonal antibody that potently and selectively binds to CGRP preventing CGRP-mediated biological effects. A single and multiple-dose ascending study (CGAA) in healthy subjects and a Phase 2a proof-of-concept study (ART-01) in patients with migraine have been completed. In study CGAA, galcanezumab was administered subcutaneously to human volunteers at single doses up to 600 mg, and repeatedly administered as 4 doses of 150 mg every other week. This study demonstrated that galcanezumab was well-tolerated and did not result in any serious adverse event (SAE) or treatment emergent adverse events (TEAEs). Study CGAE was conducted in 35 healthy Japanese and Caucasian subjects. The safety profile of galcanezumab in this study was consistent with that observed in Study CGAA. The most frequently reported adverse events (AEs) in galcanezumab-treated subjects were injection-related events, contact dermatitis (related to electrocardiogram [ECG] electrodes, as noted by the investigator), and neck pain. Events were generally reported at an equivalent rate in Japanese and Caucasian subjects.

In the proof-of-concept study, ART-01, galcanezumab was administered subcutaneously once every 14 days for 6 doses. Galcanezumab significantly reduced the number of migraine headache days compared to placebo (P=0.003) at the 12-week endpoint. Moreover, galcanezumab was statistically significantly better than placebo on all secondary efficacy endpoints. The safety data of this study are consistent with the results of studies CGAA/CGAE. No patient treated with galcanezumab discontinued due to an AE. Ten SAEs were reported, in which 2 SAEs were reported by 2 patients treated with galcanezumab and 8 SAEs were reported by 4 placebo-treated patients. None of the SAEs was judged by the investigator as related to treatment. Treatment-emergent adverse events that were reported more often by galcanezumab-treated patients than by placebo-treated patients were injection site pain (18 [17%] vs. 7 [6%]), upper respiratory tract infection (26 [24%] vs. 12 [11%]), abdominal pain (6 [6%] vs. 3 [3%]), dizziness (5 [5%] vs. 3 [3%]), injection site erythema (5 [5%] vs. 0 [0%]), rash (5 [5%] vs. 0 [0%]), and hypertension (5 [5%] vs. 0 [0%]). Galcanezumab did not cause any obvious changes in clinical chemistry or hematologic parameters, and there was no apparent effect on heart rate, blood pressure or ECG measurements (QT-interval or Fridericia's corrected QT [QTcF] interval) (Dodick et al. 2014).

The Phase 2b dose-ranging study, I5Q-MC-CGAB (CGAB), is a multisite, double-blind, randomized, placebo-controlled study of galcanezumab that was conducted in the US. This study aimed to assess the efficacy and safety of 4 doses of galcanezumab (5 mg, 50 mg, 120 mg, and 300 mg administered subcutaneously every 4 weeks over 12 weeks) in the prevention of migraine headache, compared to placebo, in outpatients suffering from EM. The primary endpoint (the effect on migraine headache days at least 1 galcanezumab dose superior to placebo) was successfully demonstrated. Based on the result of the CGAB study and the analysis on pharmacokinetic/pharmacodynamic (PK/PD) data, the dose range was optimized for Phase 3 studies (CGAG/CGAH for episodic migraine). The proposed study is a bridging study conducted in Japan aimed to confirm the safety and efficacy of galcanezumab in the prevention of migraine headache in Japan population. The study design of the proposed study is similar to CGAG/CGAH studies.

3.3. Benefit/Risk Assessment

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

4. Objectives and Endpoints

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

Table CGAN.4.1. Objectives and Endpoints

Objectives	Endpoints
Primary To test the hypothesis that at least 1 dose of galcanezumab (120 or 240 mg/month) is superior to placebo in the prevention of migraine headache in patients with episodic migraine.	The overall mean change from baseline in the number of monthly migraine headache days during the 6-month, double-blind treatment phase
Key Secondary Objectives Regardless of primary objective results, all comparisons in secondary objectives are galcanezumab 120 mg versus placebo and galcanezumab 240 mg vs. placebo.	[CI]
• To compare galcanezumab with placebo with respect to 50% response rate	• The proportion of patients with a reduction from baseline ≥50% in monthly migraine headache days during the 6-month, double-blind treatment phase
• To compare galcanezumab with placebo with respect to 75% response rate	• The proportion of patients with reduction from baseline ≥75% in monthly migraine headache days during the 6-month, double-blind treatment phase
• To compare galcanezumab with placebo with respect to 100% response rate.	• The proportion of patients with reduction from baseline equal to 100% in monthly migraine headache days during the 6-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 MSQ v2.1 (average of Months 4, 5, and 6)
• To compare galcanezumab with placebo with respect to change in use of acute (abortive) migraine treatment	• The overall 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 during the 6-month, double-blind treatment phase
• To compare galcanezumab with placebo with respect to change in global severity of the migraine condition	• The mean change from baseline in the PGI-S score (average of Months 4, 5, and 6)

Other Secondary Objectives	
• To compare galcanezumab with placebo with respect to change in headache days	• The overall mean change from baseline in the number of monthly headache days during the 6-month, double-blind treatment phase
• To compare galcanezumab with placebo with respect to change in moderate-to-severe headache days	• The overall mean change from baseline in the number of monthly moderate to severe headache days during the 6-month, double-blind treatment phase
• To compare galcanezumab with placebo with respect to 30% response rate	• The proportion of patients with reduction from baseline ≥30% in monthly migraine headache days during the 6-month, double-blind treatment phase
• To compare galcanezumab with placebo with respect to distribution of response rates	• Cumulative distribution of monthly migraine headache day response rates during the 6-month, double-blind treatment phase
• To compare galcanezumab with placebo with respect to time to 50% response	• Time to first occurrence of a ≥50% reduction from baseline in the number of monthly migraine headache days (Kaplan-Meier analysis)
• To compare galcanezumab with placebo with respect to onset of effect	• The initial month at which statistical separation in mean change from baseline in the number of monthly migraine headache days is demonstrated and maintained at all subsequent months through Month 6
• To compare galcanezumab with placebo with respect to onset of 50% sustained response	• The initial month at which statistical separation in the proportion of patients meeting at least a 50% reduction in monthly migraine headache days that is maintained at all subsequent months through Month 6
• To compare galcanezumab with placebo with respect to maintenance of 50% response	• The proportion of patients who maintain 50% response criteria for at least 3 consecutive months to the patient's endpoint, and the proportion of patients who maintain 50% response criteria for 6 consecutive months during the 6-month, double-blind treatment
• To compare galcanezumab with placebo with respect to changes in other efficacy parameters, specifically: o ICHD migraine headache days o migraine attacks o migraine headache hours o headache hours o severity of remaining migraines	• Overall mean change from baseline (during the 6-month, double-blind treatment phase) on the following monthly measures: o ICHD migraine headache days o migraine attacks o migraine headache hours o headache hours o severity of remaining migraines
• To compare galcanezumab with placebo with respect to global assessment of illness	• Overall mean PGI-I rating during the 6-month, double-blind treatment phase
• To compare galcanezumab with placebo with respect to changes in disability and quality of life	• Mean change from baseline on the following measures: o MIDAS total score and individual items at Month 6 o MSQ v2.1 total score, and Role

	Function-Preventive and Emotional Function domain scores (average of Months 4, 5, and 6) o HCRU and employment status
• To evaluate patient satisfaction with medication	• Satisfaction with medication using the PSMQ-M.
• To compare galcanezumab with placebo with respect to safety and tolerability	• Analysis of: o TEAEs o discontinuation rates o vital signs and weight o ECGs o laboratory measures o other safety parameters, including suicidality using the C-SSRS
• To evaluate immunogenicity of galcanezumab	• Throughout the study: o Development and consequences of anti-drug antibodies and neutralizing anti-drug antibodies to galcanezumab
• To evaluate PK of galcanezumab • To evaluate PD (target engagement) of galcanezumab	• Serum concentrations of galcanezumab • Plasma concentrations of CGRP
• To assess changes in efficacy outcomes during Study Period IV as collected by ePRO diary data	• In Study Period IV: o Mean change from baseline in monthly migraine headache days o Time to first loss of response among patients who met the 50% response rate criteria at the end of the double-blind treatment phase o Time to initiation of treatment with a migraine prevention medication
• To compare galcanezumab with placebo with respect to change in use of acute (abortive) migraine treatment (MHD only)	• The overall mean change from baseline in the number of monthly migraine headache days requiring medication for the acute treatment of migraine headache days during the 6-month double blind treatment phase
Exploratory CCI [redacted]	
• To explore PK/PD and exposure-response relationships	• Analysis of the relationship between baseline plasma CGRP concentrations and efficacy measures • Analysis of the relationship of serum galcanezumab concentrations to plasma CGRP concentrations, efficacy endpoints, and/or safety endpoints.
• To compare galcanezumab with placebo with respect to categorical changes in quality of life	• Percentages of patients with: o ≥50% improvement in MIDAS total

	score o change from baseline in MSQ Role Function-Restrictive domain ≥10.9 o change from baseline in MSQ Role Function-Preventive domain ≥8.3 o change from baseline in MSQ Emotional Function domain ≥12.2
• To compare galcanezumab with placebo with respect to the proportion of migraine headache days or headache days requiring medication for the acute treatment of migraine headache or headache	• Change from baseline in the proportion of monthly migraine headache days or headache days requiring medication for the acute treatment of migraine headache or headache
• To compare galcanezumab with placebo with respect to the proportion of migraine headache days requiring medication for the acute treatment of migraine headache	• Change from baseline in the proportion of monthly migraine headache days requiring medication for the acute treatment of migraine headache
• To compare galcanezumab with placebo with respect to changes in symptomatology associated with migraine or probable 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 other than aura
• To explore safety results during Study Period IV	• Analysis of the following during Study Period IV: o FEAEs o discontinuation rates o vital signs and weight o ECGs o laboratory measures o other safety parameters , including suicidality using the C-SSRS and follow-up of emergent adverse allergic reactions or hypersensitivity

Abbreviations: CGRP = calcitonin gene-related peptide; C-SSRS = Columbia–Suicide Severity Rating Scale; FEAE = follow-up-emergent adverse event; ECG(s) = electrocardiogram(s); ePRO = electronic patient-reported outcomes; HCRU = healthcare resource utilization; ICHD = International Classification of Headache Disorders; MHD = migraine headache day; MIDAS = Migraine Disability Assessment test; MSQ v2.1 = Migraine-Specific Quality of Life Questionnaire version 2.1; PGI-I = Patient Global Impression-Improvement; PD = pharmacodynamic(s); PGI-S = Patient Global Impression of Severity; PK = pharmacokinetic(s); PSMQ-M = Patient Satisfaction with Medication Questionnaire-Modified; TEAE = treatment-emergent adverse event.

Table CGAN.4.2. Migraine and Headache Endpoint Definitions

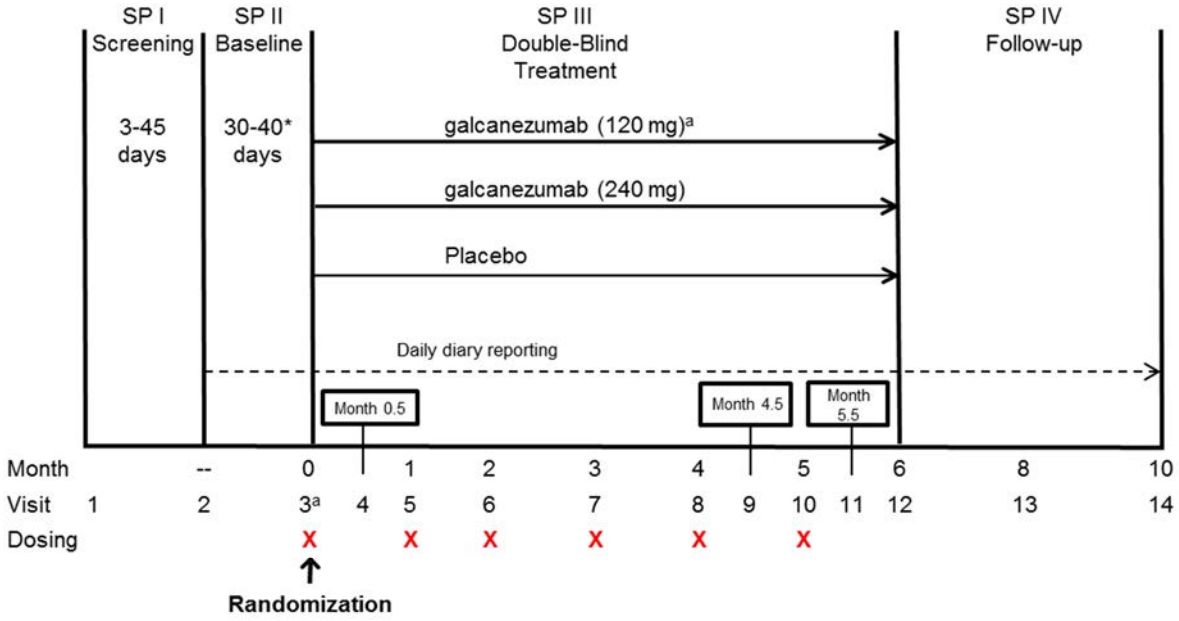
Diagnosis	Definition/Criteria
Migraine headache	A headache, with or without aura, of ≥30 minutes duration with both of the following required features (A and B): A. At least 2 of the following headache characteristics: • Unilateral location • Pulsatile quality • Moderate or severe pain intensity • Aggravation by or causing avoidance of routine physical activity AND B. During headache at least 1 of the following: • Nausea and/or vomiting • Photophobia and phonophobia *(Definition adapted from the IHS ICHD-3 beta)*
Probable migraine headache	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; that is, meet at least 2 A criteria and none of the B criteria, or meet 1 of the A criteria and at least 1 of the B criteria.
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.
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: ICHD = International Classification of Headache Disorders; IHS = International Headache Society.

5. Study Design

5.1. Overall Design

Study CGAN is a multisite, randomized, double-blind, placebo-controlled bridging study of galcanezumab in Japanese outpatients suffering from migraine. The study has 4 periods, including a prospective baseline phase to determine patient eligibility. Patients who complete Study Period III may have an option to roll-over to the open-label extension study, I5Q-JE-CGAP (CGAP). Figure CGAN.5.1 illustrates the study design.



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

[a]Patients randomized to the 120 mg dose will receive a loading dose of 240 mg at the first injection only (Visit 3).

Approximately 240 enrolled patients roll-over to I5Q-JE-CGAP study (Open Label Extension) at visit 12

Abbreviations: SP = study period.

Figure CGAN.5.1. Illustration of study design for Study I5Q-JE-CGAN.

Study Period I: The study and potential risks for both study I5Q-JE-CGAN and I5Q-JE-CGAP will be explained to the patient at Visit 1. The informed consent form (ICF) must be signed before any study procedures are performed. Patients are required to discontinue all excluded medications or migraine-prevention treatments at least 30 days prior to Visit 2. Botulinum toxin A or B in the head or neck area must be discontinued at least 4 months prior to Visit 2.

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

Study Period II: Qualified patients will enter Study Period II (prospective baseline) to determine their eligibility for the study, and to establish baseline data for comparison of endpoints during the treatment period. Beginning at Visit 2, patients will log in daily to the electronic patient-reported outcomes (ePRO) system to answer questions about the occurrence of headaches, headache duration, headache features, severity of headache, and use of headache medication. At the end of the prospective baseline period, sites will be notified whether their patients met the criteria and are eligible to be randomized to treatment at Visit 3.

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

Study Period III: At the start of the 6-month, double-blind treatment phase (Visit 3), patients meeting all eligibility requirements will be randomized to 1 of 3 treatment groups in a 2:1:1 ratio to receive placebo, 120 mg/month galcanezumab, or 240 mg/month galcanezumab, respectively.

Patients randomized to the 120 mg dose of galcanezumab will receive an initial loading dose of 240 mg (2 injections of 120 mg each at Visit 3 only). To preserve blinding throughout the study, patients in all treatment groups will receive 2 injections of investigational product at each dosing visit. At Visit 3, if available and where local regulations in Japan and ethical review boards/institutional review boards (ERBs/IRBs) 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.

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 his/her assigned treatment of study drug.

Patients will be given injections of study drug during office visits (Figure CGAN.5.1). For all treatment groups, subcutaneous injections will be administered once monthly at the dosing visits. At Visit 3 (first dose), patients will be required to remain 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 after the first injection and/or they are judged by the investigator to have risk of a significant adverse event after injection. 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 concomitant medication study tool) during the treatment phase.

Patients who do not participate in the CGAP study and who complete Study Period III, or who discontinue for any reason during Study Period III, will be expected to enter post-treatment follow-up (Study Period IV).

Patients who discontinue for any reason during Study Period III will be expected to take the measurement for Early Termination (ET).

Study Period IV: Only patients who do not participate in the CGAP study will move on to Study Period IV. During this 4-month phase, sites and patients will remain blinded to patients' treatment assignments. Patients will follow all study procedures during Study Period IV, but will

not receive galcanezumab or placebo. One month after Visit 12, if clinically warranted due to a worsening of symptoms, patients may start migraine prevention medications at the discretion of the investigator. The list of allowed preventive medications is provided in the concomitant medication study tool. At Visit 14 (Month 10), patients will return to the site for their last study visit and discharge from the study.

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

5.2. Number of Participants

Approximately 902 participants will be screened to achieve 451 randomized participants for an estimated total of 225 evaluable participants in the placebo group and 113 evaluable participants each in the galcanezumab (120 mg and 240 mg) treatment groups.

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 randomized treatment phase is considered sufficient to assess the safety and efficacy of a migraine prevention medication, and is consistent with Studies CGAH/CGAG. A 4-month, post-treatment follow-up phase is included to evaluate patient safety during wash-out of galcanezumab. This allows for a total of 5 months of observation from the time of last injection of galcanezumab. A 5-month, post-treatment observation period allows for a wash-out of approximately 5 elimination half-lives of galcanezumab, and should decrease galcanezumab serum concentrations by approximately 97% during this time. For the roll-over patients, a 5-month, post-treatment observation period will be conducted after treatment for an additional 12 months in Study CGAP.

5.5. Justification for Dose

This study is a bridging study with 2 global Phase 3 studies (I5Q-MC-CGAG [CGAG] and I5Q-MC-CGAH [CGAH]). Therefore, the doses selected for this study were the same doses used in Studies CGAG and CGAH. In Studies CGAG and CGAH, doses of 120 mg and 240 mg galcanezumab administered once monthly were selected primarily on the basis of clinical efficacy and PK/PD data from the Phase 2 dose-ranging study, I5Q-MC-CGAB (CGAB). Results from Study CGAB indicated that 120 mg was statistically significantly superior to placebo at the last 28-day period of the 3-month treatment phase in mean change in migraine headache days, as well as in other measures of efficacy and quality of life. The use of a loading dose for the 120-mg treatment arm, and the inclusion of a 240-mg treatment arm, is based on the finding that a dose higher than 120 mg achieved statistically significant separation from placebo as early as Month 1.

In the Phase 1 study (Study I5Q-MC-CGAE [CGAE]), single doses of galcanezumab up to 300 mg and three every-4-week (Q4W) 300-mg doses of galcanezumab were well tolerated in both Japanese and Caucasian subjects.

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, ECGs, and migraine history during screening and a prospective baseline period, as described in the Inclusion (Section 6.1) and Exclusion (Section 6.2) Criteria. The nature of any comorbid conditions present at the time of the physical examination and any preexisting conditions must be documented. Individuals who do not meet the criteria for participation in this study (screen failure) for specific reasons, as outlined, may be considered for rescreening once, with approval from Eli Lilly and Company (Lilly) Medical (Section 6.4). Study participants should be instructed not to donate blood or blood products during the study 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 at screening:

Patient and Disease Characteristics

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

[2] Have a diagnosis of migraine as defined by International Headache Society (IHS) International Classification of Headache Disorders- (ICHD-) 3 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. **To avoid biased reporting, patients must not be told the number of migraine headache days on which study qualification is based.**

[5] 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

[6] 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.

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

[8] Women of childbearing potential must test negative for pregnancy at the time of enrollment, based on a serum pregnancy test. 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 screening,

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.

[9] 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 [8], or for male patients who meet the criterion defined in definition 3) of inclusion criterion [8].

[10] Agree not to post any personal medical data related to the study or information related to the study on any website or social media site (for example, Facebook, Twitter, 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 at screening:

Prior/Concurrent Clinical Trial Experience

[11] 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.

[12] 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.

[13] Current use or prior exposure to galcanezumab, or other antibodies to CGRP or its receptor, including those who have previously completed or withdrawn from this study or any other study investigating antibodies to CGRP or its receptor.

Prior/Concomitant Therapy

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

[15] Known hypersensitivity to multiple drugs, monoclonal antibodies or other therapeutic proteins, or to galcanezumab and the excipients in the investigational product.

[16] Are currently receiving medication or other treatments for the prevention of migraine headaches. Patients must have discontinued such treatment at least 30 days prior to Visit 2. Botulinum toxin A and B that has been administered in the head or neck area must be discontinued at least 4 months prior to Visit 2.

[17] Failure to respond to 3 or more adequately dosed migraine preventive treatments from different classes (that is, maximum tolerated dose for at least 2 months). Failure to respond due to tolerability issues is not considered a treatment failure. Migraine preventive treatments are defined as the drugs with a recommendation grade A or grade B (in Table 1 of section II-3-2 in the Japanese Clinical Guideline of chronic headache 2013) and botulinum toxin A or B.

Diagnostics Assessments

[18] History of persistent daily headache, 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 beta.

[19] History of headache (for example, cluster headache, medication overuse headache) other than migraine or tension-type headache, as defined by IHS ICHD-3 beta within 3 months prior to randomization.

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

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

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

Medical Conditions

[23] Have ECGs showing abnormalities compatible with acute cardiovascular events and/or serious cardiovascular risk, including, but not limited to, a Fridericia's corrected QT (QTcF) interval >470 msec for women and >450 msec for men, or have had myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft, stroke, or deep vein thrombosis/pulmonary embolism within 6 months of screening, or have planned cardiovascular surgery or percutaneous coronary angioplasty.

[24] Patients with a body mass index (BMI) $\geq$40 kg/m^2 at Visit 1.

[25] 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 Lilly Medical prior to enrollment.

[26] 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 or generalized anxiety disorder whose disease state is considered stable and is 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.

[27] 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 who 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 with the ideation or behavior occurring within the past month.

[28] Women who are pregnant or nursing.

[29] Patients who have used opioids or barbiturate containing analgesic more than twice per month for the treatment of pain in more than 2 of the past 6 months (opioid administration in an emergency setting may be an exception).

[30] Patients with a history of drug or alcohol abuse/dependence within 1 year prior to Visit 1 (excessive or compulsive use as judged by the investigator), or who are 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.

[31] 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 explanation for the positive result. The results of the retest must be negative at or prior to Visit 2.

[32] 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.

Other Exclusions

[33] Have other issues that, in the opinion of the investigator, would interfere with compliance with the study requirements and completion of evaluations required for this study.

[34] 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.

[35] Are Lilly employees.

[36] Are unwilling or unable to comply with the use of data collection devices.

6.3. Lifestyle Restrictions

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

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be considered for rescreen once, with approval from Lilly Medical for only the criteria shown below. The interval between screening and rescreening must be at least 45 days or longer, if required, for the specified timeframes in the inclusion/exclusion criteria or concomitant medication list. If rescreening is performed, the individual must sign a new ICF, and will be assigned a new identification number.

- Inclusion criterion [8]
- Exclusion criterion [12]
- Exclusion criterion [14]
- Exclusion criterion [16]
- Exclusion criterion [28]

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 and 240 mg) administered once monthly with placebo. Sites will administer subcutaneous injections of the study drug (galcanezumab and/or placebo) at 6 visits during the treatment phase (Section 2).

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:

- Explaining the correct use of the investigational agent(s) to the patients, site personnel, and/or legal representatives.
- Verifying that instructions are followed properly.
- 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.

7.1.1. Packaging and Labeling

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

Clinical trial materials will be labeled according to the Japanese 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

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

To achieve between-group comparability, the randomization will be stratified by baseline migraine frequency (<8 migraine headache days versus ≥8 migraine headache days). To ensure

an appropriate balance of low- and high-frequency migraine headache-day patients, the sponsor will stop enrollment of low-frequency patients, if the number exceeds an estimated 315.

Note that the treatment arm of the long-term extension study CGAP, which is rolled over from Study CGAN, will be determined at CGAN Visit 3 (at the timing of CGAN randomization). The detail of method of treatment assignment is described in the protocol 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 a double-blind study. To preserve blinding throughout the study, patients in all treatment groups will receive 2 injections of investigational product at each dosing visit.

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.

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 (CRP) or clinical research scientist (CRS) for the patient to continue in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly CRP/CRS prior to unblinding a patient's treatment assignment, unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, Lilly must be notified immediately.

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 refrigerator 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. Study Extensions

Patients who complete this study through Visit 12 (6 months) may be eligible to participate in Study I5Q-JE-CGAP (CGAP), if enrollment criteria for Study CGAP are met. Approximately 240 patients will be rolled over to the open-label study CGAP, which has 2 arms: galcanezumab 120 mg and galcanezumab 240 mg. Patients who enroll in the CGAP study will roll over directly at the end of the CGAN double-blind treatment period (Study Period III), skipping the 4-month, follow-up period (Study Period IV).

7.8.2. Continued Access

Following a patient's completion of Study CGAN, he/she will not have continued access to investigational product. Patients who enroll in Study CGAP will continue to receive galcanezumab as part of Study CGAP.

8. Discontinuation Criteria

Patients who discontinue the study or investigational product during the double-blind treatment phase (Study Period III) will proceed immediately to the post-treatment follow-up period (Study Period IV).

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 CRP and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled patient to continue in the study, with or without treatment with investigational product.

8.2. Discontinuation from the Study

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 the study indication (prevention of migraine) during Study Period III, discontinuation from the study occurs prior to introduction of the new agent.
- If, in the opinion of the investigator, a clinically significant event (CSE) occurs that warrants discontinuation of the study drug. A CSE will be defined as a moderate-to-severe AE, abnormal clinical sign, or clinical laboratory finding that may pose a serious risk to the well-being of the patient.

- 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 good clinical practice.

Patients who discontinue the study early (Study Period 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 (Study Period 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 who 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 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. Efficacy Assessments

An ePRO system and eCRF will be used to collect primary and secondary efficacy assessments. Patient migraine headache data will be entered by the patients into an ePRO diary, and patient-rated scales/questionnaires will be collected directly via an ePRO tablet at each visit. The use of these ePRO devices and of the electronic clinical outcome assessment (eCOA) system is described in the Data Capture System section of Appendix 3 (Appendix 3.2.1).

9.1.1. Primary Efficacy Assessments

The primary efficacy endpoint is the overall mean change from baseline in the number of monthly migraine headache days during the 6-month, double-blind treatment phase (average of Months 1-6). Migraine headache day will be defined in Table CGAN.4.2. Patients will be asked to use an ePRO device (starting at Visit 2) to record headache symptoms, duration, and severity.

9.1.2. Secondary Efficacy Assessments

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

9.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate 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 or not 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. The investigator answers yes/no when making this assessment.

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

If a patient's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF, clarifying, if possible, the circumstances leading to 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 (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect

- considered significant by the investigator for any other reason: important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious, based upon appropriate medical judgment.

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. 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 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.

Nonserious AEs obtained through the questionnaire are recorded and analyzed separately. Only SAEs 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

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 will have a central overread, except for screening, and should be recorded according to the study-specific recommendations included in the ECG manual.

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

9.4.2. 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 Schedule of Activities [Section 2]). Weight will be measured at screening and at Visits 12 and 14 or at ET (see Schedule of Activities [Section 2]).

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

In addition, an immunogenicity and 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. In this case, serum concentrations of galcanezumab will be determined for immunogenicity evaluation. 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 to 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. Galcanezumab concentration information that may/would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded. Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 1 year following last patient visit for the study.

A validated assay will be used to determine serum galcanezumab concentrations. Samples will be analyzed at a laboratory approved by the sponsor. It is intended that blood samples collected from patients who received placebo should not be analyzed for determination of serum concentrations of galcanezumab.

9.6. Pharmacodynamics

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.

Plasma CGRP concentration information that may/would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Bioanalytical samples collected to measure 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.

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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 the galcanezumab as specified in the Schedule of Activities (Section 2). Immunogenicity will be assessed by a validated assay designed to detect anti-drug antibodies in the presence of the investigational product. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the 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 the 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 healthcare 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 et al. 1999; Stewart et al. 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 their 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.

Patient 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

The study will enroll approximately 451 patients. Eligible patients will be randomized in blinded fashion in a 2:1:1 ratio to placebo (target of 225 patients), galcanezumab 120 mg/month (target of 113 patients), or 240 mg/month (target of 113 patients). With the assumption of a 15% discontinuation rate and an effect size of 0.36, it is estimated that this sample size will provide approximately 88% power that at least 1 dose of galcanezumab will separate from placebo at a two-sided significance level of 0.05 based on simulations using the Dunnett test (Dunnett 1955). Assumptions in the simulations were based on the assumptions for global Phase 3 studies, with adjustment to reflect less dropout and less variability in a more homogenous Japanese study.

Approximately 902 patients may be screened to ensure randomization of 451 patients, with an estimated 383 patients completing the study.

10.2. Populations for Analyses

Populations are defined, for the purpose of analysis, in Table CGAN.10.1.

Table CGAN.10.1. Populations for Analyses

Population	Description
All Randomized Patients (ARP)	All patients who are randomized at Visit 3.
Intent-to-Treat (ITT) Population	All patients who are randomized at Visit 3 and received at least one dose of study drug. Patients in the ITT population will be analyzed according to the treatment that they were randomized to. 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 post-treatment phase (Study Period IV) as indicated by entering any post-treatment visit.
Per Protocol Set (PPS)	ITT population who has no important protocol deviation which impact efficacy analysis. Details will be specified in SAP.

Abbreviations: SAP = statistical analysis plan.

10.3. Statistical Analysis

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, analyses will be conducted on an intent-to-treat (ITT) population, which will include all patients who are randomized at Visit 3 and receive at least 1 dose of study drug. 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 post-baseline measurement.

Unless otherwise specified, hypothesis tests will be based on two-sided alpha level of 0.05. For the primary analysis and the other continuous efficacy analyses, multiplicity adjustment (120 mg versus placebo and 240 mg versus placebo), such as Dunnett's procedure, will be used if appropriate. Details will be specified in SAP.
The primary analysis will be performed using a restricted maximum likelihood-based mixed models repeated measures (MMRM) technique using the Step-down version of Dunnett's procedure (Section 10.3.3.1). The analysis is based on the double-blind period (Study Period III) only.

In addition to the MMRM approach, sensitivity analysis of covariance (ANCOVA) model using the last observation carried forward (LOCF) to account for missing data will be conducted to provide additional information for the primary and continuous secondary measures, as well as continuous health outcome measures.

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

Categorical safety measures (including percentages of patients with TEAEs, SAEs, and AEs reported as a reason for discontinuation, as well as those patients who met categorical criteria for changes in vital signs and weight, ECGs, and laboratory tests) will be analyzed using Fisher's exact test.

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 all treatment groups for Study Period III (double-blind treatment) and Study Period IV (post-treatment follow-up) both overall and by visit. In addition, the number and percentage ITT patients who roll over to CGAP will summarized for all treatment groups.

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

10.3.2.2. Patient Characteristics

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

- Demographic (age, gender, ethnic origin, height, weight, body mass index [BMI])

- Migraine headache, headache, variation of migraine/headache measures per 30-day baseline period.
- Alcohol, tobacco, caffeine, and nicotine consumption
- Medical history and preexisting conditions
- Other baseline variables used for subgroup analysis (eg, baseline anti-drug antibodies [see Section 10.3.6.2])

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 ePRO) will be summarized for all ITT patients for Study Period III and Study Period IV, separately.

10.3.2.4. Treatment Compliance

Not applicable.

10.3.2.5. Electronic Patient-Reported Outcome Diary Compliance

ePRO diary compliance at each period (including baseline, Month 1, 2, 3, … until Month 10) will be calculated. Diary compliance at each period is calculated as:

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

Actual number of diary days is calculated as the total number of days with non-missing answers.

10.3.3. Primary and Secondary Analyses

10.3.3.1. Primary Analyses

The primary efficacy objective is to assess whether at least 1 dose of galcanezumab (120 or 240 mg/month) is superior to placebo in the prevention of migraine headache in patients with episodic migraine.

The primary efficacy measure is the overall mean change from the baseline period in the number of monthly migraine headache days during the 6-month, double-blind treatment phase (average of Months 1-6; Study Period III), and the primary analysis will evaluate the efficacy of galcanezumab (120 or 240 mg/month) compared with placebo. The analysis is based on ITT population. It will be performed using a restricted maximum likelihood-based MMRM technique. The analysis will include the fixed categorical effects of treatment, 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. The primary endpoint of this study for each galcanezumab dose arm compared with placebo will be estimated as the main effect of treatment from the MMRM analysis during the 6-month

treatment phase. This provides the average treatment effect across 6 months of double-blind treatment phase. The repeated-measures analysis will include data from all 3 treatment groups.

For the multiplicity adjusted p-value calculation, the pairwise treatment effect comparisons of each dose of galcanezumab versus placebo will be conducted using the step-down version of Dunnett's procedure at the two-sided alpha level of 0.05.

For sensitivity analysis purpose, ANCOVA will be used on ITT population.

For sensitivity analysis purpose, MMRM will be used on PPS population.

10.3.3.2. Key Secondary Analyses

The key secondary measures will be analyzed for the double-blind treatment (Study Period III).

For the continuous key secondary measures, the change from baseline during the 6-month, double-blind treatment phase will be analyzed by repeated measures analyses similar to the one described in Section 10.3.3.1. For the analysis of 50%, 75%, and 100% response, the percentage of patients meeting response criteria during the 6-month double-blind treatment phase will be estimated by MMRM-CAT using the GLIMMIX procedure in SAS®.

10.3.3.3. Other Secondary and Exploratory Efficacy Analyses

The other secondary and exploratory efficacy analyses will be conducted for the double-blind treatment phase, and for the double-blind treatment and post-treatment follow-up phases (Study Period III and Study Period IV) combined. Further details regarding other secondary and exploratory efficacy analyses are summarized in the SAP.

10.3.4. Safety Analyses

The safety analyses will be conducted for the double-blind treatment and post-treatment follow-up phases, as well as the 2 periods combined. For the 2 phases combined, only repeated measures and time-to-event analyses will be conducted.

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

- adverse events
    - TEAEs
        - by preferred term
        - by SOC
        - by maximum severity
        - by outcome
        - considered to be related to investigational product by investigator
    - SAEs
    - AEs leading to discontinuation
    - follow-up-emergent adverse events (FEAEs) during Study Period IV.
- Suicidal ideation and behaviors assessed by solicited questioning using the C-SSRS
- Vital signs and weight

- ECGs
- Laboratory measurements
- Anti-galcanezumab antibody measurements

10.3.4.1. Categorical Safety Variables

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

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

10.3.4.2. Adverse Events

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

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

Similar to TEAEs, FEAEs will be analyzed.

10.3.4.3. Suicide-Related Thoughts and Behaviors

Suicide-related events occurring during the study, based on the C-SSRS, will be summarized by treatment. In particular, for each of the following suicide-related events, the number and percent of patients with the event will be enumerated by treatment: completed suicide, nonfatal suicide attempt, interrupted attempt, aborted attempt, preparatory acts or behavior, active suicidal ideation with specific plan and intent, active suicidal ideation with some intent to act without specific plan, active suicidal ideation with any methods (no plan) without intent to act, non-specific active suicidal thoughts, and wish to be dead. The number and percent of patients with self-injurious behavior with no suicidal intent occurring during treatment will also be enumerated by treatment.

In addition, the number and percent of patients who experienced at least 1 of the various composite measures will be presented. These include suicidal behavior (completed suicide, non-fatal suicidal attempts, interrupted attempts, aborted attempts, and preparatory acts or behavior),

suicidal ideation (active suicidal ideation with specific plan and intent, active suicidal ideation with some intent to act without specific plan, active suicidal ideation with any methods [no plan] without intent to act, non-specific active suicidal thoughts, and wish to be dead), and treatment-emergent suicidal ideation.

The Fisher's exact test will be used for treatment comparisons.

10.3.4.4. Vital Signs and Weight

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

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

10.3.4.5. Electrocardiogram Intervals and Heart Rate

Analyses of corrected QT interval will be calculated using 2 correction formulas. The QTcF (measured in milliseconds [msec]) will be calculated with Fridericia's formula as $QT/RR^{⅓}$. The Large Clinical Trial Population Based QT Correction (QTcLCTPB) (msec) will be calculated with the formula as $QT/RR^{0.413}$. The number and percent of patients meeting criteria for treatment-emergent abnormalities in ECG intervals (pulse rate, QRS, QTcF, and QTcLCTPB) and heart rate at any time during study will be summarized. Treatment group comparisons will be performed using the Fisher's exact test.

10.3.4.6. Laboratory Tests

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

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

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

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10.3.6. Other Analyses

10.3.6.1. Medical Resource Utilization and Health Economics

The change from baseline to each postbaseline visit for the double-blind treatment phase and for the double-blind treatment and post-treatment follow-up phases combined for MSQ v2.1 (Role Function-Restrictive, Role Function-Preventive, Emotional Function, and total score) and MIDAS (item scores and total score) will be analyzed. In addition, categorical analysis for the frequency measure will be performed.

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

10.3.6.2. Subgroup Analyses

Subgroup analyses (Table CGAN.10.2) will be performed for the primary efficacy measure (change from baseline in the number of migraine headache days) only for the ITT patients in Study Period III.

Table CGAN.10.2. Definition of Subgroup Variables

Subgroup Variable	Categories
Sex	Male, female
Baseline number of migraine headache days	2 levels of baseline migraine frequency : • <8 migraine headache days • ≥8 migraine headache days
Treatment-resistant status	Treatment-resistant status about whether a patient has failed 2 or more prophylactic treatments (Yes or No)
Having aura or not (during baseline period)	Yes or No
Baseline anti-drug antibody status	Any confirmed positive anti-drug antibody at baseline (Yes vs No)
Neutralizing anti-drug antibody status	Any positive neutralizing anti-drug antibody time point (Yes vs No) – note that neutralizing anti-drug antibody assays are performed only on confirmed-positive anti-drug antibodies
Treatment-emergent anti-drug antibody status	Any treatment-emergent anti-drug antibody (Yes vs No)

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10.3.7. Interim Analyses

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

An interim analysis may be conducted after all randomized patients complete the double-blind treatment period (Study Period III) of the study. Thus, it will be the final analysis of the primary efficacy endpoint. It will be conducted using internal, unblinded study team members who do not have direct interaction with sites.

Unblinding details are specified in the unblinding plan section of the SAP or a separate unblinding plan document.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
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
ARP	All Randomized Patients
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/subject] nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BMI	body mass index
BUN	blood urea nitrogen
CGRP	calcitonin gene-related peptide
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
COA	Clinical Outcome Assessment
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.
CPK	creatinine phosphokinase
CRP/CRS	Clinical Research Physician/Clinical Research Scientist: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.

CSE	clinically significant event
C-SSRS	Columbia–Suicide Severity Rating Scale
CSR	clinical study report
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
eCRF	electronic case report form
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the ICF directly or through their legally acceptable representatives.
EM	episodic migraine
ePRO	electronic patient-reported outcomes
ERB	Ethical Review Board
ET	early termination
FEAE	follow-up emergent adverse event: an event that first occurred or worsened during the follow-up period (Study Period IV) when compared to the double-blind treatment period (Study Period III)
FSH	follicle-stimulating hormone
GCP	good clinical practice
GGT	gamma glutamyltransferase
GLIMMIX	generalized linear mixed model
HbA1c	glycated hemoglobin
HCRU	healthcare resource utilization
HDL	high-density lipoprotein
IB	Investigator's Brochure
ICF	informed consent form
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.
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IgM	immunoglobulin M
INR	International Normalized Ratio
IRB	institutional review board
ITT	intention 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.
IUD	intrauterine device
IUS	intrauterine system
IWRS	interactive web-response system
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MHD	migraine headache day
MIDAS	Migraine Disability Assessment test
MSQ v2.1	Migraine Specific Quality of Life Questionnaire version 2.1
MMRM	mixed models repeated measures
MMRM-CAT	categorical mixed models repeated measures
PD	pharmacodynamics
PGI-I	Patient Global Impression of Improvement
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetics

PPS	Per-Protocol Set
PSMQ-M	Patient Satisfaction with Medication questionnaire-modified
Q4W	administration once every 4 weeks
QTc	corrected QT interval
QTcF	Fridericia's corrected QT interval
QTcLCTPB	Large Clinical Trial Population Based QT Correction
RBC	red blood cell
RNA	ribonucleic acid
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.
SHFU	Self-Harm Follow-Up form
SHSF	Self-Harm Supplement form
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, which and does not necessarily have to have a causal relationship with this treatment.
TPO	third-party organization
ULN	upper limit of normal
US	United States
WBC	white blood cell

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	High-density lipoprotein (HDL)
Glucose	
Ketones	
Blood	**HbA1c**
Urine leukocyte esterase[a]	
Microscopic analysis[a]	**Other**
Urine culture[a]	CCI [redacted]
	PK sample (LY2951742 serum concentration determination)
	Immunogenicity
	Urine Drug Screen[b]
	Pregnancy Test (females only)[b]
	Serum pregnancy or FSH
	Urine pregnancy test (performed by site)
	Stored Samples
	Biomarker storage
	CCI [redacted]
	RNA/Epigenetic

Abbreviations: CGRP = calcitonin gene-related peptide; DNA = deoxyribonucleic acid; FSH = follicle-stimulating hormone; HbA1c = glycated hemoglobin; PK = pharmacokinetic; RBC = red blood cell; 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/her participation in the trial.

Appendix 3.1.2. Ethical Review

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

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

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

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

Appendix 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.

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.

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 electronic case report forms (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.

Some or all of a patient's data will be directly entered into the 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 third party organization (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 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/COA 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/COA 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 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 the Lilly, or its designee (clinical research physician/clinical research scientist [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 = aspirate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; IgM = immunoglobulin M; INR = International Normalized Ratio; RBC = red blood cells; WBC = white blood cells.

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

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

Appendix 5. Protocol Amendment I5Q-JE-CGAN(a) Summary: A Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 (Galcanezumab) in Japanese Patients with Episodic Migraine

Overview

Protocol I5Q-JE-CGAN [A Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 (Galcanezumab) in Japanese Patients with Episodic Migraine] has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

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

- Added description about observation of patients after second dosing for post-injection safety monitoring.
- Deleted "signed assent from the patients" from inclusion criterion [6] because patients aged 18 and 19 years old are considered old enough to understand the informed consent document without any additional assent document.
- Changed the description of inclusion criteria [8] and [9] and exclusion criteria [13], [14], and [15] in order to clarify patient eligibility for the investigators.
- Revised description regarding the prefilled syringes since they are not currently certified in Japan.
- Updated abbreviation list: "IUD" and "IUS" added.

Revised Protocol Sections

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

2. Schedule of Activities

Serum Pregnancy (for women of childbearing potential)[i] or FSH at Visit 1 (~~all other female patients~~ for women who have evidence of cessation of menses for at least 12 months)[ɨ]

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

5.1. Overall Design

Study Period III:

At Visit 3 (first dose), patients will be required to remain at the site ~~in the office~~ 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 after the first injection and/or they are judged by the investigator to have risk of a significant adverse event after injection. Patients will continue to log in and complete the ePRO diary each day.

6.1. Inclusion Criteria

[6] Are able and willing to give signed informed consent, ~~and signed assent from the patients~~ and in the case of patients under 20 years old, informed consent signed by a parent or guardian. ~~in the case of patients under 20 years old~~

[8] Women of child-bearing potential must test negative for pregnancy at the time of enrollment, based on a serum pregnancy test. Women of non-childbearing potential are defined as

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 screening,

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 base on multiple semen examinations, as shown by their medical record.

[9] All patients~~, male and female,~~ 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~~ 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 [8], or for male patients who meet the criterion defined in definition 3) of inclusion criterion [8]. ~~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; a partner with vasectomy. Birth control is not required if the female is infertile due to surgical sterilization (at least 6 weeks after surgical bilateral oophorectomy, hysterectomy, or at least 6 weeks after tubal ligation) confirmed by medical history or menopause. Menopause is defined as spontaneous amenorrhea for at least 12 months, not induced by a medical condition, or spontaneous amenorrhea of 6-12 months and a follicle stimulating hormone (FSH) level >40 mIU/mL.~~

6.2. Exclusion Criteria

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

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

[15] Known hypersensitivity to multiple drugs, monoclonal antibodies or other therapeutic proteins, or to galcanezumab and the excipients in the investigational product.

7.1.2. Medical Devices

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

Appendix 1 Abbreviations and Definitions

IUD	intrauterine device
IUS	intrauterine system