Protocol I5Q-MC-CGAM A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study of : Galcanezumab (LY2951742) With a Long-Term Open-Label Extension in Patients With Chronic Cluster Headache

NCT02438826

Approval Date: 28-Mar-2018

1. Protocol I5Q-MC-CGAM(d)
A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 with a Long-Term Open-Label Extension in Patients with Chronic Cluster Headache

LY2951742

Study I5Q-MC-CGAM is a Phase 3 multi-center, outpatient, randomized, double-blind, placebo-controlled study of LY2951742 300 mg in patients with chronic cluster headache. The study has 5 study phases (SP): SP I (screening/washout phase), SP II (pre-randomization diary phase), SP III (treatment phase), SP IV (open-label extension phase), and SP V (post-treatment follow-up phase).

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Protocol Electronically Signed and Approved by Lilly: 18 December 2014
Amendment (a) Electronically Signed and Approved by Lilly: 27 March 2015
Amendment (b) Electronically Signed and Approved by Lilly: 22 December 2015
Amendment (c) Electronically Signed and Approved by Lilly: 10 February 2017
Amendment (d) Electronically Signed and Approved by Lilly on approval date provided below.

Approval Date: 28-Mar-2018 GMT

2. Synopsis

Study Rationale

LY2951742 (also known as galcanezumab) is a humanized monoclonal antibody that selectively binds to and neutralizes calcitonin-gene-related peptide (CGRP) that has been identified for clinical development in pain conditions relevant to the CGRP pathway such as migraine. The similarities between migraine and cluster headache, the role of CGRP in both disorders and the clinical efficacy observed with LY2951742 to date for the preventive treatment of migraine support the evaluation of the CGRP neutralizing antibody LY2951742 for the treatment of cluster headache.

The aim of this study is to assess the safety and efficacy of LY2951742 300 mg administered every 30 days for the prevention of chronic cluster headache.

Clinical Protocol Synopsis: Study I5Q-MC-CGAM

<table>
<tr><td colspan="2">Name of Investigational Product:
LY2951742</td></tr>
<tr><td colspan="2">Title of Study: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 with a Long-Term Open-Label Extension in Patients with Chronic Cluster Headache</td></tr>
<tr><td>Number of Planned Patients/Subjects:
Entered: 231
Enrolled/Randomized: Planned 162
Completed (SP III): 146</td><td>Phase of Development: 3</td></tr>
<tr><td colspan="2">Length of Study: 30 months
Estimated first patient visit: Jun 2015 Estimated last patient visit: Dec 2017</td></tr>
<tr><td colspan="2">Primary Objectives: The primary objective is to assess the efficacy of LY2951742 300 mg administered every 30 days compared with placebo in reducing the frequency of weekly cluster headache attacks in patients with chronic cluster headache. The primary outcome measure is the weekly cluster headache attack frequency. The primary endpoint is the overall mean change from baseline in weekly cluster headache attack frequency during the 12-week double-blind treatment phase with LY2951742 compared with placebo. The baseline cluster headache attack frequency is based on the last 14 days in the eligibility report (pre-randomization diary phase).

Gated Objectives:
• To assess the efficacy of LY2951742 300 mg compared with placebo in the estimated mean proportion of patients with a 50% or greater reduction from baseline in the weekly frequency of cluster headache attacks during the 12-week double-blind treatment phase.
• To assess the efficacy of LY2951742 300 mg compared with placebo in the proportion of patients meeting sustained response through Week 12. For this analysis, sustained response is defined as a 50% or greater reduction in the weekly cluster headache attack frequency from baseline to Weeks 3/4 and maintained at Weeks 5/6, Weeks 7/8, Weeks 9/10, and Weeks 11/12.</td></tr>
</table>

Other secondary objectives:

- To assess whether LY2951742 300 mg is superior to placebo on the following:
  - mean change in the weekly cluster headache attack frequency from baseline to each 2-week interval through Week 12
  - the proportion of patients with a 50% or greater reduction in the weekly cluster headache attack frequency from baseline at each 2-week interval through Week 12
  - the proportion of patients with a 30% or greater reduction in the weekly cluster headache attack frequency from baseline at each 2-week interval through Week 12
  - proportion of patients reporting a score of 1 ("very much better") or 2 ("much better") on the Patient Global Impression of Improvement (PGI-I) at Month 1, Month 2, and Month 3
- To compare LY2951742 300 mg with placebo on the following safety and tolerability measures:
  - spontaneously reported treatment-emergent adverse events (TEAEs)
  - serious adverse events (SAEs)
  - adverse events (AEs) leading to discontinuation
  - suicidal ideation and behaviors assessed by solicited questioning using the Columbia-Suicide Severity Rating Scale (C-SSRS)
- To assess the development and consequences of anti-drug antibodies (ADA) to LY2951742 in patients exposed to LY2951742; to provide samples for subsequent evaluation of neutralizing ADA (NAb).
- To evaluate the pharmacokinetics of LY2951742.

Exploratory Objectives: To assess whether LY2951742 300 mg is superior to placebo as measured by:

- Proportion of patients randomized to LY2951742 meeting "very much better" or "much better" on the PGI-I at Month 9 and Month 15
- Mean change in the weekly number of times of abortive medication use from baseline to each 2-week interval through Week 12 comparing LY2951742 with placebo
- Change in percentage of times using oxygen from baseline for each 2-week interval through Week 12 comparing LY2951742 with placebo
- Change in percentage of times using triptan from baseline for each 2-week interval through Week 12 comparing LY2951742 with placebo
- Change in percentage of times of using acetaminophen/paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs) from baseline for each 2-week interval through Week 12 comparing LY2951742 with placebo
- Responder analyses of LY2951742 compared with placebo from baseline to each 2-week interval through Week 12 for the proportion of patients meeting:
  - a 75% or greater reduction in the weekly cluster headache attack frequency
  - a 100% reduction in weekly cluster headache attack frequency
- Mean change from baseline to each 2-week interval through Week 12 in the cluster headache attack average weekly pain severity based on 5-point pain severity scale comparing LY2951742 with placebo

[redacted]

Study Design: Phase 3 multi-center, outpatient, randomized, double-blind, placebo-controlled study of LY2951742 300 mg administered every 30 days compared with placebo for the prevention of chronic cluster headache. The study has 5 study phases (SP): SP I (screening/washout phase), SP II (pre-randomization diary phase), SP III (treatment phase), SP IV (optional open-label extension phase), and SP V (post-treatment follow-up phase).

Diagnosis and Main Criteria for Inclusion and Exclusions Diagnosis and Main Criteria for Inclusion and Exclusions: The planned patient population includes adult outpatients (18 to 65 years of age inclusive) who meet the *International Classification of Headache Disorders, Third Edition, beta version*, or *ICHD-3 (ICHD-3 2013)*, diagnostic criteria for Chronic Cluster Headache and, during baseline assessment, have a maximum of 8 attacks per day and a minimum of 8 attacks. Patients should also be able to distinguish cluster headache attacks from other headaches (that is, tension-type headaches, migraine) and not be anticipated to spontaneously remit during the double-blind treatment phase in the opinion of the investigator. Patients are excluded from study participation if they are currently enrolled in another clinical trial, are using or have used CGRP or nerve growth factor (NGF) antibodies, have a lifetime history of migraine variants that could implicate or could be confused with ischemia, are taking indomethacin and/or are suspected of having another distinct trigeminal autonomic cephalalgia, or have had botulinum toxin type A or type B administered in the head or neck area within 4 months of SP II.

Investigational Product, Dosage, and Mode of Administration or Intervention: subcutaneous injections of LY2951742 300 mg administered every 30 days as three 1-mL injections.

Reference Therapy, Dose, and Mode of Administration or Comparative Intervention: subcutaneous injections of placebo (0.9% Sodium Chloride Injection, USP; volume matched) administered every 30 days during SP III.

Planned Duration of Treatment: 64 weeks + up to 16 weeks post-treatment follow-up

Screening/washout phase: up to 65 days
Pre-Randomization Diary phase: approximately 2 weeks
Treatment phase: 12 weeks
Open-label Extension phase: approximately 52 weeks
Post-treatment follow-up phase: 16 weeks

Criteria for Evaluation:

Efficacy:

Electronic Patient Reported Outcome (ePRO) diary: Patients will be asked to record the number of cluster headache attacks in their daily ePRO diary during SP II and SP III. Information regarding abortive medication use, cluster headache attack duration, and cluster headache attack pain severity will also be recorded. Pain severity will be rated using a 5-point pain scale, where 0=no pain, 1=mild pain, 2=moderate pain, 3=severe pain, and 4=very severe pain (Sumatriptan Cluster Headache Study Group 1991). Patients should record all cluster attacks regardless of attack duration.

Patient Global Impression of Improvement (PGI-I) requests patients to: Mark the box that best describes your cluster headache condition since you started taking this medicine. The options in the displayed boxes are represented on a seven-point scale, with 1=very much better and 7=very much worse.

Safety:

Safety will be assessed by summarizing and analyzing AEs, laboratory test results, vital signs, electrocardiograms (ECGs) and suicidal ideation/behavior (via the C-SSRS).

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Statistical Methods:

Statistical: The study is planned to have a minimum of approximately 162 patients randomized 1:1 to placebo or LY2951742 with the opportunity to increase the final sample size at an interim analysis if indicated in order to maintain a well powered study. To preserve blinding, details of the sample size and power calculations are omitted from this protocol and are provided in a separate document to the Ethical Review Board (ERB).

Unless otherwise specified, efficacy analyses will be conducted on an intent-to-treat (ITT) population, which include all patients who are randomized and receive at least 1 dose of investigational product (IP). Patients in the ITT population will be analyzed according to the treatment group to which they were randomized. Safety analyses for

SP III and exposure will be conducted on the safety population, which also includes all patients who are randomized and received at least 1 dose of study drug. However, patients will be analyzed by actual study treatment received most often (modal treatment; placebo or LY2951742) during the double-blind treatment phase. Safety analyses during LY2951742 -treated time and LY2951742-treated time plus post-treatment time will be conducted on the LY2951742-treated population, which includes all patients who receive at least 1 dose of LY2951742. When mean 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. Additional analyses population for analyses of study Phase IV and Phase V will be described in the statistical analysis plan (SAP).

Baseline will be the last 14 days in the eligibility report (pre-randomization diary phase). An additional baseline defined at Visit 9 (the first visit of the open-label phase) may be used for some analyses. This, in addition to details for handling missing data, will be further outlined in the SAP.

Treatment effects will be evaluated based on a 2-sided significance level of 0.05 for all the efficacy and safety analyses. The 95% confidence intervals (CIs) for the difference between treatment groups will be presented. Adjustments for multiple comparisons for the analyses corresponding to the primary and gated secondary objectives are described in the sections on the primary and secondary efficacy analyses below. There will be no adjustments for multiplicity for analyses of other data.

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or its designee. SAS® software will be used to perform most or all statistical analyses.

Efficacy – Primary: The primary analysis will be conducted by a restricted maximum likelihood-based (REML-based), mixed-effects repeated measures (MMRM) analysis using all the longitudinal observations at Weeks 1/2, 3/4, 5/6, 7/8, 9/10, and 11/12. The analysis of the primary outcome will be the main effect of treatment between LY2951742 300 mg and placebo during the 12-week double-blind treatment phase from a repeated measures analysis on mean change from baseline in the weekly attack frequency. This provides the average treatment effect across the 12-week double-blind treatment phase.

If the sample size is increased as a result of the interim analysis, the Cui, Hung, and Wang (CHW) procedure will be applied to the primary endpoint to control the type I error at a one sided α=0.025 significance level. The CHW method ensures strong control of type 1 error when the sample size is increased in a data dependent manner.

If the sample size is increased as a result of the interim analysis, an unadjusted point estimate for the primary efficacy analysis will be calculated and reported. A median unbiased point estimate and a stage-wise adjusted confidence interval for the primary efficacy analysis will be calculated and reported based on the approach described in Brannath et al. (2009) to assess sensitivity of the point estimate.

Efficacy – Gated Secondary:

For the gated secondary outcome of the estimated mean proportion of patients with a 50% or greater reduction from baseline in weekly cluster headache attack frequency during the 12-week double-blind treatment phase, a categorical, pseudo-likelihood-based repeated measures analysis of data at Weeks 1/2, 3/4, 5/6, 7/8, 9/10, and 11/12 will be used. The endpoint for comparing LY2951742 with placebo will be estimated as the main effect of treatment from the categorical MMRM analysis across Weeks 1 to 12. For the gated secondary outcome of sustained response (the proportion of patients with a reduction from baseline of 50% or greater in the weekly cluster attack frequency beginning at Weeks 3/4 and maintained at Weeks 5/6, 7/8, 9/10, and 11/12), the Koch's Nonparametric Randomization-Based Analysis of Covariance method will be utilized (Koch et al. 1998). A non-responder imputation for missing values will be used. Specifically, all patients who discontinue study treatment at any time prior to Weeks 11/12, for any reason, will be considered a non-responder at all missing assessment.

If the sample size is increased, the CHW test statistic will be calculated for the gated secondary objectives. The analysis of the secondary gatekeeper objectives will be performed if the LY2951742 versus placebo comparison is significant for the primary efficacy analysis at a one sided α=0.025 significance level.

Safety: The safety analyses will be conducted for SP III on the safety population, and during LY2951742-treated time and LY2951742-treated time plus post-treatment time on the LY2951742-treated population.
The safety and tolerability of treatment will be assessed by summarizing the following:

- Adverse events
  - treatment emergent adverse events
    - by preferred term (PT)
    - by system organ class (SOC)
    - by maximum severity
    - considered to be related to IP by investigator
  - serious adverse events
  - adverse events leading to discontinuation
- Suicidal ideation and behaviors assessed by solicited questioning using the C-SSRS
- Vital signs and weight
- Electrocardiograms
- Laboratory measurements
- Anti-drug antibodies (ADA and NAb)

Unless specified otherwise, the categorical safety analyses will include both schedule and unscheduled visits. Comparisons between treatment groups for all categorical safety measures will be made using Fisher's exact test for SP III with safety population. Descriptive statistics only will be presented for the analyses with LY2951742-treated population.

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3. Table of Contents

A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 with a Long-Term Open-Label Extension in Patients with Chronic Cluster Headache

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4. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ADA	anti-drug antibodies
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
blinding	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A double-blind study is one in which neither the patient 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
CIOMS	Council for International Organizations of Medical Sciences
CGRP	calcitonin-gene-related peptide
CI	confidence interval
CIDBF	capsaicin-induced dermal blood flow
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 trial-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 Eli Lilly and Company (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.
CRF/eCRF	case report form/electronic case report form: Sometimes referred to as clinical report form: A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRP/CRS	clinical research physician (CRP): Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist (CRS), global safety physician or other medical officer.
C-SSRS	Columbia Suicide Severity Rating Scale
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EDC	electronic data capture system
efficacy	Efficacy is the ability of a treatment to achieve a beneficial intended result under controlled conditions.
end of trial (study)	End of trial is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last [patient/subject].
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
Enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ePRO	electronic patient reported outcome
ERB/IRB	ethical review board/institutional review board: A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.
FSH	follicle stimulating hormone
GCP	good clinical practice
HLT	High Level Term
IB	Investigator's Brochure
ICD	informed consent document
ICF	informed consent form

ICH	International Council for Harmonisation
ICHD-3	International Classification of Headache Disorders, Third edition, beta
IHS	International Headache Society
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product (IP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial.
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.
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient, to the patient's participation in the clinical study.
LLT	lowest level term
LOCF	last observation carried forward
LSD	lysergic acid diethylamide
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MMRM	mixed model repeated measures
msec	milliseconds
NAb	neutralizing anti-drug antibodies
NGF	nerve growth factor
NSAID	nonsteroidal anti-inflammatory drug
OTC	over-the-counter

patient	A study participant who has the disease or condition for which the investigational product is targeted.
PGI-I	Patient Global Impression of Improvement
PK/PD	pharmacokinetics/pharmacodynamics
PT	preferred term
QTc	corrected QT interval
QTcB	corrected QT interval measured with Bazett's formula
QTcF	corrected QT interval measured with Fridericia's formula
QTcLCTPB	Large Clinical Trial Population Based QT Correction
Randomize	The process of assigning patients to an experimental group on a random basis
REML-based	restricted maximum likelihood-based
rescreen	To screen a patient who was previously declared a screen failure for the same study.
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
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. In this study, screening involves diagnostic procedures and/or tests (for example, diagnostic psychological tests, x-rays, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
SHSF	self-harm supplement form
SHFU	self-harm follow-up form
SOC	System Organ Class
SP	study phase
subject	An individual who is or becomes a participant in clinical research, either as a recipient of the investigational product(s) or as a control. A subject may be either a healthy human or a patient.
SUSARs	suspected unexpected serious adverse reactions
TBL	total bilirubin

TEAE	treatment-emergent adverse event: Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
TPO	third-party organization
UA	unstable angina
UDS	urine drug screen
ULN	upper limit of normal
V	visit
VAS	Visual Analog Scale

A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 with a Long-Term Open-Label Extension in Patients with Chronic Cluster Headache

5. Introduction

Cluster headache is a rare but disabling primary headache disorder characterized by episodic attacks of intense unilateral headache and the frequent association of autonomic symptoms such as lacrimation, conjunctival injection, and nasal congestion (ICHD-3 2013). The diagnosis of cluster headache is distinctly recognized and defined by the International Classification of Headache Disorders, Third edition, beta version (ICHD-3 2013). The natural course of illness of cluster headache can be conceptualized as consisting of 2 phases: (1) *cluster periods* (typically lasting weeks or months) composed of a series of 15-180 minute *attacks* of severe (often excruciating) unilateral headache pain attacks and cranial autonomic symptoms occurring near-daily to multiple times daily during the cluster period, and (2) attack-free remission periods that may last for weeks, months, or even years. In addition, the ICHD-3 provides an operational distinction between 2 subtypes of cluster headache, *episodic cluster headache* (the predominant form) and *chronic cluster headache* (affecting up to 20% of all cluster headache sufferers (Manzoni et al. 1983, van Vliet et al. 2003), based on the duration of the attack-free remission: ≥1 month for episodic, <1 month for chronic (Matharu and Goadsby 2002; ICHD-3 2013).

There are significant unmet needs for just about every clinical aspect of the patient with cluster headache, particularly related to the severity of the disease and treatment options. The majority of patients experiencing cluster headache attacks rate their pain intensity as near to or at the worst pain imaginable (using a Visual Analog Scale [VAS] 10 cm scale) (Torelli and Manzoni 2003). The verbatim descriptors of the pain experienced by patients are varied and complex, including drill, point, needle, punch, spear, stab wound, knife wound, stinging, piercing, shooting, hammer, pangs, throbbing, pulsating, and rhythmic (Torelli and Manzoni 2003). In the United States, there is only 1 approved abortive medication (treatment initiated at the start of a cluster headache attack to shorten overall attack duration), limited to only twice-daily use, and no approved preventive medications. The desperation in this patient population is exemplified by approximately half of patients reporting self-injurious behavior during attacks (Rozen and Fishman 2012) and many patients turning to illicit drug use, such as marijuana, cannabinoids, and hallucinogens (psilocybin, lysergic acid diethylamide [LSD], and 2-Bromo LSD), in an attempt to alleviate their suffering (Karst et al. 2010; McGeeney 2012; Tepper and Stillman 2013).

Increased plasma or serum levels of calcitonin gene-related peptide (CGRP) have been associated with painful syndromes such as migraine and cluster headache (Edvinsson and Goadsby 1994). Calcitonin gene-related peptide is a 37-amino acid neuropeptide member of a family of peptides that includes amylin, adrenomedullin and calcitonin, is one of the most abundant peptides within the nervous system (McCarthy and Lawson 1990), and is highly expressed in trigeminal ganglion neurons. The association of CGRP with cluster headache was initially demonstrated in a study of patients with spontaneous cluster headache attacks who were

found to have elevated CGRP levels compared to controls (Edvinsson and Goadsby 1994). The CGRP levels were normalized after successful treatment with either subcutaneous (SC) sumatriptan or oxygen inhalation. In another study, CGRP blood levels were elevated in 18 males during a nitroglycerin-induced cluster headache and returned to baseline after successful sumatriptan treatment or spontaneous recovery (Fanciullacci et al.1995; Fanciullacci et al. 1997). These data provide evidence that a treatment which neutralizes CGRP, such as a CGRP antibody, may be effective in managing cluster headache.

LY2951742(also known as galcanezumab) is a humanized monoclonal antibody that selectively binds to and neutralizes CGRP. LY2951742 has been identified for clinical development in pain conditions relevant to the CGRP pathway such as migraine, and, in completed studies to date, LY2951742 was shown to alter plasma CGRP concentrations, which is consistent with the binding of the antibody (LY2951742) to CGRP. The similarities between migraine and cluster headache, the role of CGRP in both disorders and the clinical efficacy observed with LY2951742 to date for the preventive treatment of migraine support the evaluation of the CGRP neutralizing antibody LY2951742 for the treatment of cluster headache.

A single and multiple-dose ascending study (Study I5Q-MC-CGAA [CGAA]) in healthy subjects and a Phase 2a proof-of-concept study (I5Q-AR-ART-01 [ART-01]) in migraine patients have been completed (de Hoon et al. 2013; Dodick et al. 2014a). In Study CGAA, LY2951742 was administered subcutaneously to healthy subjects at single doses up to 600 mg, and as a multiple dose of 150 mg every other week for a total of 4 administrations. This study demonstrated that LY2951742 was well-tolerated and did not result in any serious adverse event (SAE) (Investigator's Brochure [IB], Section 6). There were no apparent differences between LY2951742 dose groups or between LY2951742 dose groups and placebo in the frequency of any adverse events (AEs) or changes from baseline in vital signs, clinical laboratory values, or electrocardiograms (ECG) parameters (de Hoon et al. 2013).

Further details of the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of LY2951742 may be found in the IB Section 6.

In the proof-of-concept study, ART-01, LY2951742 was administered subcutaneously once every 14 days for 6 doses in patients with a history of episodic migraine. LY2951742 significantly reduced the number of migraine headache days compared to placebo ($p=0.003$) at the 12-week endpoint (Dodick et al. 2014a). Treatment-emergent adverse events reported at a rate of 5% or higher in LY2951742 and greater than placebo were upper respiratory tract infection, injection site pain, abdominal pain, dizziness, injection site erythema, rash, and hypertension (Dodick et al. 2014a). LY2951742 did not cause any obvious changes in clinical chemistry or hematologic parameters and there was no apparent effect on heart rate, blood pressure or ECG measurements (QT-interval or Fredericia's QT interval [QTcF]-interval).

More information about the known and expected benefits, risks, and reasonably anticipated AEs of LY2951742 may be found in the IB. Information on AEs expected to be related to the investigational product (IP) may be found in Section 7 (Development Core Safety Information) of the IB. Information on serious adverse events (SAEs) expected in the study population

independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the study, may be found in Section 6 (Effects in Humans) of the IB.

This study, I5Q-MC-CGAM (CGAM), will assess the safety and efficacy of LY2951742 300 mg in patients with chronic cluster headache.

6. Objectives

Note: This study employs nominal 14-day intervals from which an average weekly cluster headache attack frequency is calculated.

6.1. Primary Objective

The primary objective is to assess the efficacy of LY2951742 300 mg administered every 30 days compared with placebo in reducing the frequency of weekly cluster headache attacks in patients with chronic cluster headache. The primary outcome measure is the weekly cluster headache attack frequency. The primary endpoint is the overall mean change from baseline in weekly cluster headache attack frequency during the 12-week double-blind treatment phase with LY2951742 compared with placebo. The baseline cluster headache attack frequency is based on the last 14 days in the eligibility report (pre-randomization diary phase).

6.2. Secondary Objectives

6.2.1. Gated Objectives

- To assess the efficacy of LY2951742 300 mg compared with placebo in the estimated mean proportion of patients with a 50% or greater reduction from baseline in the weekly frequency of cluster headache attacks during the 12-week double-blind treatment phase.
- To assess the efficacy of LY2951742 300 mg compared with placebo in the proportion of patients meeting sustained response through Week 12. For this analysis, sustained response is defined as a 50% or greater reduction in the weekly cluster attack frequency from baseline to Weeks 3/4 and maintained at Weeks 5/6, Weeks 7/8, Weeks 9/10, and Weeks 11/12.

6.2.2. Other Secondary Objectives

- To assess whether LY2951742 300 mg is superior to placebo on the following:
    - mean change in the weekly cluster headache attack frequency from baseline to each 2-week interval through Week 12
    - the proportion of patients with a 50% or greater reduction in the weekly cluster headache attack frequency from baseline at each 2-week interval through Week 12
    - the proportion of patients with a 30% or greater reduction in the weekly cluster headache attack frequency from baseline at each 2-week interval through Week 12
    - proportion of patients reporting a score of 1 ("very much better") or 2 ("much better") on the Patient Global Impression of Improvement (PGI-I) at Month 1, Month 2, and Month 3

- To compare LY2951742 300 mg with placebo on the following safety and tolerability measures:
    - spontaneously reported treatment-emergent adverse events (TEAEs)
    - serious adverse events
    - adverse events leading to discontinuation
    - suicidal ideation and behaviors assessed by solicited questioning using the Columbia-Suicide Severity Rating Scale (C-SSRS).
- To assess the development and consequences of anti-drug antibodies (ADA) to LY2951742 in patients exposed to LY2951742; to provide samples for subsequent evaluation of neutralizing ADA (NAb).
- To evaluate the pharmacokinetics of LY2951742.

6.3. Exploratory Objectives

To assess whether LY2951742 300 mg is superior to placebo as measured by:

- Proportion of patients randomized to LY2951742 meeting "very much better" or "much better" on the PGI-I at Month 9 and Month 15.
- Mean change in the weekly number of times of abortive medication use from baseline to each 2-week interval through Week 12 comparing LY2951742 with placebo.
- Change in percentage of times using oxygen from baseline for each 2-week interval through Week 12 comparing LY2951742 with placebo.
- Change in percentage of times using triptan from baseline for each 2-week interval through Week 12 comparing LY2951742 with placebo.
- Change in percentage of times of using acetaminophen/paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs) from baseline for each 2-week interval through Week 12 comparing LY2951742 with placebo.
- Responder analyses of LY2951742 compared with placebo from baseline to each 2-week interval through Week 12 for the proportion of patients meeting:
    - a 75% or greater reduction in the weekly cluster headache attack frequency
    - a 100% reduction in weekly cluster headache attack frequency
- Mean change from baseline to each 2-week interval through Week 12 in the cluster headache attack average weekly pain severity based on 5-point pain severity scale comparing LY2951742 with placebo.

[redacted]

[redacted]

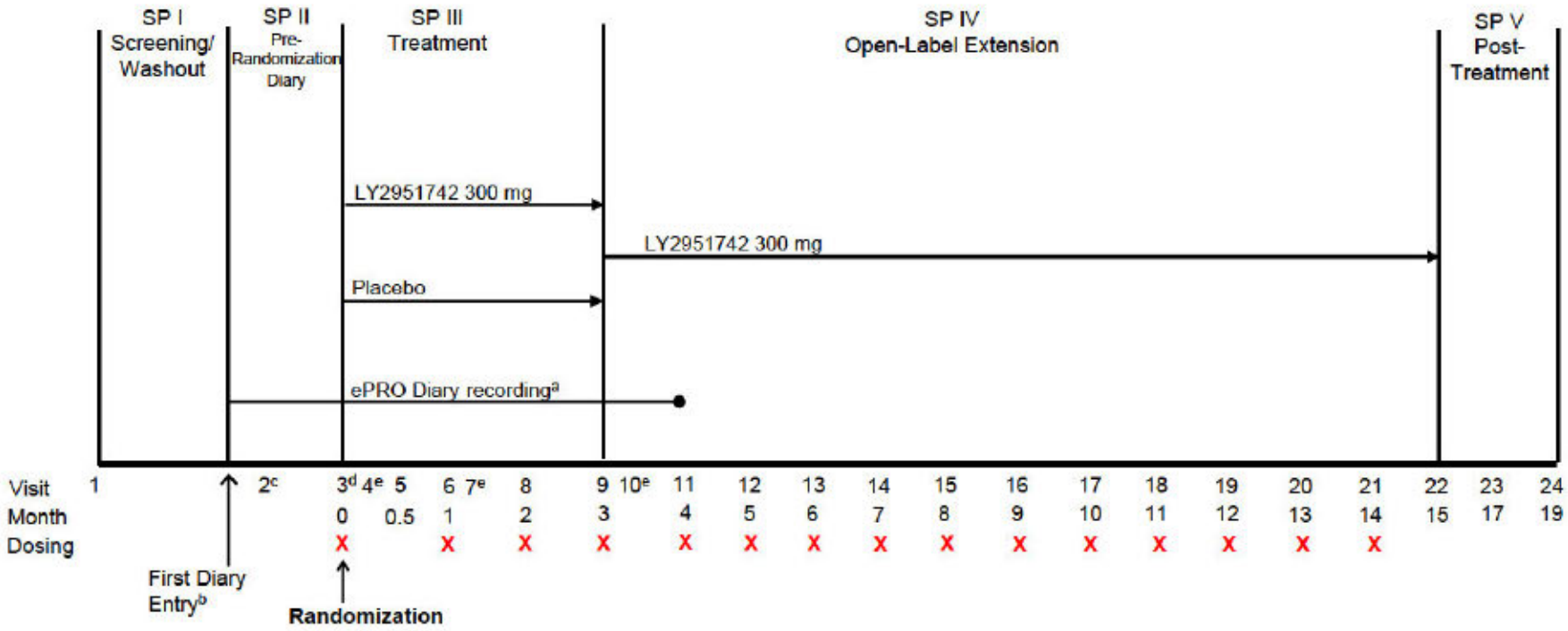
7. Investigational Plan

7.1. Summary of Study Design

Study CGAM is a Phase 3 multi-center, outpatient, randomized, double-blind, placebo-controlled study of LY2951742 300 mg for the prevention of chronic cluster headache. The study has 5 study phases (SP):

- SP I (screening/washout phase)
- SP II (pre-randomization diary phase)
- SP III (double-blind treatment phase)
- SP IV (optional open-label extension phase)
- SP V (post-treatment follow-up phase)

Figure CGAM.1 illustrates the study design.



Abbreviations: ePRO = electronic patient reported outcome; SP = study phase; X = injection of investigational product.

[a] ePRO diary reporting will be completed daily during SP II and SP III. "Day" will be defined on a 24- clock day.

[b] Patients begin recording in their diary on a daily basis and call site to schedule Visit 2 and Visit 3.

[c] **Visit 2 will occur during SP II.** The minimum time between Visit 2 and Visit 3 is 5 days.

[d] Scheduling of this office visit, Visit 3, should take into consideration that patients must have at least 14 days to record a baseline assessment of cluster headache attack frequency prior to Visit 3.

[e] Telephone visit 7 days after office visit only for assessment of spontaneously reported AEs.

Figure CGAM.1. Illustration of study design for clinical protocol I5Q-MC-CGAM.

Study Phase I is the screening/washout phase beginning at Visit 1 to the start of SP II and lasting for a minimum of 0 days to a maximum of 65 days. Patients will sign an informed consent form (ICF) at Visit 1 prior to completing study-related initial screening procedures. At Visit 1, patients will discontinue excluded medications, non-fasting laboratory samples will be collected (fasting laboratory samples are collected at visits indicated in the study schedule), and other additional baseline procedures will be performed to determine further eligibility (see Study Schedule, Attachment 1).

At Visit 1, for patients who meet initial screening criteria, an ePRO diary may be dispensed to the patient to record his or her daily cluster headache attack information and allowed use of abortive treatments (collectively referred to as 'daily cluster headache attack information' throughout the protocol). Visit 1 will be considered complete when the last scheduled procedure of the screening assessment for the patient is completed.

The patient will begin recording in his or her ePRO daily diary only after he or she has completed all Visit 1 screening procedures and wash-out of excluded medications and is experiencing a cluster headache attack. The start of the ePRO daily diary recordings represents the beginning of SP II. If not scheduled, the patient should call the office to schedule Visit 2 and Visit 3. There should be a minimum of 5 days between Visit 2 and Visit 3. The site should ensure the patient has recorded ePRO diary data for at least 14 consecutive days prior to Visit 3 to establish his or her baseline cluster headache attack frequency. Sites may schedule Visit 3 beginning 15 days from the start of SPII.

Beginning fifteen days after the start of SP II, an eligibility report will be available from the ePRO vendor for the investigative site personnel to execute that will determine the patient's eligibility based on the patient's ePRO diary data from SP II (refer to the study tool: "Eligibility Determination and Randomization Process" for the full description of valid dates to execute the eligibility report). If the patient is eligible, a blinded randomization authorization code will be listed for the patient. The site personnel, either blinded or unblinded, must log into the Eli Lilly Interactive Web Response System (IWRS) to process the patient's randomization visit (Visit 3). The site should discontinue the non-eligible patient in the IWRS at Visit 3. For patients that are eligible for randomization, the site should enter the randomization authorization code provided by the vendor.

Only the Unblinded Site Personnel should confirm the assigned packages in IWRS. The Unblinded Site Personnel should store the randomization authorization code from the vendor for each patient in a secure pharmacy record for the study.

Study Phase III is a 12-week randomized, double-blind, placebo-controlled treatment phase. Patients who meet all eligibility criteria will be randomized (1:1) at Visit 3 to 1 of the 2 treatment arms (LY2951742 300 mg or placebo).

For each visit in SP III where a dose is administered, the unblinded site personnel will prepare the IP for each patient. Each dose of IP will be administered as 3 subcutaneous (SC) injections at office Visits 3, 6, and 8. After the first administration of IP at Visit 3, the patient should remain in the office for 30 minutes for observation. The site will have scheduled phone visits

(Visits 4 and 7) with the patient approximately 1 week after the first two IP administration visits during SP III to collect spontaneously reported AEs. At Visit 5, the patient will come into the office for the collection of blood samples 2 weeks after the first dose. During SP III, the patient will continue to record his or her cluster headache attack information daily in the ePRO diary.

- For patients who discontinue early in SP III, they should enter SP V.
- For patients who complete SP III, SP IV is an optional 1-year exposure, open-label treatment phase which is described below.
- For patients who choose not to enter SP IV, they should enter SP V.

During SP IV, the unblinded site personnel will continue to prepare the IP for each patient. All patients who enter SP IV will receive open-label monthly injections of LY2951742. All study procedures at Visit 9 must be completed prior to patients receiving the first dose of LY2951742 in SP IV. Patients and investigators will remain blinded to the SP III treatment assignments during SP IV. Each dose of IP will be administered as 3 SC injections at office visits: Visits 9 and 11 through 21. Since placebo patients will be transitioning to LY2951742 at Visit 9, all patients should remain in the office for 30 minutes for observation after administration of IP. Also, during SP IV, some patients may transition to LY2951742 300 mg supplied in 3 prefilled syringes with each syringe containing 100 mg. These patients should remain in the office for 30 minutes for observation after the first prefilled syringe injection. All patients will continue to record his or her cluster headache attack information daily in the ePRO diary until Visit 11.

Study Phase V is a 16-week post-treatment phase for safety follow-up.

7.2. Discussion of Design and Control

This study is a double-blind, placebo-controlled, multi-center study consisting of 5 SPs: a screening phase, a pre-randomization diary phase to assess cluster headache attack frequency for eligibility, a double-blind, placebo-controlled treatment phase to assess treatment outcomes, an open-label extension phase, and a post-treatment follow-up phase to allow for safety monitoring after LY2951742 treatment is stopped.

The proposed duration of the double-blind treatment phase is 3 months, with the primary endpoint assessed from Weeks 1/2 through Weeks 11/12 after the first IP dose. The length of the randomized, double-blind treatment phase (3 months) is believed to be a sufficient duration to assess the efficacy of a cluster headache prevention medication given the mechanism and observed onset of action for CGRP antibodies in migraine (Dodick et al. 2014a, 2014b). The primary measure of weekly cluster headache attack frequency and use of placebo-control is consistent with current published International Headache Society guidelines (IHS 1995). Moreover, a placebo-controlled study with a duration longer than 3 months may not be tolerated by patients suffering from chronic cluster headache.

Because of the severity of patients suffering from chronic cluster headache, a requirement of patients to washout of all preventive treatments before study entry is not feasible. Therefore, the study allows use of certain allowed preventive treatments during the study as long as the patient

is on a stable dose for at least 2 months prior to the pre-randomization diary phase (SP II) and remains on that dose throughout the study.

8. Study Population

All patients must meet the following selection criteria. Eligibility of patients for study enrollment will be based on the results of a screening medical history, physical examination, clinical laboratory tests, ECG, and cluster headache history during SP I and SP II, as described in the Inclusion and Exclusion Criteria sections below. The nature of any co-morbid 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) may be considered for rescreen once, for selected criteria, with approval from Lilly Medical, as described in Section 8.3.

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

8.1. Inclusion Criteria

Patients who meet all of the following inclusion criteria are eligible for enrollment into the study:

[1] Male and female outpatients 18 to 65 years of age inclusive prior to signing informed consent.

[2] At Visit 1, patients must have a history of ***chronic cluster headache*** and distinguished from episodic cluster headache as defined by IHS ICHD-3 beta (ICHD-3 2013) (see Section 8.1.1).

[3] **Do not share this inclusion criteria with potential patients:** During SP II, have a baseline cluster headache attack frequency (based on ePRO vendor eligibility report) of:

[3a] minimum of 8 cluster headache attacks

[3b] maximum of 8 cluster headache attacks per day

Note: a patient with 2 or more consecutive days without an attack during the baseline assessment will be excluded.

[4] For patients on preventive treatment for cluster headache, must be on a stable regimen (with stable dose for at least 2 months prior to the start of SP II), which may include verapamil (maximum daily dosage: 480 mg), lithium, melatonin, valproate, gabapentin, and topiramate. Use of any other preventive treatments for cluster headache is not allowed.

[5] In the opinion of the investigator, spontaneous remission during the double-blind treatment phase is not anticipated based on the patient's history of cluster periodicity.

[6] At Visit 1, are able to distinguish cluster headache attacks from other headaches (that is, tension-type headaches, migraine).

[7] Investigator judges the patient as reliable to follow all study procedures, keep all study visits, and be compliant with study requirements.

[8] Women of child-bearing potential may participate in the study.

[8a] Women of child-bearing potential must test negative for pregnancy (based on a serum pregnancy test) at the time of enrollment and must agree to use a reliable method of birth control during the study and for 5 months following the last dose of IP.

[8b] Male patients agree to use a reliable method of birth control during the study and for 5 months following last dose of IP.

[8c] Women not of child-bearing potential are those who are infertile due to surgical sterilization (at least 6 weeks after surgical bilateral oophorectomy with or without hysterectomy or at least 6 weeks after tubal ligation) confirmed by medical history, or menopause. Menopause is defined as spontaneous amenorrhea for at least 12 months not induced by a medical condition, or spontaneous amenorrhea of 6-12 months and a follicle stimulating hormone (FSH) level >40 mIU/mL.

[9] Have not taken any of the following excluded medications or other treatments for cluster headache within the timeframe noted:

[9a] use within 14 days prior to SP II of any of the following: dihydroergotamine or ergot derivatives, methergine, opioids

[9b] use within 30 days prior to SP II of any of the following: systemic or injected corticosteroids, occipital nerve block, any other cranial or extracranial nerve block, any neurostimulation treatment

Note: Patients will be allowed to use only the following for acute/abortive treatment (treatment initiated at the start of the cluster headache attack to shorten overall attack duration) for their cluster headache attacks: high-flow oxygen, oral triptans, sumatriptan subcutaneous injections, sumatriptan nasal spray, zolmitriptan nasal spray, acetaminophen and NSAIDs.

[10] Throughout the study (informed consent through Visit 24), agree to refrain from the use of drugs of abuse per United States Federal Guidelines (Schedule I) such as, but not limited to, cannabinoids, cannabis, psilocybin (mushrooms), LSD and 2-bromo-LSD.

[11] 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, LinkedIn, Google+, etc.) until the entire trial has completed.

[12] Have given written informed consent.

8.1.1. Disease Diagnostic Criteria

The planned patient population includes adult outpatients (18 to 65 years of age inclusive) who meet the *International Headache Society's International Classification of Headache Disorders, Third Edition, beta version* (*ICHD-3 2013)* diagnostic criteria for **Chronic Cluster Headache** (as shown below).

ICHD-3 beta diagnostic criteria for Cluster Headache:

A. At least five attacks fulfilling criteria B–D

B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes (when untreated)*

C. Either or both of the following:

   1. at least one of the following symptoms or signs, ipsilateral to the headache; (a) conjunctival injection and/or lacrimation; (b) nasal congestion and/or rhinorrhea; (c) eyelid oedema; (d) forehead and facial sweating; (e) forehead and facial flushing; (f) sensation of fullness in the ear; and (g) miosis and/or ptosis

   2. a sense of restlessness or agitation

D. Attacks have a frequency between one every other day and 8 per day for more than half of the time when the disorder is active

E. Not better accounted for by another ICHD-3 diagnosis.

*During part (but less than half) of the time-course of cluster headache, attacks may be less severe and/or of shorter or longer duration.

ICHD-3 beta diagnostic criteria for Chronic Cluster Headache:

A. Attacks fulfilling criteria for **Cluster Headache**, and criterion B below.

B. Occurring without a remission period, or with remissions lasting <1 month, for at least 1 year.

8.2. Exclusion Criteria

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

[13] Current enrollment in, or discontinuation within the last 30 days prior to Visit 1 from, a clinical trial involving any investigational drug or device, or concurrent enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.

[14] Current use or any prior exposure to any CGRP antibody (including LY2951742), any antibody to the CGRP receptor, or antibody to nerve growth factor (NGF) including past participation in a clinical trial investigating CGRP, CGRP receptor, or NGF antibodies.

[15] Patients who are taking other therapeutic antibodies or are expected to take during the course of the study (for example, adalimumab, infliximab, trastuzumab, bevacizumab, etc.). Prior use of other therapeutic antibodies is allowed if an adequate wash-out has occurred (≥5 half-lives) prior to SP II.

[16] Any of the following headache-related or pain-related conditions are exclusionary:

[16a] Current diagnosis of Medication Overuse Headache as defined by ICHD-3 beta within 3 months prior to Visit 3. Note: daily triptan use for daily cluster headache attacks is allowed provided it is not resulting in a medication overuse headache (MOH) of some other headache type.

[16b] Lifetime history of migraine variants that could implicate or could be confused with ischemia; specifically, hemiplegic (sporadic or familial) migraine, ophthalmoplegic migraine, and basilar-type migraine defined by ICHD-3 beta.

[16c] Are taking indomethacin and/or are suspected of having another distinct trigeminal autonomic cephalalgia such as hemicrania continua, paroxysmal hemicrania, or short-lasting unilateral neuralgiform headache attacks (SUNCT or SUNA).

[16d] Have other significant pain problem that might confound the study assessments in the opinion of the investigator.

[17] Patients who have taken botulinum toxin type A or type B, that was administered in the head or neck area, within 4 months of SP II for treatment of cluster headache or other disorders, or for cosmetic use.

[18] Any (lifetime) treatment with deep brain stimulation.

[19] 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 medication(s).

[20] Are considered by the investigator to be at significant risk for suicide.

[21] Women who are pregnant or nursing.

[22] Any of the following cardiovascular-related conditions are exclusionary:

[22a] Prior to Visit 3 (randomization), have ECGs showing acute abnormalities of:

i. evidence of delayed ventricular repolarization including but not limited to a corrected QT (Bazett's QT interval [QTcB]) interval >470 msec for women and >450 for men, **and/or**

ii. evidence of atrioventricular (AV) depolarization of PR>220, or conduction delay of QRS>120, **and/or**

iii. evidence of ischemia or any of the qualitative findings indicative of ST or J-point elevation, excluding those findings consistent with early repolarization (non-ischemic)

[22b] History of myocardial infarction (MI), unstable angina (UA), 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.

[22c] Any lifetime history of vasospastic angina or stroke, or recent history (6 months) of emergency room visit for chest pain in which an ischemic or cardiac event was not ruled out.

[22d] Clinical evidence of peripheral vascular disease (for example, Buerger's Disease) or a diagnosis of Raynaud's Phenomenon.

[22e] Have any history of intracranial or carotid aneurysm, intracranial hemorrhage, or stroke.

[22f] Have uncontrolled high blood pressure, characterized by systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg on 2 or more blood pressure assessments prior to Visit 3.

[23] Any of the following medical conditions are exclusionary:

[23a] Have a lifetime history of seizures, except for childhood febrile seizures.

[23b] Have a history or presence of any other medical illness including but not limited to any 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.

[23c] Prior to Visit 3, patients with an elevation of ≥2X upper limit of normal (ULN) for alanine aminotransferase (ALT), or ≥1.5X ULN total bilirubin (TBL) or alkaline phosphatase (ALP) may be retested. The patient's results must be discussed and judged not clinically significant by Lilly Medical prior to enrollment.

[23d] Patients with a history of an intracranial tumor or head trauma must be discussed and judged not to indicate a medical problem that would preclude study participation by Lilly Medical prior to enrollment.

[24] Any of the following drug- or alcohol-related conditions are exclusionary:

[24a] Patients who do not agree to abstain from alcohol consumption during SP II and SP III. However, patients are encouraged to abstain from alcohol consumption throughout the entire study.

[24b] History of drug, alcohol, opioid, or barbiturate abuse/dependence within 1 year prior to SPII (excessive or habitual use as judged by the Investigator), or currently using drugs of abuse (including, but not limited to opioids, barbiturates and cannabis), or any prescribed or over-the-counter (OTC) medication in a manner that the Investigator considers indicative of abuse/dependence. This exclusion criterion does not apply to tobacco and caffeine.

[24c] History of use of psilocybin (mushrooms), LSD, or 2-bromo-LSD within 2 months prior to SP II.

[24d] Have a positive urine drug screen (UDS) for any substances of abuse prior to randomization. Note: One retest may be performed if the UDS 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 3.

[25] Completion of less than 5 of 7 days of the daily ePRO diary entries for each week during the baseline assessment (defined in Statistical Methods) as evidence of inadequate compliance.

[26] Employees of Eli Lilly and Company or investigational site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, parent, child or sibling, whether biological or legally adopted.

[27] Known hypersensitivity to multiple drugs, monoclonal antibodies or other therapeutic proteins, or to LY2951742 or to any of the inactive ingredients.

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

8.2.1. Rationale for Exclusion of Certain Study Candidates

Exclusion Criterion 13 excludes patients using drugs that cannot be mapped to a standard drug dictionary, or for which little data are known to analyze the potential relationship of AEs or drug interactions. Exclusion Criterion 14 eliminates patients who have been exposed to LY2951742, NGF, any CGRP antibody, and any CGRP receptor antibody and could induce a potential bias or compromise interpretation or integrity of the data. Exclusion criteria 15, 16, 19 through 23, 27, and 28 are for excluding patients with significant illnesses or conditions that may affect their safety or confound study results. Exclusion criteria 17 and 18 exclude patients with current or prior therapies that could negatively impact the safety of the patient or influence the analysis of the results. Exclusion Criterion 24 excludes treatments or illicit substances that may impact study results. Exclusion Criterion 25 ensures that patients are able and willing to follow the protocol schedules and procedures. Exclusion Criterion 26 prevents conflict of interest in study patients.

8.3. Rescreening

Individuals who do not meet the criteria for participation in this study (screen failure) may be considered for rescreen once, with approval from Lilly Medical, for only the following criteria:

- 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 study enrollment.
- Inclusion Criterion 3; if a patient fails eligibility due solely to the eligibility report not being executed within the required time frames, the patient may be considered for rescreen.
- Inclusion Criterion 3b; if a patient fails eligibility due to the occurrence of >8 cluster headache attacks per day, the patient may be considered for rescreen.
- Inclusion Criterion 3 "Note" section only: a patient with 2 or more consecutive days without an attack during the baseline assessment may be considered for rescreen.
- Inclusion Criterion 4, as well as other concomitant medications that require a stable dose for a specific duration prior to SP II; patients may be rescreened if additional time is needed to meet the duration requirement.
- Inclusion Criterion 9
- Exclusion Criterion 13
- Exclusion Criterion 15; patients with inadequate washout may be rescreened following an appropriate washout period.
- Exclusion Criterion 17
- Exclusion Criterion 20; these screen-fail patients may be considered for rescreen if the following conditions are met:
    - The patient was referred to an appropriate mental health professional and received treatment as necessary.
    - At least 6 months has elapsed since the screen-fail.
    - Are not considered by the investigator to be at significant risk for suicide at time of rescreening.
- Exclusion Criterion 21.
- Exclusion Criterion 22f; patients with uncontrolled high blood pressure may be considered for rescreen once their blood pressure is controlled in the opinion of the investigator and at <160/100; any use of antihypertensive medication and dose must be stable for at least 2 months prior to SP II.
- Exclusion Criterion 24d; if a patient fails eligibility due to a positive UDS, the patient may be considered for rescreen.
- Exclusion Criterion 28.

- Patients using concomitant medication(s) that require a wash-out prior to SP II, may be rescreened once an adequate wash-out (for example, 5 half-lives) has occurred.

The interval between screening and rescreening must be sufficient to meet the required 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.

8.4. Discontinuations

8.4.1. Discontinuation of Inadvertently Enrolled Patients

The criteria for enrollment must be followed explicitly. If the investigator site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the sponsor must be notified. If the sponsor identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the sponsor clinical research physician (CRP) and the investigator to determine whether the patient may continue in the study, with or without IP. Inadvertently enrolled patients may be maintained in the study and on IP when the Lilly CRP agrees with the investigator that it is medically appropriate for that patient. The patient may not continue in the study with or without IP if the Lilly CRP does not agree with the investigator's determination it is medically appropriate for the patient to continue. The investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without IP. The decision of whether to allow an inadvertently enrolled patient to continue in the study, with or without IP, will be documented in the study issues and decisions log.

8.4.2. Discontinuation of Investigational Product

Discontinuation of the IP for abnormal liver tests should be considered by the investigator when a patient meets 1 of the following conditions after consultation with the Lilly designated medical monitor:

- ALT or aspartate aminotransferase (AST) >8X ULN
- ALT or AST >5X ULN for more than 2 weeks
- ALT or AST >3X ULN and TBL level >2X ULN or prothrombin time >1.5X ULN
- ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

It is also recommended to consider discontinuation in a patient with ALP elevation which meets one of the following criteria and is deemed to be of liver origin and drug related:

- ALP >3X ULN
- ALP >2.5X ULN and TBL >2X ULN
- ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Patients who discontinue the IP early should enter the post-treatment phase. If the patient refuses to enter the post-treatment follow-up phase, they will have end-of-therapy procedures performed as shown in the Study Schedule (Attachment 1).

8.4.3. Patient Discontinuation from the Study

All patients are free to withdraw from participation in this study at any time and for whatever reason, specified or unspecified, and without prejudice.

A patient may be discontinued from the study for any of the following reasons:

- Enrollment in any other clinical trial involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Investigator Decision
    - The investigator decides that the patient should be discontinued from the study.
    - If the patient, for any reason, requires treatment with another not allowed therapeutic agent, between 30 days prior to SP II through SP IV, for the prevention of cluster headache, the investigator must discontinue that patient from the study prior to introduction of the new agent.
- Subject Decision
    - The patient requests to be withdrawn from the study.
- Sponsor Decision
    - Lilly or its designee stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).
- Adverse Event
    - If the investigator decides that the patient should be withdrawn because of an SAE or a clinically significant laboratory value, the IP is to be discontinued and appropriate measures are to be taken. Lilly or its designee is to be alerted immediately. Refer to Safety Evaluations Section 10.2.

Patients who discontinue the study early during SP III and SP IV should enter the post-treatment period; those patients who discontinue the study early during SP V will have end-of-study procedures performed as shown in the Study Schedule (Attachment 1).

8.4.4. Patients Lost to Follow-Up

A patient 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 patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

8.4.5. Discontinuation of Study Sites

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

8.4.6. 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.

9. Treatment

9.1. Treatments Administered

This study includes 2 treatment groups during SP III: placebo or LY2951742 300 mg. Each treatment group will be administered three 1 ml SC injections, by qualified site personnel, every 30 days. The designated unblinded site personnel responsible for preparing LY2951742 and placebo doses should refer to the Pharmacy Binder Dosing Instructions for LY2951742 Drug Product, 75 mg for the preparation and dosing instructions for both LY2951742 and placebo.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the investigational agent(s) to the site personnel
- verifying that instructions are followed properly
- maintaining accurate records of IP dispensing and collection
- 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 investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose clinical trial materials.

Possible injection sites include the abdomen, thigh, and upper arm. Buttocks may also be used, if more appropriate for SC injection than the other sites.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the IP so that the situation can be assessed.

9.2. Materials and Supplies

LY2951742 for injection, 75 mg, will be supplied by the sponsor as a lyophilized formulation in a glass vial (at least through SP III) and as pre-filled syringes (during SP IV) in accordance with Current Good Manufacturing Practice (cGMP). Lyophilized material will be utilized during SP III for all patients and during SP IV until prefilled syringes are available for SP IV.

The designated unblinded site personnel is responsible for preparing LY2951742 from the lyophilized formulation and placebo injections according to the Study CGAM Pharmacy Binder Dosing Instructions for LY2951742, 75 mg.

9.2.1. LY2951742 for Injection Supplied as Lyophilized Powder

Storage and Stability of Lyophilized Powder

The drug product is composed of the active ingredient, LY2951742 in citrate buffer in addition to other inactive ingredients. Unreconstituted glass vials of LY2951742 for injection, 75 mg, as lyophilized powder are stable and must be stored in a refrigerator at 2 to 8° C (35.6° to 46.4° F).

Administration of LY2951742 Prepared from Lyophilized Powder

LY2951742 or placebo will be prepared by the designated unblinded site personnel, and each dose will be identified as IP without identification of the drug or dose.

Approximately 20 minutes prior to preparing for administration to patients, the vials should be removed from the 2 to 8° C storage area and allowed to equilibrate at ambient conditions. After dose preparation, immediate transfer to the syringe is recommended for administration. Subsequently, the unblinded site personnel should complete the overlay label and apply onto the prepared syringes prior to providing the syringes to the blinded site personnel.

Drug product must be administered within 6 hours when stored at room temperature.

Individuals involved with IP preparation will not be involved in any clinical aspects of the study, including IP administration, clinical evaluations, and AE assessments.

9.2.2. LY2951742 for Injection Supplied as Prefilled Syringe

Packaging, Preparation, Labeling, and Storage

LY2951742 solution for injection will be supplied by the sponsor or its designee in accordance with cGMP. LY2951742 will be supplied as an injectable solution in a 1-mL, single-dose, disposable manual syringe. Each syringe of LY2951742 will be designed to deliver 100 mg of LY2951742. The prefilled syringes of LY2951742 for injection, 100 mg/1.0 mL should be stored in the refrigerator (2 to 8° C). The prefilled syringes should be removed from the refrigerated storage and allowed to equilibrate to room temperature for approximately 30 minutes before administration.

Administration of LY2951742 using Prefilled Syringe

Injections will be administered by the clinical staff. A dose will consist of three 1-mL prefilled syringes, with each syringe containing 100 mg of LY2951742, for a total of 300 mg LY2951742.

9.3. Method of Assignment to Treatment

A patient number will be assigned to each patient after the ICF is signed and dated. This identification number must appear on all patient-related documents.

Patients who meet all criteria for enrollment will be randomized to double-blind treatment at Visit 3. Assignment to treatment groups will be determined by a computer-generated random sequence using an IWRS. The IWRS will be used to assign double-blind IP to each patient in SP III and open-label IP in SP IV. The Unblinded Site Personnel should confirm the assigned packages prior to preparation of double-blind IP in SP III.

The IWRS system will be programed following the dynamic allocation (minimization) method of Pocock and Simon (1975) to balance the treatment arms for the factors of gender, average daily attack frequency (≤4 attacks per day, >4 attacks per day), verapamil (yes/no), and investigative site. The purpose of the algorithm is to maintain approximately the same proportion of gender, verapamil use, and baseline average daily attack frequency in each arm of the study, and to balance (based on the treatment allocation ratio) the number of patients assigned to treatment arms within each investigative site.

9.4. Rationale for Selection of Doses in the Study

The dose level proposed for the studies of LY2951742 in cluster headache is 300 mg administered every 30 days. Based on inhibition of capsaicin-induced dermal blood flow (CIDBF) and PK/PD modeling of plasma CGRP concentrations (target engagement) from prior studies, it is presumed that this dose regimen will provide a high degree of pharmacological activity (about 90% decrease in unbound plasma CGRP concentrations; >ED90 based on CIDBF), and be sufficient to test the effectiveness of LY2951742 for the treatment of cluster headache. A dose of 300 mg every 30 days is predicted to replicate the exposure and have the same effect on CIDBF and unbound plasma CGRP as 150 mg every two weeks, which yielded evidence of efficacy in migraine (Study ART-01). The safety and tolerability of LY2951742 supports dosing at 300 mg every 30 days.

9.5. Selection and Timing of Doses

Patients in this study will be assigned to 1 of 2 treatment groups: placebo or LY2951742 300 mg. Investigational product (LY2951742 or placebo) will be administered as 3 SC injections every 30 days for a total of 3 administrations during SP III.

During SP IV, LY2951742 will be administered as 3 SC injections every 30 days for a total of 12 administrations.

Investigational product injections should be administered after all other study procedures are completed for the given visit.

9.6. Continued Access to Investigational Product

LY2951742 will not be made available to patients after conclusion of the study.

9.7. Blinding

This is a double-blind study. To preserve the blinding of the study, only a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.

After the reporting database is locked for statistical analysis of the double-blind treatment phase, a limited number of sponsor personnel will be unblinded to complete the study report and prepare for regulatory submission. However, any sponsor personnel continuing with the management and oversight of the trial will remain blinded to patients' previous treatment assignment.

Emergency unblinding for AEs may be performed through the IWRS. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All unblinding events are recorded and reported by the IWRS.

If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study. In cases where there are ethical reasons to have the patient remain in the study, the investigator must obtain specific approval from a Lilly CRP for the patient to continue in the study.

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

9.8. Concomitant Therapy

Patients will be allowed to use only the following for their acute/abortive treatment for cluster headache attacks: high-flow oxygen; oral triptans, sumatriptan SC injections; sumatriptan nasal spray; zolmitriptan nasal spray; acetaminophen and NSAIDs. Patients will also be allowed to use preventive treatment for cluster headache (**provided that they are on a stable dose for at least 2 months prior to the baseline phase, and that the dose remains stable throughout the study**), limited to: verapamil ≤480 mg/day, lithium, melatonin, valproate, gabapentin, and topiramate. No other medications, treatments, procedures, or other interventions for either the abortive or preventive treatment of cluster headache are permitted. Patients will be asked to record use of their allowed standard abortive treatments in their daily ePRO diary. Patients use of allowed preventive treatments will be captured along with other allowed medications in the concomitant medication eCRF.

A list of allowed/not allowed medications are provided separately from the protocol. Site personnel should call a designated Lilly representative with any questions regarding medications not specifically cited in the list of allowed/not allowed medications. Any changes in the list of allowed/not allowed medications will be communicated to investigators and will not constitute a protocol amendment.

Patients should be instructed to consult with the investigator or study coordinator at the site before taking any new prescribed medications, OTC medications, or supplements. If the need for other concomitant medication arises, inclusion or continuation of the patient in the study may be at the discretion of the investigator after consultation with CRP/clinical research scientist (CRS) or delegate.

10. Efficacy Measures, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Study procedures and their timing (including tolerance limits for timing) are summarized in the Study Schedule (Attachment 1).

10.1. Efficacy Measures

10.1.1. Primary Efficacy Measure

ePRO Diary: Patients will be asked to record the number of cluster headache attacks in their daily ePRO diary during SP II and SP III. Patients who enter SP IV will continue to diary on a daily basis through Visit 11. Information regarding abortive medication use, cluster headache attack duration, and cluster headache attack pain severity will also be recorded. Pain severity will be rated using a 5-point pain scale, where 0=no pain, 1=mild pain, 2=moderate pain, 3=severe pain, and 4=very severe pain (Sumatriptan Cluster Headache Study Group 1991). Patients should record all cluster attacks regardless of attack duration.

10.1.2. Secondary Efficacy Measure

The Patient Global Impression of Improvement requests patients to: Mark the box that best describes your cluster headache condition since you started taking this medicine. The options in the displayed boxes are represented on a seven-point scale, with 1=very much better and 7=very much worse (Guy 1976).

10.2. Safety Evaluations

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

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

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to the study treatment or the study, or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

10.2.1. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent.

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

Cases of pregnancy that occur during maternal or paternal exposures to IP should be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

Study site personnel will record the occurrence and nature of each patient's pre-existing conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

After the ICF is signed, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs. All AEs related to protocol procedures are reported to Lilly or designee via electronic case report form (eCRF) into the Lilly designated electronic data capture system (EDC).

In addition, all AEs occurring after the patient receives the first dose of IP must be reported to Lilly or its designee via eCRF.

Any clinically significant findings from ECGs, laboratory measurements, vital sign measurements, other procedures, and so on that result in a diagnosis should be reported to Lilly or its designee using eCRF.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure, cluster headache, IP, using eCRF.

The investigator decides whether he or she interprets the observed AEs as either related to disease, to the study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to the IP, the following terminologies are defined:

- **Related**: a direct cause and effect relationship between the study treatment and the AE is likely.
- **Possibly related**: a cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible.
- **Unrelated**: without question, the AE is definitely not associated with the study treatment.

For analytical purposes only, according to Lilly's standard operating procedures all "related" and "possibly related" AEs and SAEs will be defined as related to the IP.

10.2.1.1. Serious Adverse Events

Serious adverse event collection begins after the patient has signed informed consent and has received IP. If a patient experiences an SAE after signing informed consent, but prior to receiving IP, the event will NOT be reported as serious unless the investigator feels the event may have been caused by a protocol procedure.

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

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

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse events occurring up to and including the patient's last study visit will be collected, regardless of the investigator's opinion of causation, in the clinical data collection database and the pharmacovigilance system at the sponsor.

The investigator does not need to actively monitor patients for AEs once the trial has ended, unless provided otherwise in the protocol. However, if an investigator becomes aware of SAEs occurring to a patient after the patient's participation in the trial has ended, the investigator should report the SAEs to the sponsor, regardless of the investigator's opinion of causation, and the SAEs will be entered in the pharmacovigilance system at the sponsor.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the trial may be found in the IB.

10.2.1.1.1. Suspected Unexpected Serious Adverse Reactions

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

10.2.2. Other Safety Measures

10.2.2.1. Electrocardiograms

For each patient, 12-lead digital ECGs will be collected according to the Study Schedule (see Attachment 1) as single ECGs for overread. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs than expected at a particular time point is allowed when needed to ensure high quality records.

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 patient is still present, to determine whether the subject meets entry criteria and for immediate subject management, should any clinically relevant findings be identified.

After enrollment, if a clinically significant increase in the QT/corrected QT (QTc) interval from baseline, or other clinically significant quantitative or qualitative change from baseline, is present, the investigator will assess the patient for symptoms (for example, palpitations, near syncope, syncope) and to determine if the subject can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation.

All digital ECGs will be electronically transmitted to a designated central ECG laboratory. A cardiologist at the central ECG laboratory will then conduct a full overread on the ECG (including all intervals); a report based on data from this analysis will be issued to the investigative site. All data from the overreads will be placed in the Lilly database for analytical and study report purposes.

When there are differences in ECG interpretation between the investigator (or qualified designee) and the cardiologist at the central ECG laboratory, the investigator (or qualified designee's) interpretation will be used for study entry and immediate patient management. Interpretations from the cardiologist at the central ECG laboratory will be used for data analysis and report writing purposes.

The investigator (or qualified designee) must document his/her review of the ECG printed at the time of evaluation, the final overread ECG report issued by the central ECG laboratory, and any alert reports.

10.2.2.2. Vital Signs

Blood pressure and pulse will be collected in triplicate according to the Study Schedule (see Attachment 1) and at unscheduled office visits. All sites will be provided with an automated blood pressure machine with several cuff sizes. The following guidelines will be used by investigative sites when measuring vital signs:

- Blood pressure and pulse must be measured before any blood draws.

- Blood pressure will be measured in sitting position with both feet resting on the floor after the patient has rested for at least 5 minutes.
- Blood pressure will be measured with a cuff that is appropriate to the size of the patient.
- Use the same arm for blood pressure collection throughout the study.
- Arm with cuff must be supported at approximately the heart level.
- Three sitting blood pressures and pulse measurements will be collected at approximately 30 to 60 second intervals.

10.2.2.3. Columbia-Suicide Severity Rating Scale, Self-Harm Supplement Form, and Self-Harm Follow-up Form

The C-SSRS and Self-Harm Supplement Form (SHSF) will be administered to assess and evaluate patients for suicide-related events (behavior and/or ideation) according to the Study Schedule (see Attachment 1) and at unscheduled office visits. The C-SSRS captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period (Posner et al. 2011). The scale includes suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior occurred. The SHSF captures the number of discrete events of suicidal behavior, possible suicidal behavior, or nonsuicidal self-injurious behavior and must be completed at every visit. Additionally, the Self-Harm Follow-up Form (SHFU) will be completed at any visit, including screening/baseline visits, when a suicidal or non-suicidal self-injurious behavior is identified. At any time during the study, if a patient is considered to be at significant risk for suicide by the investigator, prompt referral of the patient to a mental health professional should be considered.

10.2.3. Safety Monitoring

The Lilly CRP will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CRP/CRS will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist, and periodically review:

- trends in safety data
- laboratory analytes
- adverse events including monitoring of injection site reactions, allergic reactions, and infections

If a study patient/subject experiences elevated ALT ≥3X ULN, ALP ≥2X ULN or elevated TBL ≥2X ULN, clinical and laboratory monitoring should be initiated by the investigator. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient/subject safety and comply with regulatory guidance, the investigator is to consult with the Lilly designated medical monitor regarding collection of specific recommended clinical information and follow-up laboratory tests (see Attachment 3).

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the data monitoring committee (DMC) (an advisory group for this study formed to protect the integrity of data) can conduct additional analyses of the safety data prior to completion of the double-blind treatment phase.

10.2.4. Complaint Handling

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

For blinded studies, all product complaints associated with material packaged, labeled, and released by Lilly or delegate will be reported.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

10.3. Sample Collection and Testing

Attachment 1 lists the schedule for sample collections in this study.

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

Attachment 3 lists the selected tests that may be obtained in the event of a treatment-emergent hepatic abnormality.

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

10.3.1. Samples for Study Qualification and Health Monitoring

Blood and urine samples will be collected to determine whether patients/subjects meet inclusion/exclusion criteria and to monitor patient/subject health.

Investigators must document their review of each laboratory safety report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

10.3.2. Samples for Biomarker Research

Biomarker research is used to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of patient response (including safety) and clinical outcome.

Specimen storage is incorporated in clinical trials to enable examination of these questions through measurement of biomolecules including deoxyribonucleic acid (DNA), ribonucleic acid (RNA), proteins, lipids, other cellular elements. Where local regulations and ERBs allow, these samples will be collected for biomarker research as discussed below and specified in the Study Schedule (Attachment 1).

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

CCI [redacted]

10.3.4. Samples for Non-genetic Biomarker Research

Samples will be collected for potential non-pharmacogenetic biomarker research. Plasma samples (CCI [redacted] K+/EDTA plasma storage samples) and whole blood RNA (RNA storage sample) will be collected at the times specified in the Study Schedule (see Attachment 1) and in the amounts specified (see Attachment 4).

Samples may be used for research on the drug target, disease process (specifically including cluster headache with its variants and more broadly including pain conditions for which CGRP may be relevant), pathways associated with cluster headache, mechanism of action of LY2951742, and/or research method or in validating diagnostic tools or assay(s) related to cluster headache.

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

10.3.5. Samples for Immunogenicity Research

Blood samples for immunogenicity testing will be collected to determine antibody production against LY2951742. Immunogenicity will be assessed by a validated assay designed to detect ADA in the presence of the investigational product. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of LY2951742.

Samples, including residual aliquots, may be stored for a maximum of 15 years following last patient visit for the trial at a facility selected by the sponsor to enable further analysis of immune responses to the LY2951742. The duration allows the sponsor to respond to regulatory requests related to the LY2951742.

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10.4. Appropriateness of Measurements

All efficacy and safety assessments have been well documented and are generally regarded as reliable, accurate, and relevant in this patient population.

11. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate.
- Sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the eCRFs and study procedures.
- Make periodic visits to the study site.
- Be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax.
- Review and evaluate eCRF data and use standard edits to detect errors in data collection.
- Conduct a quality review of the database.

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of ECGs, laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

11.1. Data Capture System

An EDC system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided EDC system.

Some or all of a subject's data will be directly entered into the eCRF at the time that the information is obtained. In instances where the data cannot be directly data entered, the site will maintain source documentation in the trial files and the subject's data will be transcribed into the eCRF. Any data for which the eCRF will serve as the source document, or any other data not entered directly into the eCRF (for example, ePRO interactive voice response system [IVRS] or patient rated outcomes), will be identified and documented by site in the site's trial file. For data handled by a data management third party organization (TPO), eCRF data and some or all data that are related will be managed and stored electronically in the TPO system. Subsequent to the final database lock, validated data will be transferred to the sponsor.

For data handled internally, eCRF data and some or all data that are related will be managed by the sponsor and stored electronically in the sponsor's system.

In this study, patient cluster headache data will be collected directly via an ePRO diary as part of an ePRO/Clinical Outcome Assessment (COA) system. In addition, the patient-rated PGI-I; clinician-rated C-SSRS, SHSF and SHFU are collected at office visits as part of the ePRO/COA system. .

If ePRO/COA records are stored at a third party site, investigator sites will have continuous access to the source documents during the study and will receive an archival copy at the end of the study for retention.

Any data for which the ePRO/COA instrument record will serve to collect source data will be identified and documented by each site in that site's study file.

Case report form data collected by the TPO will be encoded by the TPO and stored electronically in the TPO's database system. Validated data will subsequently be transferred to the sponsor using standard Lilly file transfer processes.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly generic labs system. Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

The study is planned to have a minimum of approximately 162 patients randomized 1:1 to placebo or LY2951742 with the opportunity to increase the final sample size at an interim analysis if indicated in order to maintain a well powered study. To preserve blinding, details of the sample size and power calculations are omitted from this protocol and are provided in a separate document to the ERB.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

Unless otherwise specified, efficacy analyses will be conducted on an ITT population, which include all patients who are randomized and receive at least 1 dose of IP. Patients in the ITT population will be analyzed according to the treatment group to which they were randomized. Safety analyses for SP III and exposure will be conducted on the safety population, which also includes all patients who are randomized and receive at least 1 dose of study drug. However, patients will be analyzed by actual study treatment received most often (modal treatment; placebo or LY2951742) during the double-blind treatment phase. Safety analyses during LY2951742-treated time and LY2951742-treated time plus post-treatment time will be conducted on the LY2951742-treated population, which includes all patients who receive at least 1 dose of LY2951742. When mean 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. Additional analyses population for analyses of study Phase IV and Phase V will be described in the SAP.

Baseline will be the last 14 days in the eligibility report (pre-randomization diary phase). An additional baseline defined at Visit 9 (the first visit of the open-label phase) may be used for some analyses. This, in addition to details for handling missing data, will be further outlined in the SAP.

Treatment effects will be evaluated based on a 2-sided significance level of 0.05 for all the efficacy and safety analyses. The 95% CIs for the difference in least-square means (LSMeans) between treatment groups will be presented. Adjustments for multiple comparisons for the analyses corresponding to the primary and gated secondary objectives are described in the sections on the primary and secondary efficacy analyses below. There will be no adjustments for multiplicity for analyses of other data.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

Statistical analysis of this study will be the responsibility of Lilly or its designee. SAS® software will be used to perform most or all statistical analyses.

12.2.2. Patient Disposition

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

The number and percentage of ITT patients who complete the study or discontinue early will be tabulated for both treatment groups for SP III, SP IV, and SP V both overall and by visit. Reasons for discontinuation will be compared between treatment groups for SP III using Fisher's exact test. Descriptive statistics only will be presented for the treatment groups in SP IV and SP V.

12.2.3. Patient Characteristics

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

- Demographic (age, gender, race, ethnicity, country, region, height, weight, BMI)
- Baseline disease characteristics, such as:
    - number of weekly cluster headache attacks
    - number of times an abortive medication was taken
    - average severity of cluster headache pain
    - average cluster headache attack duration
    - number of times an abortive medication was taken per cluster headache attack
- Baseline alcohol, tobacco, caffeine and nicotine consumption
- Medical history and pre-existing condition
- Prior cluster headache history in last 7 days prior to Visit 1

Comparisons between treatment groups will be performed using Fisher's exact tests for categorical data and analysis of variance (ANOVA) with treatment and pooled investigative sites as independent variables in the model for continuous data.

Medical history and pre-existing conditions will be summarized by preferred term (PT) within system organ class (SOC), and comparison between treatment groups will be performed using Fisher's exact test.

12.2.4. Concomitant Therapy

The proportion of patients who received concomitant medication (including preventive medication) and abortive medications for cluster headache attacks will be summarized separately

for all ITT patients for SP III, SP IV and SP V. Treatment group comparisons will be done using Fisher's exact test for SP III with ITT population. Descriptive statistics only will be presented for the treatment groups in SP IV and SP V.

12.2.5. Treatment Compliance

Treatment compliance will be calculated for SP III and SP IV as:

$$\frac{\text{number of full doses received} * 100}{\text{number of intended full doses}}$$

Comparisons between treatments for treatment compliance will be performed using an ANOVA with treatment and pooled investigative site in the model.

12.2.6. ePRO Diary Compliance

The ePRO diary compliance at each biweekly interval (including baseline, Weeks 1/2, 3/4, 5/6, 7/8, 9/10, 11/12, 13/14, and 15/16) and for SP III (Weeks 1/2 through 11/12) will be calculated. Diary compliance at each interval is calculated as:

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

The diary entry can only be saved and submitted after all the required ePRO questions are answered, so the actual number of diary entry days represents the total number of days with non-missing answer to all the required cluster headache attack ePRO questions. The expected number of diary entry days will be calculated as (the last calendar date - the first calendar date in each interval +1).

Comparisons between diary compliance for each interval separately will be performed using an ANOVA with treatment and pooled investigative site in the model.

Compliance will also be listed by biweekly interval for each patient.

12.2.7. Primary and Gated Outcome and Methodology

12.2.7.1. Primary Outcome

The primary analysis will be conducted by a REML-based, MMRM analysis using all the longitudinal observations at Weeks 1/2, 3/4, 5/6, 7/8, 9/10, and 11/12 intervals. The analysis of the primary outcome will be the main effect of treatment between LY2951742 300 mg and placebo during the 12-week double-blind treatment phase from a repeated measures analysis on mean change from baseline in the weekly attack frequency. This provides the average treatment effect across the 12-week double-blind treatment phase.

The model for the primary analysis will include the fixed, categorical effects of treatment, gender, verapamil use, pooled investigative site, week, and treatment-by-week interaction, as well as the continuous, fixed covariates of baseline value. An unstructured covariance structure will be used to model the within-patient errors. The Kenward-Roger (Kenward and Roger 1997)

approximation will be used to estimate denominator degrees of freedom. If the model does not converge with both the Hessian and the G matrix being positive definite under the default fitting algorithm used by PROC MIXED, the Fisher's scoring algorithm will be implemented by specifying the SCORING option in SAS®. If the model still fails to converge, the model will be fit using covariance matrices of the following order specified by a decreasing number of covariance parameters until convergence is met:

- Heterogeneous Toeplitz
- Heterogeneous First-order autoregressive
- Toeplitz
- First-order autoregressive

If necessary, both the default and the scoring fitting algorithms will be used in the prespecified order before proceeding to the next covariance structure in the sequence. For models where the unstructured covariance matrix is not utilized, the sandwich estimator (Diggle and Kenward 1994) will be used to estimate the standard errors of the fixed effects parameters. The sandwich estimator is implemented by specifying the EMPIRICAL option in SAS®. When the sandwich estimator is utilized, the Kenward-Roger approximation for denominator degrees of freedom cannot be used. Instead, the denominator degrees of freedom will be partitioned into between-subject and within-subject portions by the DDFM=BETWITHIN option in SAS®.

If the sample size is increased as a result of the interim analysis, the CHW procedure (Cui et al. 1999) will be applied to the primary endpoint to control the type I error at a one sided α=0.025 significance level. The CHW method ensures strong control of type 1 error when the sample size is increased in a data dependent manner.

If the sample size is increased as a result of the interim analysis, an unadjusted point estimate for the primary efficacy analysis will be calculated and reported. A median unbiased point estimate and a stage-wise adjusted confidence interval for the primary efficacy analysis will be calculated and reported based on the approach described in Brannath et al. (2009) to assess sensitivity of the point estimate.

12.2.7.2. Gated Secondary Outcomes

For the gated secondary outcome of the estimated mean proportion of patients with a 50% or greater reduction from baseline in weekly cluster headache attack frequency during the 12-week double-blind treatment phase, a categorical, pseudo-likelihood-based repeated measures analysis of data at Weeks 1/2, 3/4, 5/6, 7/8, 9/10, and 11/12 will be used. The endpoint for comparing LY2951742 with placebo will be estimated as the main effect of treatment from the categorical MMRM analysis across Weeks 1 to 12. This analysis will be implemented using the GLIMMIX procedure in SAS® to compare treatments and include the fixed, categorical effects of treatment, gender, verapamil use, visit/week, and treatment-by-visit/week interaction, as well as the continuous, fixed covariate of baseline value.

For the gated secondary outcome of sustained response (the proportion of patients with a reduction from baseline of 50% or greater in the weekly cluster attack frequency beginning at

Weeks 3/4 and maintained at Weeks 5/6, 7/8, 9/10, and 11/12), the Koch's Nonparametric Randomization-Based Analysis of Covariance method will be utilized (Koch et al. 1998). A non-responder imputation for missing values will be used. Specifically, all patients who discontinue study treatment at any time prior to Weeks 11/12, for any reason, will be considered a non-responder at all missing assessment.

If the sample size is increased, the CHW test statistic will be calculated for the gated secondary objectives. The analysis of the secondary gatekeeper objectives will be performed if the LY2951742 versus placebo comparison is significant for the primary efficacy analysis at a one sided α=0.025 significance level.

12.2.8. Efficacy Analyses

The secondary and exploratory efficacy analyses will be conducted for SP III and SP IV.

For the continuous secondary and exploratory efficacy measures, the change from baseline to each 2 week interval post-baseline measure will be analyzed from repeated measures analyses. For the efficacy measures that are not derived from cluster headache attack frequency, the baseline average daily cluster headache attack frequency category (≤4 vs. >4) will be added as a covariate in the MMRM model.

For the categorical secondary and exploratory efficacy measures including 30% response, 50% response, 75% response and 100% response, the percentage of patients meeting response criteria at each biweekly interval will be estimated for each treatment from a categorical, pseudo-likelihood-based repeated measures analysis of longitudinal binary outcomes indicating whether patients meet response criteria. This analysis will be implemented using the GLIMMIX procedure in SAS®.

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12.2.10. Safety Analyses

The safety analyses will be conducted for SP III on the safety population, and during LY2951742-treated time and LY2951742-treated time plus post-treatment time on the LY2951742-treated population.

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

- Adverse events
  - TEAEs

        - by PT
        - by SOC
        - by maximum severity
        - considered to be related to IP by investigator
    - serious adverse events
    - adverse events leading to discontinuation
- Suicidal ideation and behaviors assessed by solicited questioning using the C-SSRS
- Vital signs and weight
- Electrocardiograms
- Laboratory measurements
- Anti-drug antibodies (ADA and NAb)

12.2.10.1. Categorical Safety Variables

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

Comparisons between treatment groups for all categorical safety measures will be made using Fisher's exact test for SP III with safety population. Descriptive statistics only will be presented for the analyses with LY2951742-treated population.

12.2.10.2. Adverse Events

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

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

12.2.10.3. Suicide-Related Thoughts and Behaviors

Suicidal ideation, suicidal behavior, and non-suicidal self-injurious behavior based on the C-SSRS will be summarized by treatment group. In particular, for each of the following events, the number and percentage of patients with the event will be enumerated by treatment:

completed suicide, non-fatal suicide attempt, interrupted attempt, aborted attempt, preparatory acts or behavior, active suicidal ideation with specific plan and intent, active suicidal ideation with some intent to act without specific plan, active suicidal ideation with any methods (not plan) without intent to act, non-specific active suicidal thoughts, wish to be dead, and non-suicidal self-injurious behavior.

In addition, the number and percentage of patients who experienced at least one of various composite measures during SP III will be presented and compared. These include suicidal acts (completed suicide and nonfatal suicidal attempts), suicidal behavior (suicidal acts, interrupted attempts, aborted attempts, and preparatory acts or behavior), treatment-emergent suicidal ideation or treatment-emergent suicidal behavior.

Fisher's exact test will be used for pairwise treatment comparisons in SP III. These measures will also be summarized during LY2951742-treated time and LY2951742-treated time plus post-treatment time in LY2951742-treated population.

12.2.10.4. Vital Signs and Weight

Vital signs collected during the study include systolic and diastolic blood pressure, pulse, and temperature. Blood pressure and pulse measurements will be taken when the patient is in a sitting position. Three measurements of sitting blood pressure and pulse will be collected at approximately 30 to 60 second intervals at every visit and those 3 sitting blood pressure and pulse measurements will be averaged and used as the value for that visit.

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

12.2.10.5. Electrocardiogram Intervals and Heart Rate

Analyses of QTc interval will be calculated with Fridericia's formula as $QT/RR^{1/3}$. The number and percent of patients meeting criteria for treatment-emergent abnormalities in ECG intervals (PR, QRS, and QTcF) and heart rate at any time during study will be summarized. Treatment group comparisons will be performed using Fisher's exact test.

In addition, descriptive summary of qualitative ECG abnormalities will be conducted which will include summaries of 11 ECG categories (Axis, Rhythm, Conduction, Ischemia, Infarction, Injury, Morphology, U-waves, T-waves, ST Segment, and Other Abnormalities) of qualitative findings at any time post-baseline.

12.2.10.6. Laboratory Tests

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

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

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

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

12.2.10.7. Immunogenicity Analyses

Refer to the SAP for details.

12.2.11. Subgroup Analyses

Refer to the SAP for details.

12.2.12. Interim Analyses

Up to 2 formal interim analyses are planned for this trial. The first interim analysis will occur during SP III which may result in increasing the sample size or stopping the trial for futility. Details will be documented in the Statistical Analysis Center SAP, the ERB supplement, and the DMC Charter.

The second interim analysis will be conducted after all patients have completed SP III, and thus, will be the final analysis of the primary efficacy endpoint. This interim analysis will be conducted using internal unblinded study team members who do not have direct interaction with sites.

In order to minimize the potential operational and statistical bias that may result from performing an interim analysis, the first interim analysis for this study will be conducted under the auspices of an independent DMC. The DMC will also independently monitor patient safety during this trial.

Only the DMC is authorized to evaluate unblinded interim efficacy and safety analyses (prior to the completion of the double-blind treatment phase). Study sites will receive information about interim results ONLY if they need to know for the safety of their patients.

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

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

The investigator is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

The ICF will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each patient. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of IP.

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are used at investigative sites(s). All ICFs must be compliant with the International Conference on Harmonisation (ICH) guideline on GCP.

The investigator must give assurance that the ERB was properly constituted and convened as required by 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). The ERB(s) will review the protocol as required.

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

13.3. Regulatory Considerations

This study will be conducted in accordance 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) the ICH GCP Guideline (E6)
3) applicable laws and regulations

The investigator or designee will promptly submit the protocol to applicable ERB(s).

Some of the obligations of the sponsor will be assigned to a TPO.

An identification code assigned by the investigator to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and/or other trial-related data.

13.3.1. Investigator Information

Licensed physicians with a specialty including, but not limited to, neurology and headache specialists will participate as investigators in this clinical trial.

13.3.2. 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.

13.3.3. Final Report Signature

The clinical study report coordinating investigator will sign the final clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The sponsor's responsible medical officer and statistician will 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.

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Attachment 1. Protocol CGAM Study Schedule

Study Schedule, Protocol I5Q-MC-CGAM: SP I to SP III

Study Phase (SP)	SP I	SP II	SP III							
Description	Screening	Pre-Randomization Diary	Treatment							Comments
Visit	1	2	3	4 (Phone visit)	5	6	7(Phone visit)	8	9	Phone visits (V4 and V7) are contacts between office visits to collect any spontaneously reported AE.
	Allowable range b/w V1 and 1st diary day: 0 to 65d	Min time: SP II – 14 to 17d; V2 and V3 – 5d								For flow of patients through SP I and SP II, please refer to the study design Section 7.1
Visit Day			Day 1	Day 7	Day 14	Day 30	Day 37	Day 60	Day 90	
Month					0.5	1		2	3	
Interval (days) since previous office visit				7	14	16	7	30	30	The interval from V3 to V6, and from V6 to V8, and from V8 to V9 should be no less than 28 days
Interval allowance (days)				+/-1	+/-1	+5/-2	+/-1	+5/-2	+5/-2	
Informed consent	X									
Inclusion/exclusion criteria	X	X	X							
Dispense ePRO diary	X									
Demographics	X									
Medical history and preexisting conditions	X									
Prior cluster headache attack history	X									
Treatment			X			X		X	X*	IP injections are to occur after all other visit procedures are completed. **Following the first dose at V3** and the first dose of open-label IP at V9, patients will be observed for 30 min in the office. ***Patients not entering SP IV will not receive treatment at V9.**

Study Schedule, Protocol I5Q-MC-CGAM: SP I to SP III

Study Phase (SP)	SP I	SP II	SP III							
Description	Screening	Pre-Randomization Diary	Treatment							Comments
Visit	1	2	3	4 (Phone visit)	5	6	7(Phone visit)	8	9	Phone visits (V4 and V7) are contacts between office visits to collect any spontaneously reported AE.
Month					0.5	1		2	3	
ECG	X								X	To be collected prior to blood draws and dosing. Patients must be supine for 5-10 min before collection and remain supine but awake during collection.
Physical examination	X									Must include a brief neurological exam.
Caffeine use	X									
Tobacco use (smoking and nonsmoking)	X									
Nicotine use	X									
Alcohol use	X									
Height	X									
Weight	X								X	
Waist and Hip Circumference	X									
Vital sign	X	X	X			X		X	X	Vital signs will also be taken at unscheduled office visits. Vital signs 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 that will be provided to the sites.
Hematology	X		X						X	
Clinical chemistry[a]	X		X						X	Except for V1, chemistry labs require fasting (no food or drink, except water, for at least 8 hrs).
Urinalysis	X								X	
HbA1C	X								X	

Study Schedule, Protocol I5Q-MC-CGAM: SP I to SP III

Study Phase (SP)	SP I	SP II	SP III							
Description	Screening	Pre-Randomization Diary	Treatment							Comments
Visit	1	2	3	4 (Phone visit)	5	6	7(Phone visit)	8	9	Phone visits (V4 and V7) are contacts between office visits to collect any spontaneously reported AE.
Month						1		2	3	
Serum Pregnancy or FSH	X									Female patients only
Urine drug screen	X									
Randomization			X							
Immunogenicity			X		X	X		X	X	Immunogenicity samples must be collected prior to dose administration if the visit is a dosing visit. Samples will be taken in the event of early termination. The timing of samples will be recorded.
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	CCI [redacted]
Plasma Storage Sample (K+/EDTA)	X	X	X		X	X		X	X	Samples must be collected prior to dose administration if the visit is a dosing visit. The timing of the samples will be recorded. These samples will be collected in an K+/EDTA container.
PK sampling					X	X		X	X	Samples must be collected prior to dose administration if the visit is a dosing visit. The timing of the samples will be recorded.
CCI [redacted]			C C							[redacted]
RNA storage sample	X	X			X	X		X	X	Sample must be collected in a Tempus tube.

Study Schedule, Protocol I5Q-MC-CGAM: SP I to SP III

Study Phase (SP)	SP I	SP II	SP III							
Description	Screening	Pre-Randomization Diary	Treatment							Comments
Visit	1	2	3	4 (Phone visit)	5	6	7 (Phone visit)	8	9	Phone visits (V4 and V7) are contacts between office visits to collect any spontaneously reported AE after the first two injections of IP.
Month						1		2	3	
PGI-I						X		X	X	
C-SSRS/SHSF, SHFU	X	X	X			X		X	X	Should also be completed at unscheduled office visits.
Recording of AEs	X	X	X	X		X	X	X	X	
Review Diary data		X	X			X		X	X	Following Informed Consent, patients will be required to complete their diaries daily beginning the day of their next cluster headache attack. Sites should review the diary compliance with the patient during specified office visits.
Concomitant medications	X	X	X			X		X	X	

Abbreviations: AE = adverse event; CCI [redacted] C-SSRS = Columbia-Suicide Severity Rating Scale; d = day; ECG = electrocardiogram; ePRO = electronic patient reported outcome diary; ET = early termination; FSH = follicle stimulating hormone; HbA1c = hemoglobin A1c; hrs = hours; min = minute; PGI-I = Patient Global Impression of Improvement; PK = pharmacokinetics; RNA = ribonucleic acid; SHSF = Self-Harm Supplement Form; SHFU = Self-Harm Follow-Up Form; SP = study phase; V = visit.

[a] Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly, or its designee, clinical research physician. See Attachment 3 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.

Study Schedule, Protocol I5Q-MC-CGAM: SP IV

Study Phase	SP IV													
Description	Open-label treatment													Comments
Visit	10 (Phone visit)	11	12	13	14	15	16	17	18	19	20	21	22	Phone visit (V10) after office Visit 9 is to collect any spontaneously reported AE after the first injection of LY2951742 in the open-label phase.
Visit Day	97	120	150	180	210	240	270	300	330	360	390	420	450	
Month		4	5	6	7	8	9	10	11	12	13	14	15	
Interval (days) since previous office visit	7	30	30	30	30	30	30	30	30	30	30	30	30	
Interval allowance (days)	+/-1	+5/-2	+5/-2	+5/-2	+5/-2	+5/-2	+5/-2	+5/-2	+5/-2	+5/-2	+5/-2	+5/-2	+5/-2	
Treatment		X	X	X	X	X	X	X	X	X	X	X		Patients will receive injections of LY2951742 after all other visit procedures are completed. During SP IV, some patients may transition to LY2951742 supplied in a prefilled syringe. For these patients they should remain in the office for 30 minutes for observation after the first prefilled syringe injection
ECG				X									X	To be collected prior to blood draws and dosing. Patients must be supine for 5-10 min before collection and remain supine but awake during collection.
Weight							X						X	
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	Vital signs will also be taken at unscheduled office visits. Vital signs 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 that will be provided to the sites.
Hematology				X			X						X	

Study Schedule, Protocol I5Q-MC-CGAM: SP IV

Study Phase	SP IV													
Description	Open-label treatment													Comments
Visit	10 (Phone visit)	11	12	13	14	15	16	17	18	19	20	21	22	Phone visit (V10) after office Visit 9 is to collect any spontaneously reported AE after the first injection of LY2951742 in the open-label phase.
Month		4	5	6	7	8	9	10	11	12	13	14	15	
Clinical chemistry[a]				X			X						X	Except for V1, chemistry labs require fasting (no food or drink, except water, for at least 8 hrs).
Urinalysis				X			X						X	
HbA1C							X						X	
Serum Pregnancy													X	Female patients only
Immunogenicity				X						X			X	Immunogenicity samples must be collected prior to dose administration if the visit is a dosing visit. Samples will be taken in the event of early termination. The timing of samples will be recorded.
[redacted]				[redacted]						[redacted]			[redacted]	CCI [redacted]
Plasma Storage Sample (K+/EDTA)				X						X			X	Samples must be collected prior to dose administration if the visit is a dosing visit. The timing of the samples will be recorded. These samples will be collected in a K+/EDTA container.
PK sampling				X						X			X	Samples must be collected prior to dose administration if the visit is a dosing visit. The timing of the samples will be recorded.
RNA storage sample				X						X			X	Sample must be collected in a Tempus tube.

Study Schedule, Protocol I5Q-MC-CGAM: SP IV

Study Phase	SP IV													
Description	Open-label treatment													Comments
Visit	10 (Phone visit)	11	12	13	14	15	16	17	18	19	20	21	22	Phone visit (V10) after office visit 9 is to collect any spontaneously reported AE after the first injection of LY2951742 in the open-label phase.
Month		4	5	6	7	8	9	10	11	12	13	14	15	
PGI-I							X						X	
C-SSRS/SHSF, SHFU		X	X	X	X	X	X	X	X	X	X	X	X	Should also be completed at unscheduled office visits.
Recording of AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	
Review Diary data		X												Patients are required to complete daily diary entries through V11. Sites should review the diary entries at the indicated visits.
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	

Abbreviations: AE = adverse event; CCI ; C-SSRS = Columbia-Suicide Severity Rating Scale; d = day; ECG = electrocardiogram; ePRO = electronic patient reported outcome diary; ET = early termination; FSH = follicle stimulating hormone; HbA1c = hemoglobin A1c; hrs = hours; min = minute; PGI-I = Patient Global Impression of Improvement; PK = pharmacokinetics; RNA = ribonucleic acid; SHSF = Self-Harm Supplement Form; SHFU = Self-Harm Follow-Up Form; SP = study phase; V = visit.

[a] Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly, or its designee, clinical research physician. See Attachment 3 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.

Study Schedule, I5-Q-MC-CGAM SP V

Study Phase	SP V		ET	
Description	Follow-Up		ET	Comments
Visit	23	24		
Visit Day	510	570		
Month	17	19		
Interval (days) since previous visit	60	60		
Interval allowance (days)	+/-8	+/-8		
ECG		X	X	To be collected prior to blood draws and dosing. Patients must be supine for 5-10 min before collection and remain supine but awake during collection.
Weight		X	X	
Vital signs	X	X	X	Vital signs will also be taken at unscheduled office visits. Vital signs 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 that will be provided to the sites.
Hematology		X	X	
Clinical chemistry[a]		X	X	Except for V1, chemistry labs require fasting (no food or drink, except water, for at least 8 hrs).
Urinalysis		X	X	
HbA1C		X	X	
Serum Pregnancy		X	X	Female patients only
Immunogenicity	X	X	X	Immunogenicity samples must be collected prior to dose administration if the visit is a dosing visit. Samples will be taken in the event of early termination. The timing of samples will be recorded.
[redacted]	[redacted]	[redacted]	[redacted]	CCI [redacted]
Plasma Storage Sample (K+/EDTA)	X	X	X	The timing of the samples will be recorded. These samples will be collected in a K+/EDTA container.
PK sampling	X	X	X	The timing of the samples will be recorded.
RNA sample storage	X	X	X	Sample must be collected in a Tempus tube.
PGI-I		X	X	
C-SSRS/SHSF, SHFU	X	X	X	Should also be completed at scheduled and unscheduled office visits.
Recording of AEs	X	X	X	
Concomitant medications	X	X	X	

Study Schedule, I5-Q-MC-CGAM SP V

Abbreviations: AE = adverse event; CCI C-SSRS = Columbia-Suicide Severity Rating Scale; d = day; ECG = electrocardiogram; ePRO = electronic patient reported outcome diary; ET = early termination; FSH = follicle stimulating hormone; HbA1c = hemoglobin A1c; hrs = hours; min = minute; PGI-I = Patient Global Impression of Improvement; PK = pharmacokinetics; RNA = ribonucleic acid; SHSF = Self-Harm Supplement Form; SHFU = Self-Harm Follow-Up Form; SP = study phase; V = visit.

[a] Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly, or its designee, clinical research physician. See Attachment 3 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.

Attachment 2. Protocol CGAM Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology:	**Clinical Chemistry:**
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume	Total bilirubin
Mean cell hemoglobin concentration	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase
Neutrophils, segmented	Alanine aminotransferase (ALT)
Lymphocytes	Aspartate aminotransferase (AST)
Monocytes	Blood urea nitrogen (BUN)
Eosinophils	Creatinine
Basophils	Uric acid
Platelets	Calcium
HbA_{1c}	Glucose (fasting)[a]
	Albumin
	Creatinine kinase (CK)
	Total cholesterol[a]
	HDL[a]
Urinalysis:	**Other**
Specific gravity	CCI [redacted]
pH	PK Sample (LY2951742 serum concentration determination)
Protein	Immunogenicity
Glucose	Urine Drug Screen[b]
Ketones	**Pregnancy Test** (females only)[c]
Blood	Serum pregnancy or FSH
Urine leukocyte esterase	
	Stored Samples
	Plasma Storage (K+/EDTA CCI [redacted])
	CCI [redacted]
	RNA

Abbreviations: HDL = high-density lipoprotein; FSH = follicle stimulating hormone; HbA_{1c} = hemoglobin A1c ; RBC = red blood cells; RNA = ribonucleic acid; WBC = white blood cells.

[a] Fasting at Visits 3, 9, 13, 16, 22, 24 or early termination.

[b] Performed at screening and may be repeated during the study at the discretion of the investigator.

[c] Performed at screening per inclusion criteria number 8 and at Visits 22, 24 and ET.

Attachment 3. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly, or its designee, clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	**Alkaline phosphatase isoenzymes[a]**
GGT	**Anti-Actin antibody[a]**
CPK	**Anti-smooth muscle antibody[a]**

Abbreviations: ALT = alanine aminotransferase; AST = aspirate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

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

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

Attachment 4. Protocol CGAM Sampling Summary

This table summarizes the maximum number of samples venipunctures and volumes for all sampling and tests during the study. Fewer samples may actually be taken, but this will not require a protocol amendment.

Protocol I5Q-MC-CGAM Sampling Summary

Purpose	Sample Type	Maximum Amount per Sample	Maximum Number Samples	Maximum Total Amount
Screening tests[a]	Blood	3.5 mL	3	10.5 mL
Standard laboratory tests[a]	Blood	3.5 mL	14	49 mL
CCI				
PK sample (determination of LY2951742 serum concentration)	Blood	2.5 mL	9	22.5 mL
CCI				
Plasma storage sample (K+/EDTA)	Blood	4 mL	12	48 mL
Immunogenicity samples	Blood	10 mL	10	100 mL
RNA storage sample	Blood	3 mL	11	33 mL
Total	Blood			375 mL
Hepatic monitoring[c]	Blood	3 - 30 mL	-	-

Abbreviation: CCI; PK = pharmacokinetics; RNA = ribonucleic acid.

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

[b] CCI

[c] Based on laboratory safety values, unscheduled hepatic monitoring testing may be performed as part of patient follow-up, in consultation with Lilly Designated Medical Monitor.

Attachment 5. Protocol Amendment Summary: I5Q-MC-CGAM(d)

Overview

Protocol I5Q-MC-CGAM (c), A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 with a Long-Term Open-Label Extension in Patients with Chronic Cluster Headache, has been amended. The new protocol is indicated by amendment (d) and will be used to conduct the study in place of any preceding version of the protocol. The overall changes and rationale for the changes made to this protocol are as follows:

- The primary endpoint was updated to be the overall treatment effect over the 12-week double-blind treatment phase, rather than the treatment effect at the single time point, weeks 3/4. This update will enable the primary efficacy endpoint to assess the sustained effect of LY2951742 over 3 months in patients with chronic cluster headache.
- Due to the update to the primary endpoint, the gated secondary objective to assess the efficacy of LY2951742 300 mg in reducing the frequency of weekly cluster headache attacks from baseline to the sequential gated time points of Weeks 5/6, 7/8, 9/10, and 11/12 to evaluate the sustained effect of LY2951742 is removed, and it is replaced with the following gated secondary objective to align with the revised primary endpoint: to assess the efficacy of LY2951742 300 mg compared with placebo in the estimated mean proportion of patients with a 50% or greater reduction from baseline in the weekly frequency of cluster headache attacks during the 12-week double-blind treatment phase.
- Clarified that baseline daily average cluster headache attack frequency categorical variable will be a covariate in the MMRM model for efficacy measures not derived from cluster headache attack frequency since it was considered possibly prognostic and was included in the dynamic allocation randomization algorithm.
- Safety population and modal treatment description for SP III were added for safety analyses since it is more appropriate to present safety results by the actual treatments patients received.
- The safety analyses for SP IV and for SP V separately were replaced by analyses during LY2951742-treated time and LY2951742-treated time plus post-treatment time in the LY2951742-treated population since it was determined that having overall estimates of safety outcomes across study phases was more medically useful than having estimates by study phase.
- Clarified the blinding of study personnel following database lock for the analysis of the double-blind treatment phase.
- Clarified the baseline patient characteristics in Section 12.2.3.
- The ePRO diary primary efficacy compliance and overall ePRO diary compliance are combined into one diary compliance calculation since no partially completed diary can be submitted. Clarified diary compliance calcuations include Weeks 15/16 and compliance for SP III will be calculated separately.

- The parameter of large clinical trial population based QT correction (QTcLCTPB) was removed for electrocardiogram (ECG) analysis per updated guidance from an internal subject matter expert group. The analysis of QTc and QTcF remain.
- Minor editorial changes throughout the protocol as found.

Revised Protocol Sections

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

Header

I5Q-MC-CGAM(~~e~~d) Clinical Protocol

Title

Protocol I5Q-MC-CGAM(~~e~~d)

2. Synopsis

Study Rationale

LY2951742 (also known as galcanezumab) is a humanized monoclonal antibody that selectively binds to and neutralizes calcitonin-gene-related peptide (CGRP) that has been identified for clinical development in pain conditions relevant to the CGRP pathway such as migraine.

Primary Objectives: The primary objective is to assess the efficacy of LY2951742 300 mg administered every 30 days compared with placebo in reducing the frequency of weekly cluster headache attacks in patients with chronic cluster headache. The primary outcome measure is the weekly cluster headache attack frequency. The primary endpoint is the overall mean change from baseline in weekly cluster headache attack frequency ~~from baseline to Weeks 3/4~~ during the 12-week double-blind treatment phase with LY2951742 compared with placebo

Gated Objectives:

- To assess the efficacy of LY2951742 300 mg compared with placebo in ~~reducing~~ the estimated mean proportion of patients with a 50% or greater reduction from baseline in the weekly frequency of ~~weekly~~ cluster headache attacks ~~in patients with chronic cluster headache from baseline to the following sequential gated time points to evaluate~~during the ~~sustained effect of LY2951742:~~12-week double-blind treatment phase.
  - ~~Weeks 5/6~~
  - ~~Weeks 7/8~~
  - ~~Weeks 9/10~~
  - ~~Weeks 11/12~~

Other secondary objectives:

- To assess the development and consequences of anti-drug antibodies (ADA) to LY2951742 in patients exposed to LY2951742; to provide samples for subsequent evaluation of neutralizing ~~ADAs (NABs) upon availability of the validated assay.~~ADA (NAb).

Exploratory Objectives:

To assess whether LY2951742 300 mg is superior to placebo as measured by:

- Proportion of patients randomized to LY2951742 meeting "very much better" or "much better" on the PGI-I at Month 9 and Month 15.
- Mean change in the weekly number of times of abortive medication use from baseline to each 2-week interval through Week 12 comparing LY2951742 with placebo.
- Change in percentage of times using oxygen ~~or triptan~~ from baseline for each 2-week interval through Week 12 comparing LY2951742 with placebo.
- Change in percentage of times using triptan from baseline for each 2-week interval through Week 12 comparing LY2951742 with placebo.

Statistical Methods:

Unless otherwise specified, efficacy analyses will be conducted on an ITT population, which include all patients who are randomized and receive at least 1 dose of IP. Patients in the ITT population will be analyzed according to the treatment group to which they were randomized. ~~The ITT population will be the primary population on which statistical analysis will be performed.~~ Safety analyses for SP III and exposure will be conducted on the safety population, which also includes all patients who are randomized and receive at least 1 dose of study drug. However, patients will be analyzed by actual study treatment received most often (modal treatment; placebo or LY2951742) during the double-blind treatment phase. Safety analyses during LY2951742-treated time and LY2951742-treated time plus post-treatment time will be conducted on the LY2951742-treated population, which includes all patients who receive at least 1 dose of LY2951742. When mean 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. Additional analyses population for analyses of study Phase IV and Phase V will be described in the SAP

Effiacy – Primary:

The primary analysis will be conducted by a REML-based, MMRM analysis using all the longitudinal observations at Weeks 1/2, 3/4, 5/6, 7/8, 9/10, and 11/12 intervals. The analysis of the primary outcome will be the main effect of treatment ~~contrast~~ between LY2951742 300 mg and placebo ~~at Weeks 3/4 of~~during the 12-week double-blind treatment phase from a repeated measures analysis on mean change from baseline in the weekly attack frequency. This provides the average treatment effect across the 12-week double-blind treatment phase.

Efficacy – Gated Secondary:

For the gated secondary outcome of the estimated mean proportion of patients with a 50% or greater reduction ~~change~~ from baseline in weekly cluster headache attack frequency during the 12-week double-blind treatment phase, a categorical, pseudo-likelihood-based repeated measures analysis of data at Weeks 1/2, 3/4, 5/6, 7/8, 9/10, and 11/12 will be used~~for Weeks 5/6, 7/8, 9/10,~~

~~and 11/12, the same MMRM analysis as specified for primary efficacy will be utilized~~. The endpoint for comparing LY2951742 with placebo will be estimated as the main effect of treatment from the categorical MMRM analysis across Weeks 1 to 12.
For the gated secondary outcome of sustained response (the proportion of patients with a reduction from baseline of 50% or greater in the weekly cluster attack frequency beginning at Weeks 3/4 and maintained at Weeks 5/6, 7/8, 9/10, and 11/12), the Koch's Nonparametric Randomization-Based Analysis of Covariance method will be utilized (Koch et al. 1998). A non-responder imputation for missing values will be used. Specifically, all patients who discontinue study treatment at any time prior to Weeks 11/12, for any reason, will be considered a non-responder at all missing assessment.
If the sample size is increased, the CHW test statistic will be calculated for the gated secondary objectives. The analysis of the secondary gatekeeper objectives will be performed if the LY2951742 versus placebo ~~versus LY2951742~~ comparison is significant for the primary efficacy analysis at a one sided α=0.025 significance level.

Safety:

The safety analyses will be conducted for SP III on the safety population, and during LY2951742-treated time and LY2951742-treated time plus post-treatment time on the LY2951742-treated population~~., SP IV, and SP V as well as SP III, SP IV, and SP V combined. For SP III, SP IV, and SP V combined, only repeated measures analysis and time to event analysis will be conducted.~~

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

- Adverse events
  - TEAEs
    - by PT
    - by SOC
    - by maximum severity
    - ~~by outcome~~
    - considered to be related to IP by investigator
  - serious adverse events
  - adverse events leading to discontinuation
- Suicidal ideation and behaviors assessed by solicited questioning using the C-SSRS
- Vital signs and weight
- Electrocardiograms
- Laboratory measurements
- Anti-~~LY2951742 antibody~~drug antibodies (ADA and NAb)

Unless specified otherwise, the categorical safety analyses will include both scheduled and unscheduled visits. Comparisons between treatment groups for all categorical safety measures will be made using Fisher's exact test for SP III with ~~ITT~~safety population. Descriptive statistics only will be presented for the analyses ~~treatment groups in SP IV and SP V~~ with ~~post~~ LY2951742 ~~treatment~~treated population

4. Abbreviations and Definitions

~~NABs~~NAb neutralizing anti-drug antibodies

5. Introduction

LY2951742 (also known as galcanezumab) is a humanized monoclonal antibody that selectively binds to and neutralizes CGRP.

6. Objectives

Note: This study employs nominal 14-day intervals from which an average weekly cluster headache attack frequency is calculated. ~~As an example, the primary endpoint of weekly cluster headache attack frequency is calculated as the average of Week 3 and Week 4, hereafter referred to as Weeks 3/4.~~

6.1. Primary Objective

The primary objective is to assess the efficacy of LY2951742 300 mg administered every 30 days compared with placebo in reducing the frequency of weekly cluster headache attacks in patients with chronic cluster headache. The primary outcome measure is the weekly cluster headache attack frequency. The primary endpoint is the overall mean change from baseline in weekly cluster headache attack frequency ~~from baseline to Weeks 3/4~~ during the 12-week double-blind treatment phase with LY2951742 compared with placebo.

6.2. Secondary Objectives

6.2.1. Gated Objectives

- To assess the efficacy of LY2951742 300 mg compared with placebo in ~~reducing~~ the estimated mean proportion of patients with a 50% or greater reduction from baseline in the weekly frequency of ~~weekly~~ cluster headache attacks ~~in patients with chronic cluster headache from baseline to the following sequential gated time points to evaluate~~during the ~~sustained effect of LY2951742:~~12-week double-blind treatment phase.
  - ~~Weeks 5/6~~
  - ~~Weeks 7/8~~
  - ~~Weeks 9/10~~
  - ~~Weeks 11/12~~

6.2.2. Other Secondary Objectives

- To assess the development and consequences of anti-drug antibodies (ADA) to LY2951742 in patients exposed to LY2951742; to provide samples for subsequent evaluation of neutralizing ~~ADAs (NABs) upon availability of the validated assay.~~ADA (NAb).

6.3. Exploratory Objectives

To assess whether LY2951742 300 mg is superior to placebo as measured by:

- Proportion of patients randomized to LY2951742 meeting "very much better" or "much better" on the PGI-I at Month 9 and Month 15.
- Mean change in the weekly number of times of abortive medication use from baseline to each 2-week interval through Week 12 comparing LY2951742 with placebo.
- Change in percentage of times using oxygen ~~or triptan~~ from baseline for each 2-week interval through Week 12 comparing LY2951742 with placebo.
- Change in percentage of times using triptan from baseline for each 2-week interval through Week 12 comparing LY2951742 with placebo.

7.2. Discussion of Design and Control

The proposed duration of the double-blind treatment phase is 3 months, with the primary endpoint assessed ~~during Weeks 3/4~~ from Weeks 1/2 through Weeks 11/12 after the first IP dose. The length of the randomized, double-blind treatment phase (3 months) is believed to be a sufficient duration to assess the efficacy of a cluster headache prevention medication given the mechanism and observed onset of action for CGRP antibodies in migraine (Dodick et al. 2014a, 2014b). The primary measure of weekly cluster headache attack frequency and use of placebo-control is consistent with current published International Headache Society guidelines (IHS 1995). Moreover, a placebo-controlled study with a duration longer than 3 months may not be tolerated by patients suffering from chronic cluster headache. ~~While Eli Lilly and Company (Lilly) considers an effect, if present, will be observed after 1 administration, it is possible 1 dose may not be sufficient for some patients. Additionally, given the need to assess for sustained effect in this chronic condition, the double-blind, placebo-controlled phase will continue for another 2 months (3 months total, with 3 IP administrations) to balance the need to see an early treatment effect with the need to assess for sustained efficacy. This primary endpoint for assessing efficacy and the use of placebo-control is consistent with current published International Headache Society guidelines (IHS 1995).~~

9.7. Blinding

This is a double-blind study. To preserve the blinding of the study, only a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.

After the reporting database is locked for statistical analysis of the double-blind treatment phase, a limited number of sponsor personnel will be unblinded to complete the study report and prepare for regulatory submission. However, any sponsor personnel continuing with the management and oversight of the trial will remain blinded to patients' previous treatment assignment.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

Unless otherwise specified, efficacy analyses will be conducted on an ITT population, which include all patients who are randomized and receive at least 1 dose of IP. Patients in the ITT population will be analyzed according to the treatment group to which they were randomized. ~~The ITT population will be the primary population on which statistical analysis will be performed.~~ Safety analyses for SP III and exposure will be conducted on the safety population, which also includes all patients who are randomized and receive at least 1 dose of study drug. However, patients will be analyzed by actual study treatment received most often (modal treatment; placebo or LY2951742) during the double-blind treatment phase. Safety analyses during LY2951742-treated time and LY2951742-treated time plus post-treatment time will be conducted on the LY2951742-treated population, which includes all patients who receive at least 1 dose of LY2951742. When mean 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. Additional analyses population for analyses of study Phase IV and Phase V will be described in the SAP.

12.2.3. Patient Characteristics

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

- Demographic (age, gender, race, ethnicity, country, region, height, weight, BMI)
- Baseline disease characteristics, such as:
    - number of weekly cluster headache attacks
    - number of times an abortive medication was taken
    - ~~mean~~ average severity of cluster headache pain
    - ~~mean~~ average cluster headache attack ~~minutes~~ duration
    - number of times an abortive medication was taken per cluster headache attack
    - ~~number of times of using the oxygen or triptan~~
    - ~~number of times of using acetaminophen/paracetamol or NSAIDs~~
    - ~~percentage of times of using the oxygen or triptan~~
    - ~~percentage of times of using acetaminophen/paracetamol or NSAIDs~~

12.2.5. Treatment Compliance

Treatment compliance will be calculated for SP III and SP IV as:

$$\frac{\text{number of full doses received} * 100}{\text{number of intended full doses}}$$

Comparisons between treatments for treatment compliance will be performed using an ANOVA with treatment and pooled investigative site in the model.

12.2.6. ePRO Diary Compliance

The ePRO diary compliance at each biweekly interval (including baseline, The ePRO diary compliance at each biweekly interval (including baseline, Weeks 1/2, 3/4, 5/6, 7/8, 9/10, 11/12 ~~and~~, 13/14, and 15/16) and for SP III (Weeks 1/2 through 11/12) will be calculated. Diary compliance at each interval is calculated as:

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

~~Two ePRO diary compliance rate will be calculated:~~

~~ePRO diary primary efficacy compliance~~

~~overall ePRO diary compliance~~

~~For ePRO diary primary efficacy compliance, the actual number of~~ The diary entry ~~days is calculated as~~can only be saved and submitted afer all the required ePRO questions are answered, so the actual number of diary entry days represents the total number of days with non-missing answer to all the required cluster headache attack ePRO questions. ~~For overall ePRO diary compliance, the actual number of diary entry days will be calculated as the total number of days with a non-missing answer to cluster headache attack ePRO questions (yes/no).~~

~~For both ePRO diary primary efficacy compliance and overall ePRO diary compliance, the~~The expected number of diary entry days will be calculated as (the last calendar date - the first calendar date in each interval +1).

Comparisons between diary compliance for each interval separately will be performed using an ANOVA with treatment and pooled investigative site in the model.

Compliance will also be listed by ~~visit~~ biweekly interval for each patient.

12.2.7. Primary and Gated Outcome and Methodology

12.2.7.1. Primary Outcome

The primary analysis will be conducted by a REML-based, MMRM analysis using all the longitudinal observations at Weeks 1/2, 3/4, 5/6, 7/8, 9/10, and 11/12 intervals. The analysis of

the primary outcome will be the main effect of treatment ~~contrast~~ between LY2951742 300 mg and placebo ~~at Weeks 3/4 of~~during the 12-week double-blind treatment phase from a repeated measures analysis on mean change from baseline in the weekly attack frequency. This provides the average treatment effect across the 12-week double-blind treatment phase.

12.2.7.2. Gated Secondary Outcomes

For the gated secondary outcome of the estimated mean proportion of patients with a 50% or greater reduction ~~change~~ from baseline in weekly cluster headache attack frequency during the 12-week double-blind treatment phase, a categorical, pseudo-likelihood-based repeated measures analysis of data at Weeks 1/2, 3/4, 5/6, 7/8, 9/10, and 11/12 will be used~~for Weeks 5/6, 7/8, 9/10, and 11/12, the same MMRM analysis as specified for primary efficacy in Section 12.2.7.1 will be utilized~~. The endpoint for comparing LY2951742 with placebo will be estimated as the main effect of treatment from the categorical MMRM analysis across Weeks 1 to 12. This analysis will be implemented using the GLIMMIX procedure in SAS® to compare treatments and include the fixed, categorical effects of treatment, gender, verapamil use, visit/week, and treatment-by-visit/week interaction, as well as the continuous, fixed covariate of baseline value.

For the gated secondary outcome of sustained response (the proportion of patients with a reduction from baseline of 50% or greater in the weekly cluster attack frequency beginning at Weeks 3/4 and maintained at Weeks 5/6, 7/8, 9/10, and 11/12), the Koch's Nonparametric Randomization-Based Analysis of Covariance method will be utilized (Koch et al. 1998). A non-responder imputation for missing values will be used. Specifically, all patients who discontinue study treatment at any time prior to Weeks 11/12, for any reason, will be considered a non-responder at all missing assessment.

If the sample size is increased, the CHW test statistic will be calculated for the gated secondary objectives. The analysis of the secondary gatekeeper objectives will be performed if the LY2951742 versus placebo ~~versus LY2951742~~ comparison is significant for the primary efficacy analysis at a one sided α=0.025 significance level.

12.2.8. Efficacy Analyses

The secondary and exploratory efficacy analyses will be conducted for SP III and SP IV.

For the continuous secondary and exploratory efficacy measures, the change from baseline to each 2 week interval post-baseline measure will be analyzed from repeated measures analyses. For the efficacy measures that are not derived from cluster headache attack frequency, the baseline average daily cluster headache attack frequency category (<4 vs. >4) will be added as a covariate in the MMRM model.

~~In addition to the repeated measures analyses, for some of the secondary efficacy measures, the mean change from baseline to last observation carried forward (LOCF) endpoint for each treatment will be estimated for the continuous efficacy measures using ANCOVA models.~~

12.2.10 Safety Analyses

The safety analyses will be conducted for SP III on the safety population, and during LY2951742-treated time and LY2951742-treated time plus post-treatment time on the LY2951742-treated population., ~~SP IV, and SP V as well as SP III, SP IV, and SP V combined. For SP III, SP IV, and SP V combined, only repeated measures analysis and time to event analysis will be conducted.~~

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

- Adverse events
  - TEAEs
    - by PT
    - by SOC
    - by maximum severity
    - ~~by outcome~~
    - considered to be related to IP by investigator
  - serious adverse events
  - adverse events leading to discontinuation
- Suicidal ideation and behaviors assessed by solicited questioning using the C-SSRS
- Vital signs and weight
- Electrocardiograms
- Laboratory measurements
- Anti-~~LY2951742 antibody~~drug antibodies (ADA and NAb)

12.2.10.1. Categorical Safety Variables

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

Comparisons between treatment groups for all categorical safety measures will be made using Fisher's exact test for SP III with ~~ITT~~safety population. Descriptive statistics only will be presented for the analyses ~~treatment groups in SP IV and SP V~~ with ~~post-~~LY2951742-~~treatment~~treated population.

12.2.10.3. Suicide-Related Thoughts and Behaviors

In addition, the number and percentage of patients who experienced at least one of various composite measures during SP III~~, SP IV, and SP V separately~~ will be presented and compared. These include suicidal acts (completed suicide and nonfatal suicidal attempts), suicidal behavior (suicidal acts, interrupted attempts, aborted attempts, and preparatory acts or behavior), treatment-emergent suicidal ideation or treatment-emergent suicidal behavior.

Fisher's exact test will be used for pairwise treatment comparisons in SP III. These measures will also be summarized during LY2951742-treated time and LY2951742-treated time plus post-treatment time in LY2951742-treated population.

12.2.10.4. Vital Signs and Weight

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

12.2.10.5. Electrocardiogram Intervals and Heart Rate

Analyses of QTc interval will be calculated ~~using 2 correction formulas. The QTcF (measured in milliseconds [msec]) will be calculated~~ with Fridericia's formula as QT/RR⅓. ~~The Large Clinical Trial Population Based QT Correction (QTcLCTPB) (msec) will be calculated with the formula as QT/RR$^{0.413}$.~~ The number and percent of patients meeting criteria for treatment-emergent abnormalities in ECG intervals (PR, QRS, and QTcF~~, and QTcLCTPB~~) and heart rate at any time during study will be summarized. Treatment group comparisons will be performed using Fisher's exact test.

12.2.10.6. Laboratory Tests

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

14. References

Dodick DW, Goadsby PJ, Spierings ELH, Scherer JC, Sweeney SP, Grayzel DS. Safety and efficacy of LY2951742, a monoclonal antibody to calcitonin gene-related peptide, for the prevention of migraine: a phase 2, randomised, double-blind, placebo-controlled study. Lancet Neurol. 2014a;13(9):885-892.

Dodick DW, Goadsby PJ, Silberstein SD, Lipton RB, Olesen J, Ashina M, Wilks K, Kudrow D, Kroll R, Kohrman B, Bargar R, Hirman J, Smith J; ALD403 study investigators. Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide, for the prevention of frequent episodic migranes: a randomized, double-blind, placebo-controlled, exploratory phase 2 trial. *Lancet Neurol*. 2014b;13(11):1100-1107.

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