Summary of Study Design:

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

Treatment Arms and Duration:

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

Number of Patients:

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

Statistical Analysis:

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

The primary analysis will evaluate the efficacy of galcanezumab compared with placebo on the overall mean change from baseline in the number of monthly migraine headache days during the 3-month double-blind treatment phase. Migraine headache day is defined to include both migraine and probable migraine days. The primary analysis will be performed using a restricted maximum likelihood-based mixed model repeated measures technique.

Table CGAW.1. Schedule of Activities

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

Objectives and Endpoints

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

Patients are required to discontinue all excluded medications or treatments for migraine prevention at least 5 days prior to Visit 2. Botulinum toxin A or B in the head or neck area for therapeutic use must be discontinued at least 3 months prior to Visit 2. Nerve blocks or device use, such as transcranial magnetic stimulation, in the head or neck area or for migraine prevention are not allowed within 30 days before Visit 2.

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

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

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

Study Period III: At the start of the 3-month double-blind treatment phase (Visit 3), patients meeting all eligibility requirements will be randomized in a 1:1 ratio to receive 120 mg/month galcanezumab (with an initial 240-mg loading dose) or placebo. At Visit 3, if available and where local regulations and ethical review boards (ERBs) allow, patients will also watch a training video designed to address patient expectations with regard to participation in a placebo-controlled trial and the difference between medical treatment and research. To preserve blinding, patients in both treatment groups will receive 2 injections of investigational product at the first dosing visit (2 galcanezumab injections of 120 mg or 2 placebo injections) and then 1 injection of investigational product (120-mg galcanezumab or placebo) for the next 2 dosing visits.

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

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

5.5. Justification for Dose

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

9.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report and ECG.

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

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect. However, any worsening of the primary study condition should be recorded as an AE.

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

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

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

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

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

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

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

9.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (ie, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- when a condition related to the investigational device (eg, prefilled syringe) necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned.

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the patient has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines (see Section 9.2) if it is considered reasonably possibly related to study procedure.

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

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

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

consultation with Lilly Medical. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Hepatic Safety Data Collection
Additional safety data should be collected via the eCRF if one or more of the following conditions occur:

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

9.5. Pharmacokinetics

Not applicable.

9.6. Pharmacodynamics

Not applicable.

9.7. Genetics

9.7.1. Whole Blood Sample for Pharmacogenetic Research

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

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

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

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

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

10.3.3.2. Key Secondary Analyses

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

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

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

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

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

10.3.5. Health Economics

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

10.3.6. Subgroup Analyses

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

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

Additional details are available in the SAP.

10.3.7. Interim Analyses

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

enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ePRO	electronic patient-reported outcomes
EQ-5D-5L	European Quality of Life 5-Dimensions 5-Levels
ERB	ethical review board
CCI	[redacted]
CCI	[redacted]
GCP	good clinical practice
HCRU	Health Care Resource Utilization questionnaire
IB	Investigator's Brochure
ICF	informed consent form
ICHD-3	International Classification of Headache Disorders – 3rd edition
IHS	International Headache Society
Informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
ITT	intent to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
LOCF	last observation carried forward
LSMean	Least Squares Mean
MDD	major depressive disorder

Schedule of Activities

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

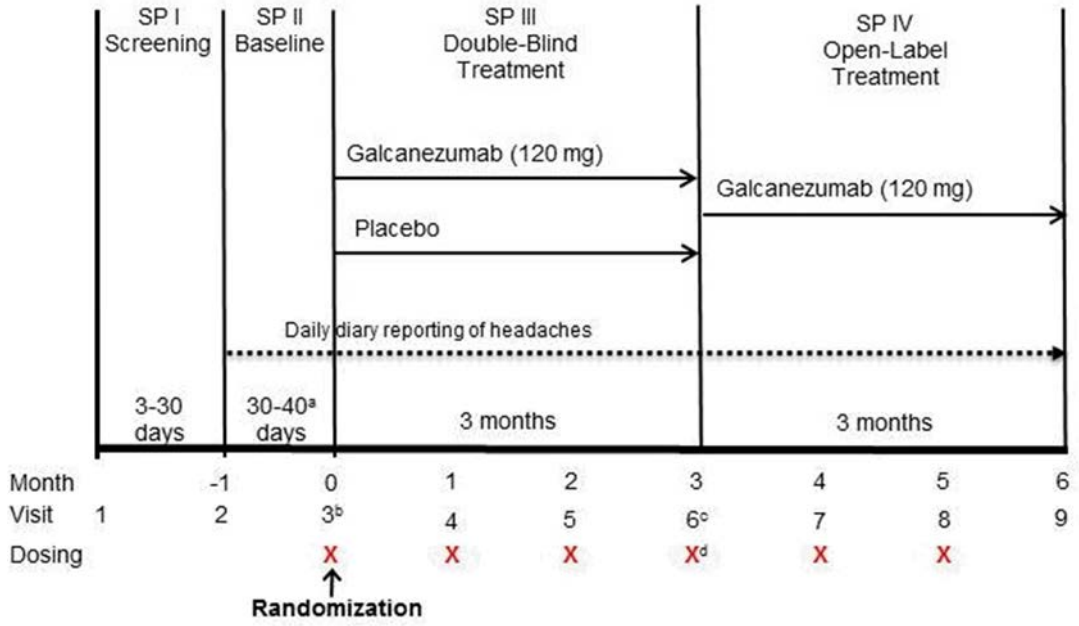
5. Study Design

5.1. Overall Design

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

Study governance considerations are described in detail in Appendix 3.

Figure CGAW.1 illustrates the study design.



Abbreviation: SP = study period.

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

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

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

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

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

Study Period I: The study and potential risks will be explained to the patient at Visit 1. The informed consent form (ICF) must be signed before any study procedures are performed.

- laboratory measurements

Unless specified otherwise, the categorical safety analyses will include both scheduled and unscheduled visits. Comparisons between treatment groups for all categorical safety measures will be made using Fisher's exact test for Study Period III with the safety population. Descriptive statistics only will be presented for the analyses in Study Period IV.

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

10.3.4.1. Treatment-Emergent Adverse Events

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

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

10.3.4.2. Vital Signs

Vital signs collected during the study include systolic and diastolic blood pressure, pulse, and temperature. Blood pressure and pulse measurements will be taken when the patient is in a sitting position.

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

10.3.4.3. Electrocardiogram Intervals and Heart Rate

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

10.3.4.4. Laboratory Tests

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

2. Schedule of Activities

Objectives and Endpoints

Objectives	Endpoints
Other Secondary Objectives (continued)	
• To compare galcanezumab with placebo with respect to changes in disability and quality of life	• Changes from baseline to Month 3 on the following measures: • Migraine Disability Assessment test (MIDAS) total score and individual items • MSQ v2.1 total score, and Role Function-Preventive and Emotional Function domain scores • Health Care Resource Utilization (HCRU) and Employment Status • European Quality of Life Questionnaire 5-Dimensions 5-Levels (EQ-5D-5L) • 4-item Migraine Interictal Burden Scale (MIBS-4) • Work Productivity and Activity Impairment Questionnaire (WPAI)
• To compare galcanezumab with placebo with respect to change in patient global impression of the severity of migraine	• Mean change from baseline in the Patient Global Impression of Severity (PGI-S) at Month 3
• To compare galcanezumab with placebo with respect to changes in migraine attacks (episodic migraine subpopulation only)	• The overall mean change from baseline in the number of monthly migraine attacks during the 3-month double-blind treatment phase in patients with episodic migraine
• To compare galcanezumab with placebo with respect to 30% response rate (chronic migraine subpopulation only)	• The percentage of chronic migraine patients with ≥30% reduction from baseline in monthly migraine headache days during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to safety and tolerability	• Analysis of: o treatment-emergent adverse events (TEAEs) o serious adverse events (SAEs) o discontinuation due to adverse events (AEs) o discontinuation rates o vital signs and weight o electrocardiograms (ECGs) o laboratory measures
• To assess changes in efficacy, safety, and functional outcomes during Study Period IV (open-label treatment)	• In Study Period IV: o Mean changes in all continuous measures of efficacy, safety, and functional outcomes that are also assessed in the double-blind phase o Among patients previously treated with galcanezumab who meet 50% response criteria at Month 3 in the double-blind treatment phase, the proportion of patients who demonstrate 50% response for all 3 months in the open-label treatment phase

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

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

5.2. Number of Participants

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

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

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

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

6. Study Population

All patients must meet the following selection criteria. Eligibility of patients for study enrollment will be based on the results of a screening medical history, physical examination, neurological examination, clinical laboratory tests, electrocardiograms (ECGs), and migraine history during screening and a prospective baseline period, as described in Sections 6.1 and 6.2. The nature of any comorbid conditions present at the time of the physical examination and any pre-existing conditions must be documented. Individuals who do not meet the criteria for participation in this study (screen failure) for specific reasons as outlined may be considered for rescreening once, with approval from Eli Lilly and Company (Lilly) Medical (see Section 6.4).

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

6.1. Inclusion Criteria

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

Patient and Disease Characteristics

[1] Patients are 18 to 75 years of age (inclusive) at the time of screening.

[2] Have a diagnosis of migraine as defined by IHS ICHD-3 guidelines (1.1, 1.2, or 1.3) (ICHD-3 2018), with a history of migraine headaches of at least 1 year prior to Visit 1, and migraine onset prior to age 50.

[3] Prior to Visit 1, have a history of at least 4 migraine headache days and at least 1 headache-free day per month on average within the past 3 months.

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

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

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

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

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

9.2.2. Complaint Handling

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

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

9.3. Treatment of Overdose

Refer to the IB.

9.4. Safety

9.4.1. Electrocardiograms

For each patient, a single 12-lead digital ECG will be collected according to the Schedule of Activities (Section 2). Electrocardiograms should be collected prior to blood draws and dosing. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms will have a central overread and should be recorded according to the study-specific recommendations included in the ECG manual.

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

9.4.2. Vital Signs

Vital signs will include body temperature, blood pressure, and pulse. Blood pressure and pulse will be measured as a single measurement in the sitting position prior to blood draws and dosing, according to the Schedule of Activities (Section 2) and following the study-specific recommendations included in the Manual of Operations for the study.

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

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

9.8. Biomarkers

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

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

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

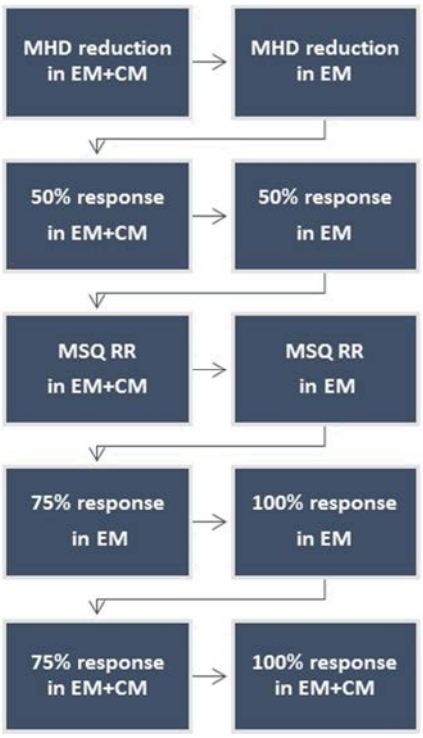
All biomarker samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel. Samples will be destroyed according to a process consistent with local regulations.

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

9.9. Health Economics

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

Migraine-Specific Quality of Life Questionnaire version 2.1: The Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) is a self-administered health status instrument that was developed to address the physical and emotional impact on functioning that is of specific concern to individuals suffering from migraine headaches. The instrument consists of 14 items that address 3 domains: (1) Role Function-Restrictive; (2) Role Function-Preventive; and (3) Emotional Function (Jhingran et al. 1998b). The restrictive domain specifically measures disability as related to the impact on performance of normal activities, with the preventive domain addressing complete functional impairment and the emotional domain assessing the feelings related to disabling monthly migraine headache days. Responses are given using a



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

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

10.3.3.3. Other Secondary and Tertiary Analyses

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

10.3.4. Safety Analyses

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

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

Study sites, patients, and all Lilly personnel directly involved in the continuing trial will remain blinded to patients' double-blind treatment assignment. Unblinding details are specified in the unblinding plan section of the SAP or a separate unblinding plan document.

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

MIBS-4	4-item Migraine Interictal Burden Scale
MIDAS	Migraine Disability Assessment
MMRM	mixed model repeated measures
MSQ (v2.1)	Migraine-Specific Quality of Life Questionnaire version 2.1
PGI-S	Patient Global Impression of Severity
CCI	[redacted]
QTcF	Fridericia's corrected QT interval
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SOC	system organ class
SUSARs	suspected unexpected serious adverse reactions
TBL	total bilirubin
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
VAS	visual analog scale
WPAI	Work Productivity and Activity Impairment Questionnaire

Schedule of Activities

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