Protocol I5Q-MC-CGAY(a)

A Randomized, Placebo-Controlled, Single-Dose Study to Assess the Pharmacokinetics, Safety, and Tolerability of Galcanezumab in Healthy Chinese Subjects

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A Randomized, Placebo-Controlled, Single-Dose Study to Assess the Pharmacokinetics, Safety, and Tolerability of Galcanezumab in Healthy Chinese Subjects

Galcanezumab (LY2951742)

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Clinical Pharmacology Protocol Approved on: 28 Jun 2018

Amendment (a) Electronically Signed and Approved by Lilly on date provided below.

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1. Protocol Synopsis

Title of Study:
A Randomized, Placebo-Controlled, Single-Dose Study to Assess the Pharmacokinetics, Safety, and Tolerability of Galcanezumab in Healthy Chinese Subjects.

Rationale:
Galcanezumab is a humanized monoclonal antibody being developed for migraine prophylaxis. This is a study of galcanezumab in Chinese subjects and the results will be used to support registration for this indication in China.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary To investigate the pharmacokinetics (PK) of galcanezumab following a single subcutaneous (SC) administration of galcanezumab to healthy Chinese subjects.	C_{max} and area under the concentration versus time curve from time zero to infinity (AUC[0-∞]) of galcanezumab.
Secondary To investigate the safety and tolerability of a single SC administration of galcanezumab to healthy Chinese subjects.	Incidence of adverse events (AEs) and serious AEs.

Summary of Study Design:

Study I5Q-MC-CGAY is a single-center, randomized, subject- and investigator-blind, placebo-controlled, parallel-group, single-dose study in healthy Chinese subjects. Healthy males and females, as determined by medical history, physical examination, vital signs, clinical laboratory tests, and electrocardiograms, will be enrolled. Subjects are to be native Chinese, at least 18 years of age, with a body mass index between 18.5 and 35.0 kg/m^2, inclusive, at screening. Females must test negative for pregnancy and females of childbearing potential must agree to use a reliable method of contraception during the study and for 5 months after dosing. Subjects will be excluded if they have allergies to either monoclonal antibodies, diphenhydramine, epinephrine, or methylprednisolone

Treatment Arms and Planned Duration for an Individual Subject:
Each subject will have a screening visit within 28 days prior to dosing. Subjects will be randomized within a cohort to receive galcanezumab or placebo: Subjects in Cohort A will receive a single dose of 120 mg galcanezumab or placebo; Cohort B will receive a single dose of 240 mg galcanezumab or placebo. Dosing of cohorts may be conducted in parallel or sequentially at the discretion of the Investigator.

Subjects will be admitted to the clinical research unit on Day -1 and may be discharged after all assessments have been completed on Day 3. Subjects may remain inpatient up to Day 15 to improve visit compliance, at the discretion of the investigator. A single SC dose of galcanezumab or placebo will be administered according to

randomization on the morning of Day 1. Subjects will return for outpatient visits for up to 5 months after dosing for safety, tolerability, immunogenicity, and PK assessments.

Number of Subjects:
Approximately 30 subjects may be enrolled in this study to adjust for any discontinuations and try to ensure that approximately 20 subjects complete the study (10 per cohort; 8 galcanezumab and 2 placebo). The sample size is customary for Phase 1 studies evaluating safety, tolerability, and PK, and is not powered on the basis of statistical hypothesis testing.

Statistical Analysis:

There will be no formal statistical analyses. The PK, safety, tolerability, and immunogenicity data will be summarized using standard descriptive statistics, as appropriate.

2. Schedule of Activities

Study Schedule Protocol I5Q-MC-CGAY

Week			0					1			2	3	4	6	8	10	12	16	20
Day[a]	SCR[b]	- 1	1	2	3	5	6	8	10	12	15	22	29	43	57	71	85	113	141[c]
Visit Window (days)											±1	±2	±2	±3	±3	±3	±3	±3	±3
CRU admission/visits[d]	X	Inpatient stay				X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization			X																
Study drug injection			X[e]																
Informed Consent	X																		
Eligibility assessment	X																		
Medical history	X																		
Recording of AEs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam[g]	X	X	Predose		X			X			X		X	X	X		X	X	
Body temperature	X																		
Height, weight[h]	X		Predose																X
Vital signs (hours)[i]	X		Predose, 8	24	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Single 12-lead ECG (hours)	X	X		24														X	X (ED only)
Clinical Laboratory tests	X	X	Predose								X				X			X	X (ED only)
Serology: HIV, HBV, HCV	X																		
Urine drug screen, ethanol breath test[j]	X	X																	
Chest x-ray and T-SPOT test	X																		
Pregnancy test[k]	X	X																	X
Galcanezumab PK blood sampling (hours)[l]			8	24	48	96	120	168	216	264	336	504	672	1008	1344	1680	2016	2688	3360
PGx blood sampling			Predose																
Immunogenicity blood sampling[m]			Predose								X		X		X		X		X

Abbreviations: AE = adverse event; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; PK = pharmacokinetics; PGx = pharmacogenetics; SCR = screening; T-SPOT = T-SPOT® tuberculosis test.

a If these procedures cannot be done on the same day, they should be done at closest time possible.

b Screening evaluations to be performed within 28 days prior to dosing.

c Also procedures for early discontinuation.

d Subjects will be admitted to the CRU on Day -1, and may be discharged on Day 3 after the procedures scheduled at 48 hours after dosing have been completed. Subjects may remain inpatient up to Day 15 to improve visit compliance, at the discretion of the investigator. Unless specified, safety monitoring procedures should be done close to the dosing time on Day 1, except for screening and the day before dosing.

e Per randomization scheme. Where possible, subjects to stay in the semi-recumbent position for 4 hours following study drug administration.

f The investigator will record additional details regarding AEs related to injection sites and hypersensitivity events.

g Complete physical examination to be performed at screening and at the final visit for each subject; symptom-directed physical examination only at other visits and as clinically indicated.

h Height to be measured at screening only.

i Vital signs include sitting blood pressure and pulse rate.

j Additional urine drug screen and breath ethanol tests may be performed at the investigator's discretion.

k Females only. Blood pregnancy test will be done on screening; urine test at other times as indicated, or when performed at the investigator's discretion.

l It is preferred that on days without dosing the PK samples should be taken close to the Day 1 dosing time. Nominal PK sampling times are given as targets to be achieved within reasonable limits. Additional samples may be taken (see Section 9.6.1).

m Additional samples may be taken (see Section 9.6.1).

3. Introduction

3.1. Study Rationale

This is a study of galcanezumab in Chinese subjects. The main purpose of this study is to evaluate the pharmacokinetics (PK), safety, and tolerability of galcanezumab in healthy Chinese subjects. The results from this study will be used to support registration for migraine prophylaxis in China.

3.2. Background

Galcanezumab (LY2951742) is a humanized monoclonal antibody that binds to calcitonin gene-related peptide (CGRP), a peptide that is widely expressed in the central and peripheral nervous system and acts as a local facilitator of inflammatory processes. Lilly is currently evaluating galcanezumab for the prophylaxis of migraine and cluster headache.

3.2.1. Clinical Experience with Galcanezumab

Four clinical pharmacology studies with galcanezumab have been completed to date in healthy subjects. The subject population included 446 healthy subjects of whom 419 subjects received at least 1 dose of galcanezumab (dose range 1 to 600 mg).

Two Phase 2 studies and the double-blinded phase of three Phase 3 studies in migraine patients have completed, and demonstrated consistent efficacy in migraine prevention. The treatment phase of a further Phase 3 open-label study in migraine patients has also completed. Additional Phase 3 studies in migraine patients are ongoing, including 2 studies conducted in Japanese patients. In the completed Phase 2 studies, a total of 380 migraine patients received repeated doses of galcanezumab; 150 mg every 2 weeks in 1 study, or 5 to 300 mg every 4 weeks in the other. In the completed Phase 3 studies, safety and efficacy of galcanezumab were tested in migraine patients who received either placebo or galcanezumab at doses of 120 mg monthly, after a 240 mg loading dose, or 240 mg monthly. Safety and efficacy profiles of both doses were comparable.

In September 2018, galcanezumab (Emgality™) was approved in the US for the prevention of migraine in adults. Additionally, galcanezumab was approved in the EU in November 2018, for the prophylaxis of migraine in adults who have at least 4 migraine days per month. The approved dose of galcanezumab is a loading dose of 240 mg followed by monthly doses of 120 mg.

In addition to migraine prevention, safety and efficacy of galcanezumab were also tested in 2 completed Phase 3 studies in patients with episodic and chronic cluster headache at 300 mg monthly dose.

3.2.1.1. Clinical Pharmacokinetic Data

Galcanezumab exhibited PK properties consistent with an immunoglobulin G monoclonal antibody. Based on population PK analysis, the apparent clearance of galcanezumab was approximately 0.008 L/h (34% inter-individual variability), the half-life associated with the terminal elimination phase ($t_{1/2}$) was 27 days and the mean maximum observed drug

concentration (C_{max}) is expected to be achieved by 5 to 7 days after subcutaneous administration. Galcanezumab exposure increases proportionally with dose. Race is not a statistically significant covariate of galcanezumab PK.

3.2.1.2. Clinical Safety Data

Two serious adverse events (SAEs) were reported in subjects who received galcanezumab during the clinical pharmacology program: a death due to drowning, which was not considered by the investigator to be related to investigational product and atrial fibrillation, which was considered to be possibly related to investigational product. Other than the subject who died, no subjects discontinued from any clinical pharmacology study because of an adverse event (AE).

In the clinical pharmacology program, the incidences of common treatment-emergent adverse events (TEAEs), including headache, injection site erythema, injection site pain, and upper respiratory tract infection, were similar to those of subjects who received at least 1 dose of placebo, and frequency did not appear dose dependent. A low frequency (1%) of TEAEs related to cardiovascular safety occurred in subjects who received at least 1 dose of galcanezumab, and none occurred in subjects who received placebo. No consistent blood pressure, heart rate, or electrocardiogram (ECG) findings were observed across treatment groups, including placebo. There were no reports of TEAEs related to suicidal ideation and behavior.

In an integrated analysis of data from all 6 ongoing or completed migraine patient studies, 67.0% of patients in the galcanezumab-pooled dose group reported at least one TEAE. The common TEAEs (reported by ≥1.5% of patients before rounding) in this group included injection site pain, nasopharyngitis, upper respiratory tract infection, and injection site reaction (ISR). A total of 81 patients (3.1%) in the galcanezumab-pooled dose group discontinued due to AEs. Those AEs that led to discontinuation in >2 patients in this group were: ISR, migraine, urticaria, injection site erythema, and rash. Serious hypersensitivity cases of urticaria have been reported in migraine patients receiving galcanezumab; non-serious adverse drug reactions included ISR, vertigo, constipation, and pruritus.

Nine of 160 subjects developed treatment-emergent antidrug antibody after a single dose of 240 mg galcanezumab solution in a clinical pharmacology study. Overall, the presence of antidrug antibodies (ADAs) did not affect the PK, efficacy, or safety of galcanezumab. Aggregate findings from healthy subjects and patients who developed treatment-emergent ADA did not reveal a relationship between injection site reactions or hypersensitivity reactions and immunogenicity

More information about the known and expected benefits, risks and reasonably anticipated AEs may be found in the Investigator's Brochure (IB). Information on AEs expected to be related to the investigational product may be found in Section 7 (Development Core Safety Information) of the IB.

3.3. Benefit/Risk Assessment

This study will evaluate single doses of 120 and 240 mg galcanezumab. The justification of these doses can be found in Section 5.5. No clinically significant safety or tolerability concerns

have been identified in subjects to date for galcanezumab up to the highest single dose given (600 mg). In this study, there is no anticipated therapeutic benefit for the subjects. Potential risks include but are not limited to hypersensitivity reactions. The risk profile of galcanezumab remains supportive of further clinical development.

More information about the known and expected benefits, risks, SAEs and reasonably anticipated AEs of galcanezumab are to be found in the IB.

4. Objectives and Endpoints

Table CGAY.1 shows the objectives and endpoints of the study.

Table CGAY.1. Objectives and Endpoints

Objectives	Endpoints
Primary To investigate the PK of galcanezumab following a single SC administration of galcanezumab to healthy Chinese subjects.	C_{max} and area under the concentration versus time curve from time zero to infinity (AUC[0-∞]) of galcanezumab.
Secondary To investigate the safety and tolerability of a single SC administration of galcanezumab to healthy Chinese subjects.	Incidence of AEs and SAEs.
Exploratory To evaluate galcanezumab with respect to immunogenicity in healthy Chinese subjects.	Development of ADAs to galcanezumab.

5. Study Design

5.1. Overall Design

This is a Phase 1, single-center, randomized, subject- and investigator-blind, placebo-controlled, parallel-group, single-dose study in healthy Chinese subjects. Subjects will be assigned to 1 of 2 cohorts and randomized to receive galcanezumab or placebo (4:1 ratio), as described in Section 7.2. Subjects will receive the following treatments:

- Cohort A: a single dose of 120 mg galcanezumab or placebo
- Cohort B: a single dose of 240 mg galcanezumab or placebo

Dosing of cohorts may be conducted in parallel or sequentially at the discretion of the Investigator.

Subjects will be admitted to the clinical research unit (CRU) on Day -1 and may be discharged after all assessments have been completed on Day 3. Subjects may remain inpatient up to Day 15 to improve visit compliance, at the discretion of the investigator. A single SC dose of galcanezumab or placebo will be administered according to randomization on the morning of Day 1. Subjects will return for outpatient visits for up to 5 months after dosing for safety, tolerability, immunogenicity, and PK assessments.

Safety and tolerability will be assessed throughout the study by means of vital sign measurements, clinical laboratory tests, ECG, physical examinations (as indicated), and AE recording.

Study governance considerations are described in detail in Appendix 3.

5.2. Number of Participants

Approximately 30 subjects may be enrolled to ensure that approximately 20 subjects complete the study. Up to 15 subjects will be enrolled in each of 2 cohorts and randomized to receive either galcanezumab or placebo (4:1 ratio), to ensure that approximately 8 subjects receiving galcanezumab and 2 subjects receiving placebo complete each cohort. For purposes of this study, a subject will be considered to have completed the study when they complete the follow-up procedures at approximately 20 weeks, as shown in the Schedule of Activities (Section 2).

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 subject.

5.4. Scientific Rationale for Study Design

The subject- and investigator-blinded, randomized, placebo-controlled design minimizes bias on safety and tolerability assessments, and allows a more robust comparison among galcanezumab and placebo doses.

The selection of healthy subjects is appropriate and in keeping with standard regional practices for clinical pharmacology studies. The inclusion and exclusion criteria are chosen to select subjects who are known to be free from any significant illness and from any condition that could affect their safety or interfere with meeting the study objectives.

The approximately 20-week PK sampling is based on clinical PK data for galcanezumab following administration of single doses of up to 600-mg to healthy subjects ($t_{1/2}$ was 27 days). Based upon the available clinical PK data for galcanezumab, the duration of this study is adequate to achieve the study objectives.

5.5. Justification for Dose

Galcanezumab 120 mg and 240 mg were selected for this study because these doses were evaluated in the Phase 3 China registration trials for the treatment of migraine prophylaxis.

6. Study Population

Eligibility of subjects for the study will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests and ECG.

The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

Screening may occur up to 28 days prior to dosing. Subjects who are not dosed within 28 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

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

6.1. Inclusion Criteria

Subjects are eligible for inclusion in the study only if they meet all of the following criteria at screening and/or admission:

[1] are native Chinese (all 4 biological grandparents and both biological parents to be of Chinese origin)

[2] are overtly healthy males or females, as determined by medical history and physical examination

[2a] female subjects:

All females must test negative for pregnancy at the time of enrollment based on a serum pregnancy test and females of childbearing potential must agree to use a reliable method of birth control during the study as well as for 5 months after dosing. Acceptable methods of birth control for this study include oral contraceptives, implantable contraceptives, injectable contraceptives, a contraceptive patch, barrier methods (such as diaphragms with contraceptive jelly, cervical caps with contraceptive jelly, condoms with contraceptive foam, or intrauterine devices), or a partner with vasectomy. Birth control is not required if the female is infertile due to surgical sterilization (hysterectomy, or at least 6 weeks after surgical bilateral oophorectomy or tubal ligation) confirmed by medical history or menopause. Menopause is defined as spontaneous amenorrhea for at least 12 months not induced by a medical condition, or spontaneous amenorrhea of 6-12 months and a follicle-stimulating hormone level >40 mIU/mL.

[3] are at least 18 years old, at the time of screening

[4] have a body mass index (BMI) between 18.5 and 35.0 kg/m^2, inclusive, at screening

[5] have clinical laboratory test results within normal reference range for the population or investigative site, or results with acceptable deviations that are judged to be not clinically significant by the investigator

[6] have venous access sufficient to allow for blood sampling as per the protocol

[7] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures

[8] are able and willing to sign the informed consent form (ICF)

6.2. Exclusion Criteria

Subjects will be excluded from study enrollment if they meet any of the following criteria at screening and/or enrollment:

[9] are investigative site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling

[10] are Lilly employees or are employees of third-party organizations involved with the study

[11] are currently enrolled in a clinical study 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, in a clinical study involving an investigational product. If the previous investigational product has a long half-life, 5 half-lives or 30 days (whichever is longer) should have passed

[13] have previously completed or withdrawn from this study or any other study investigating galcanezumab, and have previously received the investigational product

[14] have known allergies to galcanezumab, related compounds or any components of the formulation, or history of significant atopy

[15] have received treatment with any CGRP antibody (including galcanezumab), or antibody against CGRP receptor (including erenumab), or have received biologic agents (such as monoclonal antibodies) within 4 months or 5 half-lives (whichever is longer) prior to dosing

[16] have a history of multiple or severe allergies or has had an anaphylactic reaction to prescription or non-prescription drugs or food

[17] have allergies to either monoclonal antibodies, diphenhydramine, epinephrine, or methylprednisolone

[18] have an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study

[19] have clinically significant abnormality in vital signs as determined by the investigator

[20] have a history or presence of significant cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the study medication; or of interfering with the interpretation of data

[21] have a history of previous or presence of current neuropsychiatric disorders

[22] regularly use known drugs of abuse and/or show positive findings on drug screening

[23] show evidence of human immunodeficiency virus (HIV) infection and/or positive human HIV antibodies

[24] show evidence of hepatitis C and/or positive hepatitis C antibody

[25] show evidence of hepatitis B and/or positive hepatitis B surface antigen

[26] have a history or show evidence of active tuberculosis (TB) as documented by medical history and examination, chest x-rays (posterior anterior and lateral), and TB testing (positive [not indeterminate] T-SPOT® TB test). One repeat of the T-SPOT® TB test is permitted following an indeterminate result. For more details, see Section 9.5.7.

[27] are women who are lactating

[28] have used or intend to use over-the-counter or prescription medication within 7 days prior to dosing and during the study without agreement by sponsor (including traditional Chinese medicine, herbal supplements, systemic glucocorticoids, immunomodulatory drugs, drugs with propensity for dermal reactions, drugs with known liver toxicity, etc). Stable doses of hormone replacement therapy (HRT; including estrogen, estrogen/progesterone combination, and thyroid replacement therapy) are allowed for inclusion. Occasional paracetamol/acetaminophen up to a 2-g dose in a 24-hour period, stool softener, or nasal saline preparations may be allowed for inclusion at the discretion of the investigator.

[29] have donated blood of more than 400 mL or has undergone major surgery within the 4 weeks prior to admission

[30] are unwilling to abide by caffeine restrictions as specified in Section 6.3.2

[31] have an average weekly alcohol intake that exceeds 21 units per week (males up to age 65) and 14 units per week (males over 65 and females), or are unwilling to stop alcohol consumption 48 hours prior to admission to CRU and during residence in the CRU (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits)

[32] have had lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years

[33] currently smoke in excess of 5 cigarettes/day or use tobacco or nicotine substitutes (within the last 6 months of screening), or subjects unwilling to refrain from smoking or are unable to abide by CRU restrictions

[34] in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study

6.2.1. Rationale for Exclusion of Certain Study Candidates

Criteria [9] and [10] prevent conflict of interest in study participants. Criteria [11] through [34] exclude medical conditions, medication intolerance, and concomitant medication use that may confound the assessment of study endpoints or interfere with study implementation by the CRU (Criteria [30], [33]) or that may both constitute a risk for the subject and confound assessment of study endpoints: (Criteria [11]-[29], [31]-[32], [34]).

6.3. Lifestyle and/or Dietary Requirements

Throughout the study, subjects may undergo medical assessments and review of compliance with requirements before continuing in the study.

6.3.1. Meals and Dietary Restrictions

Standardized meals will be provided during each subject's stay in the CRU.

6.3.2. Caffeine, Alcohol, and Tobacco

Subjects should maintain to their regular habit of caffeine- or xanthine-containing food and drinks during the outpatient days. Two servings of xanthine-containing food and drinks per day will be allowed while subjects are resident at the CRU.

Alcohol will not be permitted from 48 hours prior to admission until discharge from the CRU.

While resident in the CRU, subject should abide by the CRU guidelines for smoking. Subjects will be questioned about their smoking habits at screening.

6.3.3. Activity

Subjects should avoid strenuous physical activity 48 hours prior to CRU admission until at least 30 days after dosing.

6.3.4. Contraception

Females of childbearing potential must agree to use a reliable method of birth control during the study and for 5 months after dosing (see Section 6.1). Birth control is not required if the female is infertile due to surgical sterilization (hysterectomy, or at least 6 weeks after surgical bilateral oophorectomy or tubal ligation) confirmed by medical history or menopause.

6.3.5. Blood or Plasma Donations

Blood or plasma donations must not be made during the study, until 150 days after dosing.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be re-screened.

Any subject with a routine screening laboratory assessment that falls outside of the specified parameters may undergo repeat laboratory testing 1 time, based on investigator judgment, without being considered a screen failure. If the laboratory assessment again falls outside of the specified parameters on the re-test, then the subject is to be considered a screen failure.

7. Treatment

7.1. Treatment Administered

Investigational product doses and formulations are summarized in Table CGAY.2.

Table CGAY.2. Treatments Administered

	Cohort A		Cohort B	
Product:	**Galcanezumab**	**Placebo**	**Galcanezumab**	**Placebo**
Total dose:	120 mg	-	240 mg	-
Concentration:	120 mg/mL	-	120 mg/mL	-
No. of injections	1 x 1 mL	1 x 1 mL	2 x 1 mL	2 x 1 mL
Route of administration	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous
Formulation and presentation:	Solution in a prefilled syringe	Placebo solution in a prefilled syringe	Solution in a prefilled syringe	Placebo solution in a prefilled syringe

Injections will be administered by the clinical staff in the abdomen. The subjects and clinical site staff will be blinded to the treatment; the sponsor will be unblinded. The dose volumes and number of injections for subjects in each cohort are presented in Table CGAY.2.

Galcanezumab or placebo will be administered as SC injections into the abdomen. The location of the injection(s) will be recorded. Multiple injections making up a single dose (i.e. for Cohort B) should be apart from each other, so ISRs, if any, can be observed separately. Subjects may stay in the semi-recumbent position for 4 hours following study drug administration, where possible.

The investigator or designee is responsible for:

- explaining the correct use of the investigational product(s) to the site personnel
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection
- and returning all unused medication to Lilly or its designee at the end of the study

Note: In some cases, sites may destroy the material if, during the investigative site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical materials.

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. The syringes (and contents) containing either galcanezumab or placebo will be visibly indistinguishable from each other. Syringes will be supplied in single syringe cartons, with the appropriate quantity of syringes dispensed specific to the planned dispensing schedule of the investigational product.

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

7.2. Method of Treatment Assignment

Subjects who meet the study entry criteria will be randomized to receive either galcanezumab or placebo in a 4:1 ratio via a computer-generated random sequence using an interactive web-response system (IWRS).

7.2.1. Selection and Timing of Doses

Doses will be administered according to randomization on the morning of Day 1. The actual time of all dose administrations will be recorded in the subject's electronic case report form (eCRF).

7.3. Blinding

Blinding will be maintained throughout the conduct of the study as described in the separate Blinding Plan.

This will be a subject- and investigator-blinded study. The subjects and clinical staff will be blinded to which treatment (galcanezumab or placebo) the subjects are assigned to. The sponsor will be unblinded.

Emergency unblinding for AEs may be performed through the IWRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used ONLY if the subject's well-being requires knowledge of the subject's treatment assignment. All calls resulting in an unblinding event are recorded and reported by the IWRS.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted for medical management of the event. The subject's safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

7.4. Dose Modification

Dose adjustments are not permitted in this study.

7.5. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained, as communicated by the sponsor, during transit for all investigational product received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive investigational product or study materials, and only authorized site staff may supply or administer investigational product. All investigational product should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

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

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

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation and final disposition records).

7.6. Treatment Compliance

The investigational product will be administered at the clinical site, and documentation of treatment administration will occur at the site.

7.7. Concomitant Therapy

Stable doses of HRT, including estrogen, estrogen/progesterone combination, and thyroid replacement therapy, will be allowed during the study. Unless agreed by the sponsor, over-the-counter medications or other prescription medications are to be avoided within 7 days prior to dosing and during the study (especially traditional Chinese medicine, herbal supplements, systemic glucocorticoids, immunomodulatory drugs, drugs with propensity for dermal reactions, drugs with known liver toxicity, etc).

If the need for concomitant medication arises, inclusion or continuation of the subject may be at the discretion of the investigator after consultation with a Lilly Clinical Pharmacologist (CP) or Clinical Research Physician (CRP). Occasional paracetamol/acetaminophen, up to a 2-g dose in a 24-hour period, stool softener, or nasal saline preparations may be used at the discretion of the investigator. Any additional medication used during the course of the study must be documented.

7.8. Treatment after the End of the Study

This section is not applicable for this study.

8. Discontinuation Criteria

Subjects discontinuing from the study prematurely for any reason must complete AE and follow-up procedures per Section 2 of this protocol.

8.1. Discontinuation from Study Treatment

Not applicable for this single-dose study.

8.1.1. Discontinuation of Inadvertently Enrolled Subjects

If the sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly CP/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 Lilly CP/CRP to allow the inadvertently enrolled patient to continue in the study.

8.2. Discontinuation from the Study

Subjects will be discontinued in the following circumstances:

- Enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- Investigator Decision
    - the investigator decides that the subject should be discontinued from the study
- Subject Decision
    - the subject, or legal representative, requests to be withdrawn from the study.

8.3. Subjects Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact subjects who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, detailing the study procedures and their timing (including tolerance limits for timing).

Appendix 2 lists the clinical laboratory tests that will be performed for this study.

Appendix 4 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

Unless otherwise stated in 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

This section is not applicable for this study.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of subjects 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 subject.

The investigator is responsible for the appropriate medical care of subjects 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 subject to discontinue the investigational product before completing the study. The subject 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.

After the ICF is signed, study site personnel will record, via eCRF, the occurrence and nature of each subject's preexisting conditions. Additionally, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

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 concomitant treatment or pathologies.

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

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

9.2.1. Serious Adverse Events

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

- 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
- 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
- when a condition related to the PFS 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.

Study site personnel must alert the Lilly CRP/CP, or its designee, of any SAE as soon as practically possible.

Additionally, study site personnel must alert Lilly Global Patient Safety, 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.

Although all AEs are recorded in the eCRF after signing informed consent, SAE reporting to the sponsor begins after the subject has signed informed consent and has received investigational product. However, if an SAE occurs after signing informed consent, but prior to receiving investigational product, AND is considered reasonably possibly related to a study procedure then it MUST be reported.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued from and/or completed the study (the subject 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.

Pregnancy (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.

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 reports as related to investigational product or procedure. 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.

9.2.2. Complaint Handling

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

Subjects should be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

9.3. Treatment of Overdose

For the purposes of this study, an overdose of galcanezumab is considered any dose higher than the dose assigned through randomization. There is no specific antidote for galcanezumab. In case of known or suspected overdose, it is recommended that the subject be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

9.4. Pharmacokinetics

At the visits and times specified in the Schedule of Activities, venous blood samples of approximately 2 mL (maximum 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. The actual date and time (24-hour clock time) of each sampling will be recorded.

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

9.4.1. Bioanalysis

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

Concentrations of galcanezumab will be assayed using a validated method. Analyses of samples collected from placebo-treated subjects are not planned.

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

9.5. Safety

9.5.1. Laboratory Tests

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

All safety laboratory tests will be conducted at a local laboratory.

9.5.2. Vital Signs

For each subject, vital signs measurements should be conducted according to the Schedule of Activities (Section 2) and as clinically indicated.

Blood pressure and pulse rate should be measured after at least 5 minutes in the sitting position.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. If orthostatic measurements are required, subjects should be supine for at least 5 minutes and stand for at least 2 minutes.

9.5.3. Electrocardiograms

For each subject, a single 12-lead digital ECG will be collected according to the Schedule of Activities (Section 2). Any clinically significant findings from ECGs that result in a diagnosis and that occur after the subject receives the first dose of the investigational product, should be reported to Lilly, or its designee, as an AE via eCRF.

Electrocardiograms must be recorded before collecting any blood for safety or PK tests. Subjects must be supine for at least 5 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the subject is still present, to determine whether the subject meets entry criteria at the relevant visit(s) and for immediate subject management, should any clinically relevant findings be identified.

If a clinically significant finding is identified after enrollment, the investigator will determine if the subject can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in subject management is needed, and must document his/her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an AE.

9.5.4. Injection Site Assessments

The investigator will record additional details regarding AEs related to injection sites and hypersensitivity events. If an ISR occurs, it will be closely monitored until resolution. Investigational site staff will be provided with separate instructions/training in how to consistently evaluate ISRs and their severity.

9.5.5. Physical Examination

Physical examinations and routine medical assessments will be conducted as specified in the Schedule of Activities (Section 2) and as clinically indicated.

9.5.6. Body Weight

Body weight will be recorded as specified in the Schedule of Activities (Section 2) and as clinically indicated.

9.5.7. Tuberculosis Testing

Subjects will be tested as indicated in the Schedule of Activities (Section 2) for evidence of active TB, which includes a T-SPOT® TB test. If the first test result is indeterminate, 1 repeat is allowed. If the repeat result is indeterminate, the subject will be excluded from the study.

Subjects who have had household contact with a person with active TB must be excluded unless appropriate and documented prophylaxis treatment for TB has been completed. Subjects with any history of active TB are excluded from the study, regardless of previous or current TB treatments.

9.5.8. Safety Monitoring

The Lilly CP or CRP/scientist will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CP or CRP will review the following data:

- trends in safety data
- laboratory analytes
- AEs including monitoring of ISRs and allergic reactions.

When appropriate, the Lilly CP or CRP will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, additional analyses of the safety data will be conducted by the personnel included in the Blinding Plan.

9.6. Pharmacodynamics

9.6.1. Immunogenicity Assessments

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 10 mL each will be collected to determine antibody production against galcanezumab. Treatment-emergent antidrug antibodies (TE-ADAs) are defined in Section 10.3.3. In the event of drug hypersensitivity reactions (immediate or non-immediate), additional samples will be collected as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. If additional immunogenicity testing samples are taken at an unscheduled visit due to a hypersensitivity reaction then a corresponding PK sample will also be taken at that time. Instructions for the collection and handling of blood samples will be

provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of galcanezumab at a laboratory approved by the sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of galcanezumab using a validated assay.

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and Ethical Review Boards (ERBs) allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to the investigational product. Any samples remaining after 15 years will be destroyed.

9.7. Genetics

A blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities, where local regulations 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 exposure or response to galcanezumab and to investigate genetic variants thought to play a role in migraine and/or cluster headache. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the subject number. These samples and any data generated can be linked back to the subject only by the investigative site personnel.

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and/or ERBs impose shorter time limits, for the study at a facility selected by Lilly or its designee. 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 the development of galcanezumab or after galcanezumab is commercially available.

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

9.8. Biomarkers

This section is not applicable for this study.

9.9. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Approximately 30 subjects may be enrolled in this study to adjust for any discontinuations and try to ensure that approximately 20 subjects complete the study (10 per cohort; 8 galcanezumab and 2 placebo). The sample size is customary for Phase 1 studies evaluating safety and PK, and is not powered on the basis of statistical hypothesis testing.

Subjects who receive treatment may not be replaced.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

A detailed description of subject disposition will be provided at the end of the study.

10.2.2. Study Participant Characteristics

The subject's age, sex, weight, height, BMI, race/sub-race, tobacco/nicotine habits, or other demographic characteristics will be recorded and may be used in the PK, safety, and immunogenicity analyses as quantitative or classification variables

10.3. Statistical Analyses

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or its designee.

Pharmacokinetic and immunogenicity analyses will be conducted on the full analysis set. This set includes all data from all randomized subjects receiving at least 1 dose of the investigational product according to the treatment the subjects actually received.

Safety analyses will be conducted for all enrolled subjects, whether or not they completed all protocol requirements.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for population PK analysis purposes.

10.3.1. Pharmacokinetic Analyses

10.3.1.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameters for galcanezumab will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be C_{max} and AUC(0-∞) of galcanezumab. Other noncompartmental parameters, such as area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration (AUC[0-t_{last}]), time of maximum observed drug concentration (t_{max}), $t_{1/2}$, apparent clearance, and apparent volume of distribution may be reported.

10.3.1.2. Pharmacokinetic Statistical Inference

The PK parameter estimates for galcanezumab will be summarized using appropriate descriptive statistics.

10.3.2. Safety Analyses

10.3.2.1. Clinical Evaluation of Safety

All investigational product and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of symptoms for each treatment will be presented by severity and by association with investigational product as perceived by the investigator. Symptoms reported to occur prior to enrollment will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the medical regulatory dictionary.

The number of investigational product-related SAEs will be reported.

10.3.2.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety lab parameters and vital signs. The parameters will be listed, and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

10.3.3. Evaluation of Immunogenicity

The frequency and percentage of subjects with preexisting ADA and with TE-ADA+ 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 TE-ADA+ subjects the distribution of maximum titers will be described. The frequency of neutralizing antibodies will also be tabulated in TE-ADA+ subjects.

The relationship of ADA to PK parameters and safety endpoints may be assessed.

10.3.4. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the Lilly CP, CRP/investigator, or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

11. References

None cited.

Appendix 1. Abbreviations and Definitions

Term	Definition
TE-ADA	Treatment-emergent antidrug antibody
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 AE 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.
AUC	area under the concentration versus time curve
AUC(0-∞)	area under the concentration versus time curve from time zero to infinity
AUC(0-t_{last})	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
blinding	A procedure in which one or more parties to the study are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the subject is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the subject are not. A double-blind study is one in which neither the 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
CGRP	calcitonin gene-related peptide
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum observed drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CP	clinical pharmacologist
CRP	clinical research physician: 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.

CRU	clinical research unit
ECG	electrocardiogram(s)
eCRF	electronic case report form
ED	early discontinuation
enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the study are those who have been assigned to a treatment.
enter	Subjects entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	Ethical Review Board
FSH	follicle-stimulating hormone
GCP	good clinical practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
informed consent	A process by which a subject 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 subject'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 (IP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, 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.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
ISR	injection site reaction

IWRS	interactive web-response system
Legal Representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.
Non-investigational product (non-IP)	A product that is not being tested or used as a reference in the clinical study, but is provided to subjects and used in accordance with the protocol, such as: concomitant or rescue/escape medication for preventative, diagnostic, or therapeutic reasons, medication to ensure adequate medical care, and/or products used to induce a physiological response.
PD	pharmacodynamic(s)
PFS	pre-filled syringe
PGx	pharmacogenetics
PK	pharmacokinetic(s)
randomize	the process of assigning subjects to an experimental group on a random basis
RBC	red blood cells
SAE	serious adverse event
SC	subcutaneous
SCR/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.
SUSARs	suspected unexpected serious adverse reactions
$t_{1/2}$	half-life associated with the terminal elimination phase
TB	tuberculosis
TE-ADA	Treatment-emergent antidrug antibody
TEAE	treatment-emergent adverse event: Any 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
t_{max}	time of maximum observed drug concentration
WBC	white blood cells

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests

Hematology[a]
- Hematocrit
- Hemoglobin
- Erythrocyte count (RBC)
- Mean cell volume
- Mean cell hemoglobin
- Mean cell hemoglobin concentration
- Leukocytes (WBC)
- Platelets
- Absolute counts of:
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils
- Cell morphology

Urinalysis[a]
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Bilirubin
- Urobilinogen
- Blood
- Nitrite
- Microscopic examination of sediment[b]

Clinical Chemistry[a]
- Sodium
- Potassium
- Glucose, random
- Blood urea nitrogen (BUN)
- Total protein
- Albumin
- Total bilirubin
- Alkaline phosphatase (ALP)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Creatinine

Serology[c]
- Hepatitis B surface antigen
- Hepatitis C antibody
- HIV

Ethanol testing[d]

Urine drug screen[d]

Pregnancy test[e]

FSH (females only; to confirm postmenopausal status)[c]

T-SPOT® TB test[c]

Abbreviations: FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; RBC = red blood cells; TB = tuberculosis; WBC = white blood cells.

[a] All safety laboratory tests will be conducted by the local laboratory.

[b] Test only if dipstick result is abnormal.

[c] Performed at screening only.

[d] Urine drug screen and ethanol breath testing may be repeated prior to admission to the clinical research unit and as indicated.

[e] Females only. Blood pregnancy test will be done on screening, and may be repeated using urine test prior to admission to the clinical research unit and as indicated.

Appendix 3. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the subject understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each subject 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 subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject's willingness to continue his or her participation in the study.
- providing a copy of the ICF to the participant or the participant's legal representative and retaining a copy on file.

Recruitment

Lilly or its designee is responsible for the central recruitment strategy for patients. Individual investigators may have additional local requirements or processes. Study-specific recruitment material should be approved by Lilly.

Ethical Review

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

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on 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

Regulatory Considerations

This study will be conducted in accordance with the protocol and with:

1) 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
2) applicable ICH GCP Guidelines
3) applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third-party organization.

Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Final Report Signature

The investigator or designee will sign the clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

The sponsor's responsible medical officer and statistician will sign/approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

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.
- provide training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the electronic case report form (eCRF), 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/or 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 subject data recorded against source documents at the study site. The study may be audited by Lilly 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 the original source documents.

Data Collection Tools/Source Data

An electronic data capture system will be used in this study. The site must define and retain all source records and must maintain a record of any data where source data are directly entered into the data capture system.

Data Protection

Data systems used for the study will have controls and requirements in accordance with local data protection law.

The purpose and use of subject personal information collected will be provided in a written document to the subject by the sponsor.

Study and Site Closure

Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Discontinuation of the Study

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 4. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study. Fewer venipunctures and blood draws may actually occur, but this will not require a protocol amendment.

Protocol I5Q-MC-CGAY Sampling Summary

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	28	1	28
Clinical laboratory tests[a]	8	6	48
Galcanezumab Pharmacokinetics[b]	2.5	17	42.5
Immunogenicity[b]	10	6	60
Pharmacogenetics	10	1	10
Total			188.5
Total for clinical purposes [rounded up to nearest 10 mL]			190

[a] Additional samples may be drawn if needed for safety purposes.

[b] Additional samples may be drawn in the event of hypersensitivity reactions.

Appendix 5. Protocol Amendment I5Q-MC-CGAY(a) Summary A Randomized, Placebo-Controlled, Single-Dose Study to Assess the Pharmacokinetics, Safety, and Tolerability of Galcanezumab in Healthy Chinese Subjects

Overview

Protocol I5Q-MC-CGAY [A Randomized, Placebo-Controlled, Single-Dose Study to Assess the Pharmacokinetics, Safety, and Tolerability of Galcanezumab in Healthy Chinese Subjects] 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:

Table CGAY.3. Amendment Summary for Protocol I5Q-MC-CGAY Amendment(a)

Section # and Name	Description of Change	Brief Rationale
3.2.1. Clinical Experience with Galcanezumab	The dose ranges of Phase 2 and 3 studies have been added to the clinical background. Information about galcanezumab marketed approval also added.	The additional background has been added to provide a summary of all galcanezumab dose ranges used to date in clinical studies as well as detailing the approved dose.
2. Schedule of Activities 5.1 Overall Design	Wording has been added to allow visits within Day -1 to Day 15 to be inpatient if necessary.	Inpatient visits aim to improve subject visit compliance for those subjects who reside far from the clinical site.
2. Schedule of Activities 6.2. Exclusion Criteria 9.5.7. Tuberculosis Testing Appendix 2. Clinical Laboratory Tests	Exclusion criterion 26 has been expanded to exclude subjects with a history of tuberculosis (TB) and outline a mandatory T-SPOT® TB test and chest x-ray examination. Section 9.5.7 created to supplement exclusion criterion 26 and provide more detail regarding exclusion of subjects with exposure to TB. TB test and chest x-ray have been added to the Schedule of Activities at screening and the TB test has been added to the Clinical Laboratory Tests table.	To provide solid evidence supporting an absence of active tuberculosis in subjects.

Section # and Name	Description of Change	Brief Rationale
7.1. Treatment Administered	Reference to the clinical pharmacist being unblinded has been removed. Requirement to dose in a sitting position during dosing has been removed and flexibility has been added for subject positioning postdose. Detail regarding preparation and storage of investigational product removed.	To clarify that only the sponsor will be unblinded. Positioning during and after galcanezumab dosing updated to reflect protocols in the same program. Investigational product detail moved to a more relevant section of the protocol (Section 7.5).
7.2. Method of Treatment Assignment	Clarification added regarding subject randomization via a computer-generated random sequence using an interactive web-response system (IWRS).	Change reflects randomization method used by the study site.
7.3 Blinding	Reference to the clinical pharmacist being unblinded has been removed. The method of unblinding has been changed from emergency codes to being performed through the IWRS.	To clarify that only the sponsor will be unblinded. Change reflects the unblinding procedure when using an IWRS.
7.5. Preparation/Handling/Storage/ Accountability	Detail regarding investigational product storage and preparation instructions has been added.	To ensure investigational product details are in the relevant section of the protocol.
9.5.1. Laboratory Tests Appendix 2. Clinical Laboratory Tests	The location of safety test analysis has been updated to the local laboratory at all time points rather than a central vendor.	Change allows subject safety data to be reviewed within a timely manner at the clinical site.
10.3.2.2. Statistical Evaluation of Safety	Removed ECG parameters from list of safety parameters that will be assessed.	ECGs will not be databased therefore do not require statistical evaluation.
Appendix 4. Blood Sampling Summary	Maximum blood volumes per sample for screening tests and clinical laboratory tests have been updated.	Change reflects blood volume requirements for safety testing at the local laboratory.

The synopsis and abbreviations list have been updated accordingly with the outlined changes above and are not detailed on the following pages.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

2. Schedule of Activities

- A row was added to the schedule for 'Chest x-ray and T-SPOT test' to be performed at screening only.
- The abbreviation 'T-SPOT = T-SPOT® tuberculosis test' was added to the abbreviation footnote.
- Footnote 'd' was updated as follows:

  [d] Subjects will be admitted to the CRU on Day -1, and ~~will~~ may be discharged on Day 3 after the procedures scheduled at 48 hours after dosing have been completed. Subjects may remain inpatient up to Day 15 to improve visit compliance, at the discretion of the investigator. Unless specified, safety monitoring procedures should be done close to the dosing time on Day 1, except for screening and the day before dosing.

3.2.1. Clinical Experience with Galcanezumab

Four clinical pharmacology studies with galcanezumab have been completed to date in healthy subjects. The subject population included 446 healthy subjects of whom 419 subjects received at least 1 dose of galcanezumab (dose range 1 to 600 mg). Two Phase 2 studies and the double-blinded phase of three Phase 3 studies in migraine patients have completed, and demonstrated consistent efficacy in migraine prevention. The treatment phase of a further Phase 3 open-label study in migraine patients has also completed. Additional Phase 3 studies in migraine patients are ongoing, including 2 studies conducted in Japanese patients. In the completed Phase 2 studies, a total of 380 migraine patients received repeated doses of galcanezumab; 150 mg every 2 weeks in 1 study, or 5 to 300 mg every 4 weeks in the other. In the completed Phase 3 studies, safety and efficacy of galcanezumab were tested in migraine patients who received either placebo or galcanezumab at doses of 120 mg monthly, after a 240 mg loading dose, or 240 mg monthly. Safety and efficacy profiles of both doses were comparable.

In September 2018, galcanezumab (Emgality™) was approved in the US for the prevention of migraine in adults. Additionally, galcanezumab was approved in the EU in November 2018, for the prophylaxis of migraine in adults who have at least 4 migraine days per month. The approved dose of galcanezumab is a loading dose of 240 mg followed by monthly doses of 120 mg.

In addition to migraine prevention, safety and efficacy of galcanezumab were also tested in 2 completed Phase 3 studies in patients with episodic and chronic cluster headache at 300 mg monthly dose.

5. Study Design

Subjects will be admitted to the clinical research unit (CRU) on Day -1 and ~~will~~ may be discharged after all assessments have been completed on Day 3. Subjects may remain inpatient up to Day 15 to improve visit compliance, at the discretion of the investigator.

6.2. Exclusion Criteria

[26] have a history or show evidence of active tuberculosis (TB) as documented by ~~based on~~ medical history and examination, chest x-rays (posterior anterior and lateral), and TB testing (positive [not indeterminate] T-SPOT® TB test). One repeat of the T-SPOT® TB test is permitted following an indeterminate result. For more details, see Section 9.5.7.

7.1. Treatments Administered

Investigational product doses and formulations are summarized in Table CGAY.2. ~~Further details for the preparation of all investigational products will be provided in the pharmacy manual.~~

…

~~The prefilled syringe (PFS) of galcanezumab or placebo (excipients only) for injection should be stored in the refrigerator (2 to 8°C). The PFS should be removed from the refrigerated storage and allowed to equilibrate to room temperature for approximately 30 minutes before administration.~~

Injections will be administered by the clinical staff in the abdomen. The subjects and clinical site staff ~~(except pharmacist)~~ will be blinded to the treatment; the ~~pharmacist and~~ sponsor will be unblinded. The dose volumes and number of injections for subjects in each cohort are presented in Table CGAY.2.

Galcanezumab or placebo will be administered as SC injections into the abdomen ~~while the subject is in a sitting position~~. The location of the injection(s) will be recorded. Multiple injections making up a single dose (i.e. for Cohort B) should be apart from each other, so ISRs, if any, can be observed separately. Subjects ~~should~~ may stay in the semi-recumbent position for 4 hours following study drug administration, where possible.

7.2. Method of Treatment Assignment

Subjects who meet the study entry criteria will be randomized to receive either galcanezumab or placebo in a 4:1 ratio via a computer-generated random sequence using an interactive web-response system (IWRS).

7.3. Blinding

This will be a subject- and investigator-blinded study. The subjects and clinical staff ~~(except pharmacist)~~ will be blinded to which treatment (galcanezumab or placebo) the subjects are assigned to. The ~~pharmacist and the~~ sponsor will be unblinded.

~~Emergency codes will be available to the investigator. A code, which reveals the treatment for a specific study subject, may be opened during the study only if the subject's well-being requires knowledge of the subject's treatment assignment.~~Emergency unblinding for AEs may be performed through the IWRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used ONLY if the subject's well-being requires knowledge of the subject's treatment assignment. All calls resulting in an unblinding event are recorded and reported by the IWRS.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted for medical management of the event. The subject's safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

~~Upon completion of the study, all codes must be returned to Lilly or its designee.~~

7.5. Preparation/Handling/Storage/Accountability

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

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

9.5.1. Laboratory Tests

~~With the exception of safety laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the study.~~ All safety laboratory tests will be conducted at a local laboratory.

9.5.7. Tuberculosis Testing

Subjects will be tested as indicated in the Schedule of Activities (Section 2) for evidence of active TB, which includes a T-SPOT® TB test. If the first test result is indeterminate, 1 repeat is allowed. If the repeat result is indeterminate, the subject will be excluded from the study.

Subjects who have had household contact with a person with active TB must be excluded unless appropriate and documented prophylaxis treatment for TB has been completed. Subjects with any history of active TB are excluded from the study, regardless of previous or current TB treatments.

10.3.2.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety lab parameters and~~,~~ vital signs~~, and ECG parameters~~.

Appendix 2. Clinical Laboratory Tests

- A 'T-SPOT® TB test' was added to the table to be performed at screening only.
- The abbreviation 'TB = tuberculosis' was added to the abbreviation footnote.
- Footnote 'a' was updated as follows:

  [a] ~~Day -1 tests to be conducted by the local laboratory; other scheduled assessments to be conducted at a central laboratory.~~ All safety laboratory tests will be conducted by the local laboratory.

Appendix 4. Blood Sampling Summary

Protocol I5Q-MC-CGAY Sampling Summary

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	~~45~~ 28	1	~~45~~ 28
Clinical laboratory tests[a]	~~9~~ 8	6	~~54~~ 48
Galcanezumab Pharmacokinetics[b]	2.5	17	42.5
Immunogenicity[b]	10	6	60
Pharmacogenetics	10	1	10
Total			~~211.5~~ 188.5
Total for clinical purposes [rounded up to nearest 10 mL]			~~220~~ 190

[a] Additional samples may be drawn if needed for safety purposes.

[b] Additional samples may be drawn in the event of hypersensitivity reactions.

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