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

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

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

Objectives and Endpoints

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

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

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

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

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

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

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

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

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

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

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

5.5. Justification for Dose

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

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

Investigators must document their review of each laboratory safety report.

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

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

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

The investigator will decide whether he or she interprets the observed AEs as reasonably possibly related to migraine, to the investigational product, study device, study procedure, or other concomitant treatment or pathologies. The investigator will answer yes/no when making this assessment.

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

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

9.2.1. Serious Adverse Events

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

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

a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned

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

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

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy that occurs during the study, including those in which conception occurred within 5 months after last administration of investigational product, should be reported using the SAE process to collect data on the outcome for both mother and fetus.

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

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

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

9.2.2. Complaint Handling

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

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

9.3. Treatment of Overdose

No data are available at this stage of development.

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

10.3.3.2. Secondary Analyses

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

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

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

10.3.3.3. Tertiary Efficacy Analyses

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

10.3.4. Safety Analyses

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

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

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

10.3.4.5. Laboratory Tests

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

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

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

10.3.5. Pharmacokinetic Analyses

Galcanezumab concentrations will be illustrated graphically and summarized descriptively. If warranted and based on availability of data, the relationship of serum galcanezumab concentrations to efficacy endpoints, safety endpoints, or ADA may be explored. Patient and healthy subject data, including but not limited to serum galcanezumab concentrations, from other clinical studies evaluating galcanezumab may be combined with data from this study to support additional analyses. Such analyses may be reported separately.

10.3.6. Evaluation of Immunogenicity

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

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

10.3.7. Other Analyses

10.3.7.1. Health Economics

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

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

10.3.7.2. Subgroup Analyses

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

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

Table CGAX.4. Definition of Subgroup Variables

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

Abbreviation: MHD = migraine headache day.

10.3.8. Interim Analyses

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

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

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

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

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

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

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

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

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

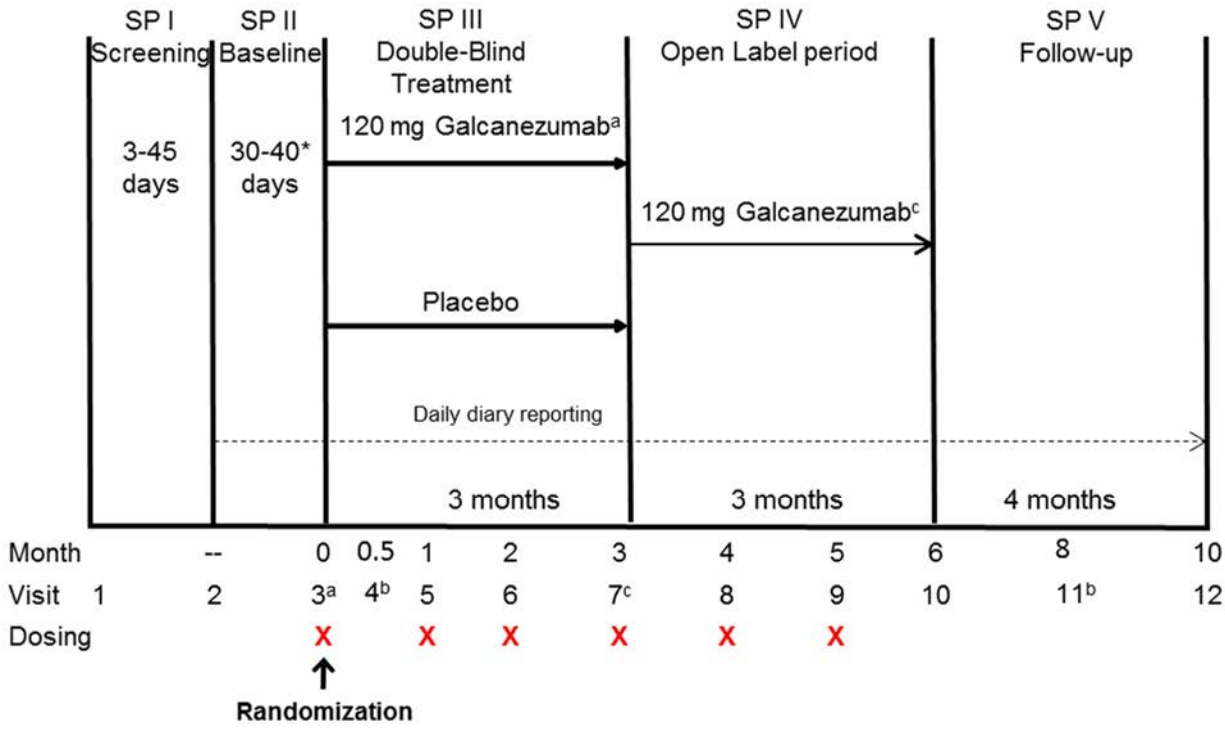
Study Period (SP)	SP I-Screening	SP II-Prospective Baseline	SP III Double-Blind Treatment				
(Target) Interval (days) since previous visit			30-45	14	16	30	30
Allowable range (days) between visits	3-45	30-40[a]					
Interval allowance (days)				+/- 5	+/- 2	+/- 2	+/- 2
Visit	1	2	3	4[b]	5[l]	6	7
Month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

5. Study Design

5.1. Overall Design

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

Figure CGAX.1 illustrates the study design.



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

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

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

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

Abbreviations: SP = study period.

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

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

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

Summary of Study Design:

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

Treatment Arms and Duration:

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

Objectives and Endpoints

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

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

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

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

5.2. Number of Participants

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

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

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

6. Study Population

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

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

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

6.1. Inclusion Criteria

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

Patient and Disease Characteristics

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

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

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

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

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

Informed Consent and Patient Agreements

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

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

9.4. Safety

9.4.1. Electrocardiograms

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

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

9.4.2. Vital Signs

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

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

9.4.3. Laboratory Tests

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

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

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

9.4.4. Samples for Immunogenicity Research

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

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

- laboratory measurements

10.3.4.1. Categorical Safety Variables

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

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

10.3.4.2. Adverse Events

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

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

10.3.4.3. Vital Signs and Weight

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

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

10.3.4.4. Electrocardiogram Intervals and Heart Rate

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

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PGI-S	Patient Global Impression of Severity
PHQ-9	Patient Health Questionnaire-9
QTcF	Fridericia's corrected QT interval
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SOC	system organ class
SUSARs	suspected unexpected serious adverse reactions
TBL	total bilirubin
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
US	United States

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

Overview

Protocol I5Q-MC-CGAX (A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Galcanezumab in Patients with Episodic Migraine – the PERSIST Study) has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are described in the following table:

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

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