Protocol Addendum I5Q-JE-CGAP (1)

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

NCT02959190

Approval Date: 2-Sep-2016

1. Protocol Addendum I5Q-JE-CGAP (1) A Phase 3, Long-Term, Open-Label Safety Study of LY2951742 (Galcanezumab) in Japanese Patients with Migraine

LY2951742 (galcanezumab)

This addendum is to be performed in addition to all procedures required by protocol I5Q-JE-CGAP or any subsequent amendments to that protocol.

Eli Lilly Japan K.K. in Japan
Hyogo, Japan

Protocol Addendum (1) Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 02-Sep-2016 GMT

2. Table of Contents

Protocol Addendum I5Q-JE-CGAP (1) A Phase 3, Long-Term, Open-Label Safety Study of LY 2951742 (galcanezumab) in Japanese Patients with Migraine

Section **Page**

List of Tables

Table **Page**

List of Figures

Figure **Page**

3. Rationale for Addendum

Study I5Q-JE-CGAP (Study CGAP) is a multisite, randomized, long-term (1-year), two arms, open-label study. This study will be evaluating the safety and effectiveness of galcanezumab (120 mg/month and 240 mg/month) in the prevention of migraine headache. As shown in protocol I5Q-JE-CGAP (protocol CGAP), Japanese patients with episodic migraine (EM) will roll over from Study I5Q-JE-CGAN. In addition to these patients with EM, Japanese patients with chronic migraine (CM) will be also enrolled in the study CGAP. The objective of this addendum is to evaluate safety and effectiveness of galcanezumab in Japanese patients with CM. Schedule of Activities, Objective and Endpoints, Study Design, Study Population, Treatments, and Statistical Consideration are described in this protocol addendum (1).

4. Protocol Additions

The content below will apply to patients with CM enrolled in Study CGAP. The rest of the parts of the protocol should be referred to the main protocol.

2. Schedule of Activities

This is for the patients with CM.

Study Period (SP)	**SP I-Screening**	**SP II-Prospective Baseline**	**SP III – Treatment**														**SP IV – Follow-up**	
(Target) Interval (days) since previous visit			**30-45**	**14**	**16**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**60**	**60**
Allowable range (days) between visits	**3-45**	**30-40[a]**																
Interval allowance (days) compared from previous visit				±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16/ ET**	**17**	**18/ ET**
Month			**0**	**(D14)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**14**	**16**
Assessments and Procedures																		
Informed consent	X																	
Inclusion/Exclusion	X	X	X															
Demographics	X																	
Physical examination[b]	X																	
Height	X																	
Weight	X									X						X		X
Waist and hip circumference	X																	
Medical history	X																	
Pre-specified migraine history/ pre-therapy		X																
Substance use	X																	
Prior Therapy (Migraine Medication)	X																	
ECG[c]	X		X							X						X		X
Vital signs[d]	X		X		X	X	X	X	X	X			X			X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period (SP)	SP I-Screening	SP II-Prospective Baseline	SP III – Treatment														SP IV – Follow-up	
(Target) Interval (days) since previous visit			**30-45**	**14**	**16**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**60**	**60**
Allowable range (days) between visits	**3-45**	**30-40[a]**																
Interval allowance (days) compared from previous visit				±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16/ ET**	**17**	**18/ ET**
Month			**0**	**(D14)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**14**	**16**
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of migraine and headache days[e]		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Paper-diary training to patients		X																
Clinical Laboratory Tests and Sampling Schedules																		
Hematology	X		X				X			X			X			X		X
Clinical chemistry	X		X				X			X			X			X		X
HbA1c			X							X						X		X
Urinalysis[f]	X		X							X						X		X
Serum Pregnancy (for women of childbearing potential)[g] or FSH at Visit 1 (for women who have evidence of cessation of menses for at least 12 months)	X															X		X
Urine pregnancy[g]			X		X	X	X	X	X	X	X	X	X	X	X			
Urine Drug Screening	X																	
Immunogenicity[h]			X	X	X	X	X			X			X			X		X

Study Period (SP)	SP I-Screening	SP II-Prospective Baseline	SP III – Treatment														SP IV – Follow-up	
(Target) Interval (days) since previous visit			**30-45**	**14**	**16**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**60**	**60**
Allowable range (days) between visits	**3-45**	**30-40[a]**																
Interval allowance (days) compared from previous visit				±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16/ ET**	**17**	**18/ ET**
Month			**0**	**(D14)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**14**	**16**
Biomarker storage sample[h]			X		X		X			X			X			X		X
CCI [redacted]		X	X	X	X	X	X			X			X			X		X
PK blood sample[h]			X	X	X	X	X			X			X			X		X
CCI [redacted]		X																
Whole blood RNA/epigenetic sample[h]			X							X						X		X
Study drug administered[i]			X		X	X	X	X	X	X	X	X	X	X	X			
Scales, Questionnaires, and Outcome Measures																		
MIDAS			X				X			X			X			X		X
MSQ (v2.1)			X		X	X	X	X	X	X			X			X	X	X
HCRU and Employment Status			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
PSMQ-M					X					X						X		X
PGI-S			X		X	X	X	X	X	X						X		X
PGI-I					X	X	X	X	X	X			X			X		X
C-SSRS/ SHSF, SHFU[j]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: CGRP = Calcitonin-gene related peptide; CRP = Lilly Clinical Research Physician; CRS = Lilly Clinical Research Scientist; C-SSRS = Columbia Suicide Severity Rating Scale; D14 = Day 14; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ET = early termination; FSH = follicle stimulating hormone; HbA1c = glycated haemoglobin; HCRU = Health Care Resource Utilization; MIDAS = Migraine Disability Assessment test; MSQ (v2.1) = Migraine Specific Quality of Life Questionnaire; PGI-I = Patient Global Impression of Improvement; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetics; PSMQ-M = Participant Satisfaction with Medication Questionnaire-Modified; RNA = ribonucleic acid; SP = Study Period; SHSF = Self-harm supplement form; SHFU = Self-harm follow-up form.

Note: Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and follow-up may be required with patients in consultation with the Lilly, or its designee (CRP/CRS). See Appendix 4 of the protocol for more details regarding specific hepatic monitoring tests. If the patient has discontinued the trial and returns for hepatic follow-up, the site should use the 800 series as the visit designation.

[a] The eligibility period of the prospective baseline assessment will last from 30 to 40 days. Investigators and patients may have up to an additional 5 days to schedule their Visit 3 appointment (beyond the 40 days); however, eligibility will be based on the 30-40 day period.

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

[c] Electrocardiograms as single, 12-lead digital will be performed at Visit 1, Visit 3, Visit 10,Visit16, and Visit 18 or early termination. Note: The Visit 3 ECG should be collected prior to blood draws and dosing. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. For screening only, ECG results will be read locally.

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

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

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

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

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

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

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

4. Objectives and Endpoints

Table CGAP(1).1 provides definitions for the terms referenced below.

Table CGAP(1).1. Migraine Definition for Patients with Chronic Migraine

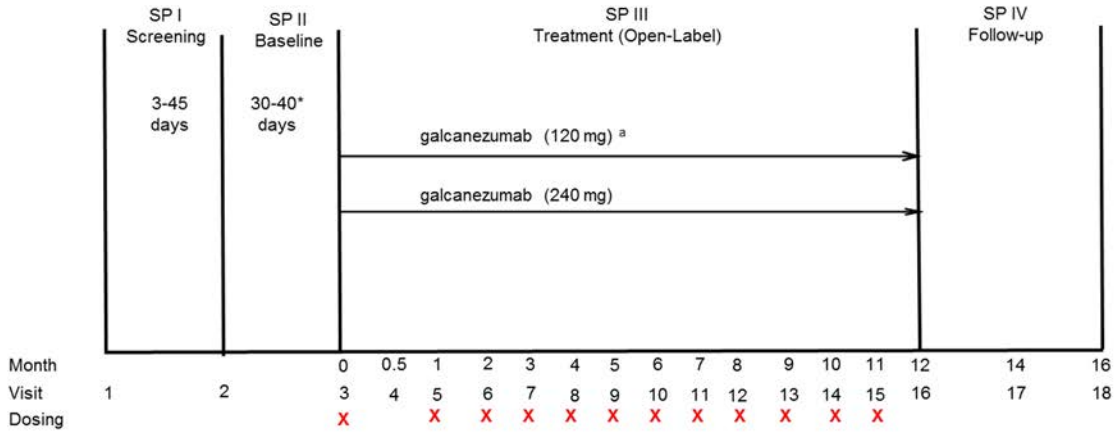
Diagnosis	Definition/Criteria
Migraine headache (Only Patients with CM)	A headache, with or without aura, of ≥30 minutes duration which meets criteria A and B or meets criterion C: A. At least 2 of the following headache characteristics: • Unilateral location • Pulsatile quality • Moderate or severe pain intensity • Aggravation by or causing avoidance of routine physical activity AND B. During headache at least one of the following: • Nausea and/or vomiting • Photophobia and phonophobia OR C. The headache is believed by the patient to be migraine at onset and is relieved by a triptan or ergot derivative *(Definition adapted from the IHS ICHD-3 beta)*
Probable migraine headache (Only Patients with CM)	A headache missing 1 of the migraine features in the IHS ICHD-3 beta definition such that one feature in criteria A is missing or one feature in criteria B is missing; that is, meet at least 2 A criteria and none of the B criteria or meet 1 of the A criteria and at least 1 of the B criteria. It must not meet criterion C.

Abbreviations: ICHD = International Classification of Headache Disorders; IHS= International Headache Society

5. Study Design

5.1. Overall Design

Figure CGAP(1).1 illustrates the study design for CM patients.



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

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

Note: The Visit 3 injections are under blind condition for all patients. From Visit 5, patients receive either one 120 mg injection (120 mg arm) or two 120 mg injections (240mg arm) without blinding

Figure CGAP(1).1. Study design for patients with chronic migraine.

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

Patients are required to discontinue all excluded medications or treatments for migraine prevention at least 30 days prior to Visit 2. Botulinum toxin A or B in the head or neck area must be discontinued at least 4 months prior to Visit 2.

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

Study Period II (SPII): 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 open-label treatment period. Patients will be trained to keep track of their migraine and headache days as well as their medication use days using a paper-based headache diary (paper diary) by the site staff. Retraining will be conducted as necessary based upon review of paper-diary data.

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

Study Period III (SPIII): At Visit3, patients meeting all eligibility requirements will be randomized to receive galcanezumab 120 mg/month, or galcanezumab 240 mg/month in a 1:1 ratio.

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

5.2. Number of Participants

Approximately 60 patients with CM will be enrolled (30 patients per arm [120 mg arm or 240 mg arm]).

5.4. Scientific Rationale for Study Design

The length of the open-label treatment of galcanezumab for 1 year is considered sufficient to assess the consistent effectiveness and safety on the patients with CM in comparison to those on the patients with EM. A 4-month post-treatment follow-up phase is included to evaluate patient safety during wash-out of galcanezumab. This allows for a total of 5 months of observation from the time of last injection of galcanezumab. A 5-month post-treatment observation period allows for a wash-out of approximately 5 elimination half-lives of galcanezumab and should decrease galcanezumab serum concentrations by approximately 97% during this time.

5.5. Justification for Dose

Doses of 120 mg and 240 mg administered once monthly were selected for the patients with CM in the global phase III study (Study CGAI) primarily on the basis of clinical efficacy and pharmacokinetic/pharmacodynamic data from the phase 2 dose-ranging study, which enrolled patients with EM (Study CGAB). The same doses in patients with EM and CM are warranted because the basic pathophysiology of headache is analogous and the mechanism of action of galcanezumab is the same in both patient populations. Also, the doses for current standard of care medications are the same for patients with EM and CM.

6. Study Population

All CM patients who enter this study 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 the prospective baseline period, as described in the Inclusion and Exclusion Criteria sections. The nature of any comorbid conditions present at the time of the physical examination and any 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 re-screening once, with approval from Lilly Medical (See Section 6.4 Screen Failures in this addendum). Study participants should be instructed not to donate blood or blood products during the study or for 5 months following the last administration of investigational product. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

6.1. Inclusion Criteria

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

Patient and Disease Characteristics

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

[2] Have a diagnosis of chronic migraine as defined by the IHS ICHD-3 beta guidelines (1.3) (ICHD-3 2013), that is, a headache occurring on 15 or more days per month for more than 3 months, which has the features of migraine headache on at least 8 days per month.

[3] Migraine onset prior to age 50.

[4] Prior to Visit 1, a history of at least 1 headache-free day per month for the past 3 months

[5] From Visit 2 to Visit 3 (prospective baseline period), have a frequency of at least 15 headache days, of which at least 8 must have the features of migraine headache (see definitions in Table CGAP(1).1). To avoid biased reporting, patients must not be told the number of migraine headache days on which study qualification is based.

[6] From Visit 2 to Visit 3 (prospective baseline period), have at least one headache-free day.

[7] From Visit 2 to Visit 3 (prospective baseline period), must achieve sufficient compliance with paper diary headache entries as demonstrated by completion of at least 80% of diary entries

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

[9] Are reliable and willing to follow study procedures, including all follow-up visit

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

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

Or

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

Or

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

[11] All patients must agree to use a reliable method of birth control during the study as well as for 5 months after the last dose of investigational product. Acceptable methods of birth control for this study are 1) combination of condom and oral contraceptives, 2) combination of condom and hormonal releasing intrauterine system (IUS), or 3) combination of condom and copper intrauterine device (IUD). These contraception methods are not required for female patients of non-childbearing potential, defined in inclusion criterion [10], or for male patients who meet the criterion defined in definition 3) of inclusion criterion [10].

[12] Agree not to post any personal medical data related to the study or information related to the study on any website or social media site (for example, Facebook, Twitter, LINE, Mixi, etc.) until the entire trial has completed.

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at screening:

Prior/Concurrent Clinical Trial Experience

[13] Are currently enrolled in any other clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

[14] Have participated within the last 30 days or within 5 half-lives (whichever is longer) in a clinical trial involving an investigational product. If the investigational product's half-life is not known, 6 months should have passed prior to Visit 1.

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

[16] Have participated in SPI and/or SPII of Study CGAN.

Prior/Concomitant Therapy

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

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

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

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

[21] History of persistent daily headache, cluster headache or migraine subtypes including hemiplegic (sporadic or familial) migraine, ophthalmoplegic migraine, and migraine with brainstem aura (basilar-type migraine) defined by IHS ICHD-3 beta.

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

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

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

Medical Conditions

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

Diagnostics Assessments

[26] Patients with a body mass index ≥40 kg/m^2.

[27] Any liver tests outside the normal range at Visit 1 that are clinically significant. Alanine aminotransferase (ALT) >2X upper limit of normal (ULN), or total bilirubin level (TBL) >1.5X ULN, or alkaline phosphatase (ALP) >2X ULN must be discussed and judged not clinically significant by Lilly Medical prior to enrollment.

[28] Evidence of significant active or unstable psychiatric disease by medical history, such as bipolar disorder, schizophrenia, personality disorders, or other serious mood or anxiety disorders. Note: Patients with major depressive disorder or generalized anxiety disorder whose disease state is considered stable and expected to remain stable throughout the course of the study, in the opinion of the investigator, may be considered for inclusion if they are not on excluded medications.

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

[30] Women who are pregnant or nursing.

[31] Patients who have used opioids or barbiturate containing analgesic >3X per month for the treatment of pain in more than 2 of the past 6 months (opioid administration in an emergency setting may be an exception).

[32] History of drug or alcohol abuse/dependence within 1 year prior to Visit 1 (excessive or compulsive use as judged by the Investigator), or currently using drugs of abuse (including opioids, barbiturates and marijuana), or any prescribed or over-the-counter medication in a manner that the Investigator considers indicative of abuse/dependence.

[33] Have a positive urine drug screen for any substances of abuse at Visit 1. Note: A retest is allowed if the urine drug screen is positive for any prescribed substance or if, in the judgment of the investigator, there is an acceptable explanation for the positive result. The results of the retest must be negative at or prior to Visit 2.

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

Other Exclusions

[35] In the opinion of the investigator, have other issues which would interfere with compliance with the study requirements and completion of evaluations required for this study.

[36] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[37] Are Lilly employees.

[38] Are unwilling or unable to comply with the use of a data collection device.

6.4. Screen Failures

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

- ✓ Inclusion criterion [1]. If patients are less than age 18 at time of informed consent, they may be rescreened if they reach age 18 during the study enrollment period.
- ✓ Inclusion criterion [10]
- ✓ Exclusion criterion [14]
- ✓ Exclusion criterion [17]
- ✓ Exclusion criterion [19]
- ✓ Exclusion criterion [30]

Patients using a concomitant medication that requires a stable dose for a specific duration prior to Visit 2 may be rescreened if additional time is needed to meet the duration requirement.

7. Treatment

7.1. Treatments Administered

Table CGAP(1).2 shows the treatment regimens for CM patients.

Table CGAP(1).2. Treatment Regimen for the patients with chronic migraine

Assignment	Regimen	
	Dose at V3	Dose V5-15
galcanezumab 120 mg	galcanezumab 240 mg, subcutaneous (2 injections of 120 mg using pre-filled syringe)	galcanezumab 120 mg monthly, subcutaneous (1 injection of 120 mg using pre-filled syringe
galcanezumab 240 mg	galcanezumab 240 mg monthly, subcutaneous (2 injections of 120 mg using pre-filled syringe)	

7.2. Method of Treatment Assignment

Approximately 60 patients with CM will be enrolled. Thirty patients will be randomized to 120 mg arm, and 30 patients to 240 mg arm (randomization ratio 1:1). Therefore, after the randomization, CM patients will be assigned to one of two arms;

CM120: Study CGAP 120 mg galcanezumab with loading dose

CM240: Study CGAP 240 mg galcanezumab

10. Statistical Considerations

10.1. Sample Size Determination

Analysis of CM data:

Approximately 60 patients with CM will be enrolled (30 patients for the CGAP 120mg arm, 30 patients for the CGAP 240mg arm). It is assumed that 30% of patients will not complete a 12-month treatment period.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

Unless specified otherwise, data for the patients with CM in Study CGAP will be reported by the following treatment groups;

1) CM120: CM patients who are randomized to galcanezumab 120 mg in Study CGAP
2) CM240: CM patients who are randomized to galcanezumab 240 mg in Study CGAP

Unless otherwise specified, safety and effectiveness analyses will be conducted on an intent-to-treat (ITT) basis, which is to include all patients who receive at least one dose of study drug. When change from baseline is assessed, the patient will be included in the analysis only if he/she has a baseline and a post-baseline measurement. In principle, any statistical analysis will be performed in a descriptive manner due to limited sample size and open-label treatment.

For analysis for the patient with CM, baseline is Visit 3 assessment in Study CGAP unless otherwise specified.

Details will be described in the statistical analysis plan (SAP) document.

Leo Document ID = 0ccc690c-0f9f-4806-9a1c-e4139d2a9c50

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Approver: PPD
Approval Date & Time: 02-Sep-2016 15:45:03 GMT
Signature meaning: Approved