

Protocol I5Q-MC-CGAL(d)

A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 in Patients with Episodic Cluster Headache

NCT02397473

Approval Date: 29-Mar-2018

1. Protocol I5Q-MC-CGAL(d)
A Phase 3 Randomized, Double-Blind, Placebo-Controlled
Study of LY2951742 in Patients with Episodic Cluster
Headache

Confidential Information

The information contained in this protocol is confidential and is intended for the use of clinical investigators. It is the property of Eli Lilly and Company or its subsidiaries and should not be copied by or distributed to persons not involved in the clinical investigation of LY2951742, unless such persons are bound by a confidentiality agreement with Eli Lilly and Company or its subsidiaries. This document and its associated attachments are subject to United States Freedom of Information Act (FOIA) Exemption 4.

LY2951742

Study CGAL is a Phase 3 multi-center, outpatient, randomized, double-blind, placebo-controlled study of LY2951742 300 mg in the prevention of episodic cluster headache. The study consists of 4 study phases (SP): SP I (screening/washout), SP II (pre-randomization diary), SP III (randomized, double-blind, placebo-controlled treatment), and SP IV (post-treatment follow-up).

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol Electronically Signed and Approved by Lilly: 18 December 2014
Amendment (a) Electronically Signed and Approved by Lilly: 12 February 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: 29-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) and has been identified for clinical development in pain conditions relevant to the CGRP pathway such as migraine and cluster headache. 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 prevention 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 every 30 days in the prevention of episodic cluster headache.

Clinical Protocol Synopsis: Study I5Q-MC-CGAL

Name of Investigational Product: LY2951742 (a humanized monoclonal antibody that binds to and neutralizes CGRP)	
Title of Study: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 in Patients with Episodic Cluster Headache	
Number of Planned Patients: Entered: 231 Enrolled/Randomized: Planned 162 Completed: 146	Phase of Development: 3
Length of Study: approximately 18 months Estimated first patient visit: Apr 2015 Estimated last patient visit: Sep 2016	
Primary Objective: The primary objective of this study is to assess the efficacy of LY2951742 300 mg every 30 days compared with placebo in reducing the frequency of weekly cluster headache attacks in patients with episodic cluster headache. The primary outcome measure will be the weekly cluster headache attack frequency. The primary endpoint will be the overall mean change from baseline in weekly cluster headache attack frequency across Weeks 1 to 3 with LY2951742 compared with placebo. Baseline is defined as the last 7 days in the eligibility report (pre-randomization diary phase).	
Gated Objective: To assess the efficacy of LY2951742 compared with placebo in the proportion of patients meeting response at Week 3. For this analysis, response is defined as a reduction from baseline of 50% or greater in the weekly cluster headache attack frequency.	

Other Secondary Objectives:

- To assess whether LY2951742 is superior to placebo on the following:
 - a. The proportion of patients with a 50% or greater reduction in the weekly number of cluster headache attacks from baseline for each weekly interval through Week 8
 - b. The proportion of patients with a 30% or greater reduction in the weekly number of cluster headache attacks from baseline for each weekly interval through Week 8
 - c. Mean change in the weekly cluster headache attack frequency from baseline for each weekly interval through Week 8
 - d. 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 Week 4 and Week 8.
- To compare the safety and tolerability of LY2951742 with placebo in patients with episodic cluster headache using the following measures:
 - a. spontaneously reported treatment-emergent adverse events (TEAEs)
 - b. serious adverse events (SAEs)
 - c. discontinuation rates
 - d. 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 (PK) of LY2951742.

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

- Mean change in the weekly number of times an abortive medication was taken from baseline for each weekly interval through Week 8 comparing LY2951742 with placebo.
- Change in percentage of times using oxygen from baseline for each weekly interval through Week 8 comparing LY2951742 with placebo.
- Change in percentage of times using triptan from baseline for each weekly interval through Week 8 comparing LY2951742 with placebo.
- Change in percentage of times of using acetaminophen/paracetamol or NSAIDs from baseline for each weekly interval through Week 8 comparing LY2951742 with placebo.
- The proportion of patients with a 75% or greater reduction in the weekly number of cluster headache attacks from baseline for each weekly interval through Week 8 comparing LY2951742 with placebo.
- The proportion of patients with a 100% reduction in the weekly number of cluster headache attacks from baseline for each weekly interval through Week 8 comparing LY2951742 with placebo.
- Mean change in the cluster headache attack average weekly pain severity (based on 5-point scale) from baseline through Week 8 comparing LY2951742 with placebo.

CCI

Study Design: Phase 3 multi-center, outpatient, randomized, double-blind, placebo-controlled study of LY2951742 300 mg once monthly compared with placebo for the prevention of episodic cluster headache. The study has 4 study phases (SP): SP I (screening/washout), SP II (pre-randomization diary), SP III (randomized, double-blind, placebo-controlled treatment), and SP IV (post-treatment follow-up).

Diagnosis and Main Criteria for Inclusion and Exclusions: The planned patient population are adult outpatients (18 to 65 years of age inclusive) who meet the *International Classification of Headache Disorders, Third Edition, beta version*, or *ICHD-3-beta*, diagnostic criteria for Episodic Cluster Headache and have a baseline weekly cluster headache attack frequency of 1) a maximum of 8 attacks per day and 2) a minimum of 1 cluster headache attack every other day and at least 4 total attacks during baseline assessment. Patients must also have a prior history of a cluster period lasting at least 6 weeks and should be able to distinguish cluster headache attacks from other headaches (i.e. tension-type headaches, migraine). 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 cephalgias, or have had botulinum toxin type A or B administered in the head or neck area within 4 months of SP II.

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

Reference Therapy, Dose, and Mode of Administration or Comparative Intervention: placebo (0.9% Sodium Chloride Injection, USP; volume matched) administered every 30 days as three 1-mL SC injections

Planned Duration of Treatment: 8 weeks double-blind treatment + up to 16 weeks post-treatment follow-up

Screening/washout phase: minimum of 0 days to maximum of 12 months

Pre-randomization diary phase: 10 to 15 days

Treatment phase: 8 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. 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 adverse events (AEs), laboratory test results, vital signs, electrocardiograms (ECGs) and suicidal ideation/behavior (via the C-SSRS).

CCI

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 during SP III 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 during SP III will be conducted on the safety population, which also includes all patients who were randomized and receive at least 1 dose of study drug. However, patients will be analyzed by actual study treatment received most often (modal treatment) during the double-blind treatment phase. When change from baseline is assessed, the patient will be included in the analysis only if he/she has a baseline and a post-baseline measurement. For analyses of the post-treatment phase, the post-treatment population will be used. Post-treatment population will be defined as all patients who entered the post-treatment phase (SP IV) as indicated by entering any post-treatment visit. Details related to handling of missing data will be described in the statistical analysis plan (SAP).

Treatment effects will be evaluated based on a 2-sided significance level of 0.05 for all the efficacy and safety analyses unless otherwise stated. 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.

Categorical comparisons between treatment groups will be performed using Fisher's exact tests, where appropriate. 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 changes, will be described in the SAP and/or 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 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 from Week 1 to Week 3. The analysis of the primary outcome will be the main effect of treatment between LY2951742 300 mg and placebo across Weeks 1 to 3 of the treatment phase from a repeated measures analysis on mean change from baseline in the weekly attack frequency. This provides the average treatment effect over the 3-week period. **Baseline is defined as the last 7 days in the eligibility report (pre-randomization diary phase).**

Efficacy – Gated Secondary: The gated secondary outcome, 50% response, is the proportion of patients meeting the response criteria at Week 3 and will be assessed using Fisher's exact test. A non-responder imputation for missing values will be used. Specifically, all patients who discontinue study treatment at any time prior to Week 3, for any reason, will be considered a non-responder at all missing assessments.

Safety: The safety analyses will be conducted for SP III and SP IV.

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

- AEs
 - TEAEs
 - By preferred term
 - By system organ class
 - By maximum severity
 - Considered to be related to IP by investigator
 - Serious Adverse Events (SAEs)
 - AE leading to discontinuation
- Suicidal ideation and behaviors assessed by solicited questioning using the C-SSRS
- Vital signs and weight
- ECGs
- Laboratory measurements
- Anti-drug antibody

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 the safety population. Descriptive statistics only will be presented for the treatment groups in SP IV with the post-treatment population.

CCI

3. Table of Contents

A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 in Patients with Episodic Cluster Headache

Section	Page
1. Protocol I5Q-MC-CGAL(d) A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 in Patients with Episodic Cluster Headache	1
2. Synopsis	2
3. Table of Contents	7
4. Abbreviations and Definitions	12
5. Introduction	17
6. Objectives	20
6.1. Primary Objective	20
6.2. Secondary Objectives	20
6.2.1. Gated Objective	20
6.2.2. Other Secondary Objectives	20
6.3. Exploratory Objectives	21
7. Investigational Plan	22
7.1. Summary of Study Design	22
7.2. Discussion of Design and Control	24
8. Study Population	25
8.1. Inclusion Criteria	25
8.1.1. Disease Diagnostic Criteria	27
8.2. Exclusion Criteria	27
8.2.1. Rationale for Exclusion of Certain Study Candidates	30
8.3. Rescreening	30
8.4. Discontinuations	32
8.4.1. Discontinuation of Inadvertently Enrolled Patients	32
8.4.2. Discontinuation of Investigational Product	32
8.4.3. Patient Discontinuation from the Study	33
8.4.4. Patients Lost to Follow-Up	34
8.4.5. Discontinuation of Study Sites	34
8.4.6. Discontinuation of the Study	34
9. Treatment	35

9.1. Treatments Administered	35
9.2. Materials and Supplies	35
9.3. Method of Assignment to Treatment	36
9.4. Rationale for Selection of Doses in the Study	36
9.5. Selection and Timing of Doses	36
9.6. Continued Access to Investigational Product	37
9.7. Blinding	37
9.8. Concomitant Therapy	37
10. Efficacy, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements	39
10.1. Efficacy Measures	39
10.1.1. Primary Efficacy Measure	39
10.1.2. Secondary Efficacy Measure	39
10.2. Safety Evaluations	39
10.2.1. Adverse Events	39
10.2.1.1. Serious Adverse Events	40
10.2.1.1.1. Suspected Unexpected Serious Adverse Reactions	41
10.2.2. Other Safety Measures	41
10.2.2.1. Electrocardiograms	41
10.2.2.2. Vital Signs	42
10.2.2.3. Columbia-Suicide Severity Rating Scale, Self-Harm Supplement Form, and Self-Harm Follow-up Form	43
10.2.3. Safety Monitoring	43
10.2.4. Complaint Handling	43
10.3. Sample Collection and Testing	44
10.3.1. Samples for Study Qualification and Health Monitoring	44
10.3.2. Samples for Biomarker Research	44
10.3.4. Samples for Non-genetic Biomarker Research	45
10.3.5. Samples for Immunogenicity Research	46
10.4. Appropriateness of Measurements	46
11. Data Quality Assurance	47
11.1. Data Capture System	47
12. Sample Size and Statistical Methods	49
12.1. Determination of Sample Size	49
12.2. Statistical and Analytical Plans	49

12.2.1. General Considerations	49
12.2.2. Patient Disposition	50
12.2.3. Patient Characteristics	50
12.2.4. Concomitant Therapy	50
12.2.5. Treatment Compliance	50
12.2.6. ePRO Diary Compliance	51
12.2.7. Primary and Gated Outcome and Methodology	51
12.2.7.1. Primary Outcome	51
12.2.7.2. Gated Secondary.....	52
12.2.8. Other Efficacy Analyses.....	52
CCI	
12.2.10. Safety Analyses.....	53
12.2.10.1. Categorical Safety Variables.....	53
12.2.10.2. Adverse Events.....	53
12.2.10.3. Suicide-Related Thoughts and Behaviors.....	53
12.2.10.4. Vital Signs and Weight	54
12.2.10.5. Electrocardiogram Intervals and Heart Rate.....	54
12.2.10.6. Laboratory Tests.....	54
12.2.10.7. Immunogenicity Analyses	55
12.2.11. Subgroup Analyses	55
12.2.12. Interim Analyses	55
13. Informed Consent, Ethical Review, and Regulatory Considerations	56
13.1. Informed Consent.....	56
13.2. Ethical Review	56
13.3. Regulatory Considerations	56
13.3.1. Investigator Information.....	57
13.3.2. Protocol Signatures	57
13.3.3. Final Report Signature	57
14. References	58

List of Figures

Figure	Page
Figure CGAL.1. Illustration of study design for clinical protocol I5Q-MC-CGAL.	22

List of Attachments

Attachment		Page
Attachment 1.	Protocol CGAL Study Schedule.....	60
Attachment 2.	Protocol CGAL Clinical Laboratory Tests	68
Attachment 3.	Hepatic Monitoring Tests for Treatment-Emergent Abnormality.....	70
Attachment 4.	Protocol CGAL Sampling Summary.....	71
Attachment 5.	Protocol Amendment Summary: I5Q-MC-CGAL(d).....	72

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
ACOVA	analysis with analysis of covariance
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
BUN	blood urea nitrogen
CGRP	calcitonin-gene-related peptide
CIDBF	capsaicin-induced dermal blood flow
CIOMS	Council for International Organizations of Medical Sciences
CMH	Cochran-Mantel-Haenszel
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.
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
ECG	electrocardiogram
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.
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
GPS	Global Patient Safety
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICHD-3	International Classification of Headache Disorders-3 beta
IHS	International Headache Society
IND	Investigational New Drug application

INR	international normalized ratio
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
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
OTC	over the counter
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PD	pharmacodynamics
PGI-I	Patient Global Impression of Improvement

PK	pharmacokinetics
PR	pulse rate
PT	preferred term
QTc	corrected QT interval
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. For this study, the terms enrolled and randomized are interchangeable.
RBC	red blood cells
REML	restricted maximum likelihood-based
rescreen	To screen a patient who was previously declared a screen failure for the same study.
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.
SD	standard deviation
SHSF	Self-Harm Supplement Form
SHFU	Self-Harm Follow-Up Form
SOC	system organ class
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.
SUNCT (SUNA)	short-lasting unilateral neuralgiform headache attacks
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
WBC	white blood cells

A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 in Patients with Episodic 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 (*International Classification of Headache Disorders, Third Edition, beta version [ICHD-3] 2013*). The diagnosis of cluster headache is distinctly recognized and defined by the ICHD-3. The natural course of illness of cluster headache can be conceptualized as consisting of two phases: (1) *cluster periods* (typically lasting weeks or months) composed of a series of 15 to 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 two 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 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 one approved abortive medication (treatment initiated at the start of the attack to shorten the overall duration of the attack); 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, 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 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 (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. 2014). 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 four 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 clinically meaningful 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 electrocardiogram (ECG) parameters (de Hoon et al. 2013). Further details of the safety, pharmacokinetic (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 at 150 mg once every 14 days for six 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. 2014). Treatment-emergent adverse events (TEAEs) 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. 2014). 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 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 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-CGAL (CGAL), will assess the safety and efficacy of LY2951742 300 mg every 30 days in patients with episodic cluster headache.

6. Objectives

6.1. Primary Objective

The primary objective is to assess the efficacy of LY2951742 300 mg every 30 days compared with placebo in reducing the frequency of weekly cluster headache attacks in patients with episodic cluster headache. The primary outcome measure will be the weekly cluster headache attack frequency. The primary endpoint will be the overall mean change from baseline in weekly cluster headache attack frequency across Weeks 1 to 3 with LY2951742 compared with placebo. Baseline is defined as the last 7 days in the eligibility report (pre-randomization diary phase).

6.2. Secondary Objectives

6.2.1. Gated Objective

To assess the efficacy of LY2951742 compared with placebo in the proportion of patients meeting response at Week 3. For this analysis, response is defined as a reduction from baseline of 50% or greater in the weekly cluster headache attack frequency.

6.2.2. Other Secondary Objectives

- To assess whether LY2951742 is superior to placebo on the following:
 - a. The proportion of patients with a 50% or greater reduction in the weekly number of cluster headache attacks from baseline for each weekly interval through Week 8
 - b. The proportion of patients with a 30% or greater reduction in the weekly number of cluster headache attacks from baseline for each weekly interval through Week 8
 - c. Mean change in the weekly cluster headache attack frequency from baseline for each weekly interval through Week 8
 - d. 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 Week 4 and Week 8.
- To compare the safety and tolerability of LY2951742 with placebo in patients with episodic cluster headache using the following measures:
 - a. spontaneously reported TEAEs
 - b. SAEs
 - c. discontinuation rates
 - d. 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 is superior to placebo as measured by:

- Mean change in the weekly number of times an abortive medication was taken from baseline for each weekly interval through Week 8 comparing LY2951742 with placebo.
- Change in percentage of times using oxygen from baseline for each weekly interval through Week 8 comparing LY2951742 with placebo.
- Change in percentage of times using triptan from baseline for each weekly interval through Week 8 comparing LY2951742 with placebo.
- Change in percentage of times of using acetaminophen/paracetamol or NSAIDs from baseline for each weekly interval through Week 8 comparing LY2951742 with placebo.
- The proportion of patients with a 75% or greater reduction in the weekly number of cluster headache attacks from baseline for each weekly interval through Week 8 comparing LY2951742 with placebo.
- The proportion of patients with a 100% reduction in the weekly number of cluster headache attacks from baseline for each weekly interval through Week 8 comparing LY2951742 with placebo.
- Mean change in the cluster headache attack average weekly pain severity (based on 5-point scale) from baseline through Week 8 comparing LY2951742 with placebo.

A large, bold, red logo consisting of the letters 'CCl' in a sans-serif font. The letters are outlined in white. The logo is centered on a solid black rectangular background.

7. Investigational Plan

7.1. Summary of Study Design

Study CGAL is a Phase 3 multi-center, outpatient, randomized, double-blind, placebo-controlled study of LY2951742 300 mg in the prevention of episodic cluster headache. The study has 4 study phases (SP): SP I (screening/washout), SP II (pre-randomization diary), SP III (randomized, double-blind, placebo-controlled treatment), and SP IV (post-treatment follow-up) (Figure CGAL.1). Patients who discontinue the study during the double-blind treatment phase should enter the post-treatment follow-up phase.

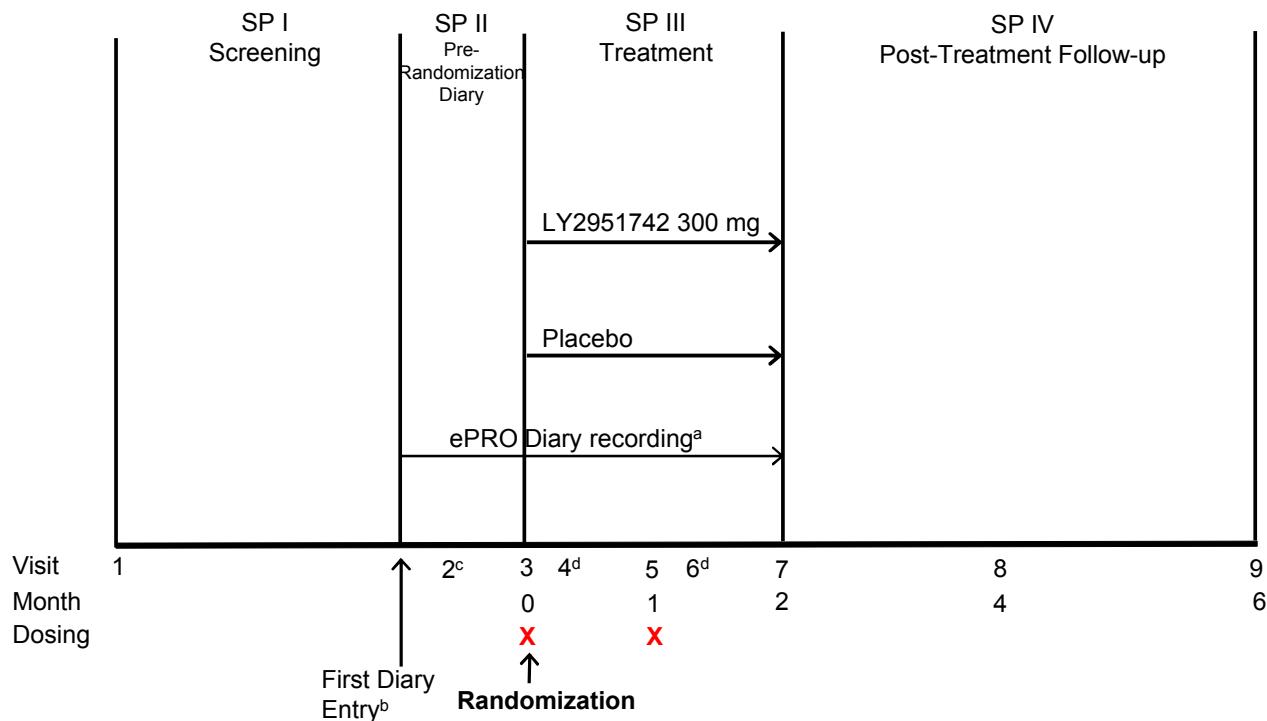


Figure CGAL.1. Illustration of study design for clinical protocol I5Q-MC-CGAL.

Study Phase I is the screening/washout phase starting at Visit 1 to the start of SP II and lasting for a minimum of 0 days to a maximum of 12 months. Patients will sign an informed consent document at Visit 1 prior to completing study-related initial screening procedures. For those patients who meet initial screening criteria, an electronic patient reported outcome (ePRO) diary will be dispensed during SP I to the patient. Patients will be instructed on how to use the ePRO diary to record daily cluster headache attack information and use of allowed 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.

Below is a description of patient flow through SP I and SP II. Patients can enter into SP I in one of two clinical states: (1) remission; or (2) while in an active cluster period (see inclusion criteria #3 and #4):

(1) Patients who enter SP I while in remission

These patients will complete SP I screening procedures at Visit 1 and remain in SP I until the onset of their next cluster period. The patient will begin recording in the ePRO diary on the day of their first cluster headache attack (which marks the start of SP II) and continue to record in the diary on a daily basis whether or not an attack was experienced on a given day. At the onset of this cluster period, the patient must contact their investigator to schedule a Visit 2 and Visit 3. The minimum time between Visit 2 and Visit 3 is five days to allow for laboratory and diagnostic screening test results to be completed and reviewed. At Visit 2, laboratory samples will be collected, and other additional baseline procedures will be performed to determine further eligibility (see Study Schedule, [Attachment 1](#)). As stated above, the investigator needs to ensure appropriate washout of excluded medications has occurred before patients begin recording their baseline cluster headache attack data and enter SP II.

(2) Patients who enter SP I while in an active cluster headache period

These patients who meet initial screening eligibility can move directly into SP II (the baseline phase) **as long as they do not need to wash out of any excluded medications**. Following informed consent, the Visit 1 and Visit 2 procedures are completed at the initial visit (Visit 1).

For **all** patients, SP II begins on the day that the patient first records a cluster headache attack in their ePRO diary. The minimum duration of SP II is 10 days of daily ePRO diary recording prior to Visit 3, and the preferred maximum duration of SP II is 14 days of daily ePRO diary recording prior to Visit 3. Therefore, sites may schedule Visit 3 beginning 11 days from the start of SP II.

Beginning eleven 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 data from SP II (sites should 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 system 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.

SP III is an 8-week randomized, double-blind, placebo-controlled treatment phase. Patients who meet all eligibility criteria will be randomized to LY2951742 300 mg or placebo. The unblinded site personnel will prepare the IP for each patient. Each dose of IP will be administered as 3 SC injections at office visits Visit 3 and Visit 5. After the first administration of IP at V3, the patient should remain in the office for 30 minutes for observation. The site will have a scheduled phone visit (Visit 4 and Visit 6) with the patient approximately one week after each IP administration to collect spontaneously reported AEs. During SP III, the patient will continue to record their cluster headache attack information daily in the ePRO diary.

Study Phase IV is a 16-week post-treatment phase for safety follow-up. Patients who discontinue early in SP III should enter the post-treatment phase (SP IV).

7.2. Discussion of Design and Control

This study is a double-blind, placebo-controlled, multi-center study consisting of 4 study phases: a screening/washout phase, a pre-randomization diary phase to assess cluster headache attack frequency, a double-blind, placebo-controlled treatment phase to assess treatment outcomes, and a post-treatment phase to allow for safety monitoring after LY2951742 treatment is stopped.

The proposed duration of the double-blind treatment phase is 8 weeks, with the primary endpoint assessed across Weeks 1 to 3 after the first IP dose. While Eli Lilly and Company (Lilly) considers an effect, if present, will be observed after one administration, it is possible one dose may not be sufficient for some patients. Inclusion of a placebo-control for another month (following the second IP injection) will allow for the assessment of the efficacy of LY2951742 through 8 weeks. This duration and use of placebo-control is consistent with current published International Headache Society guidelines (IHS 1995), in which a duration of at least 2 weeks is recommended when assessing prophylaxis treatment.

The study will allow the use of certain abortive treatments (those initiated at the start of a cluster headache attack to shorten overall attack duration) for cluster headache attacks, but will require exclusion of all preventive therapies to directly assess the superiority of LY2951742 over placebo as a preventive treatment.

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 (See 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 are eligible to be included in the study only if they meet all of the following criteria:

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 ***episodic cluster headache*** and distinguished from chronic cluster headache as defined by IHS ICHD-3 beta (ICHD-3 2013) (see Section 8.1.1).
3. At Visit 1, have a prior history of a cluster period lasting 6 weeks or greater.
4. At Visit 1, for patients currently in an active cluster period:
 - a. In opinion of investigator, would be expected to continue in the current period for at least another 6 weeks based on previous cluster period history.
 - b. They are not taking any excluded medications that require washout (see Criteria #9).

Note: patients not meeting criteria a and b must be a screen fail, but they may be considered for rescreening.

5. **Do not share this inclusion criteria with potential patients:** During SP II, have a baseline weekly cluster headache attack frequency (based on ePRO vendor eligibility report) preceding Visit 3 of:
 - a. minimum of 1 cluster headache attack every other day and at least 4 total attacks
 - b. 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.

6. At Visit 1, are able to distinguish cluster headache attacks from other headaches (i.e. 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.
 - a. 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 investigational product.
 - b. Male patients agree to use a reliable method of birth control during the study and for 5 months following last dose of investigational product.
 - c. 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 to 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 time frame noted:

- a. use within 14 days prior to SP II of any of the following: dihydroergotamine or ergot derivatives; gabapentin; lithium; melatonin; methergine; topiramate; valproate; verapamil, opioids
- b. 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 are allowed to use only the following for acute/abortive treatment for their cluster headache attacks: high-flow oxygen; oral triptans, sumatriptan subcutaneous injection; sumatriptan nasal spray; zolmitriptan nasal spray; acetaminophen and NSAIDs.

10. Throughout the study (Informed Consent through Visit 9), 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 (IHS ICHD-3-beta)*, diagnostic criteria for **Episodic 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 to 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; (g) miosis and/or ptosis,
 - 2. a sense of restlessness or agitation.
- D. Attacks have a frequency between one every other day and eight 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 Episodic Cluster Headache:

- A. Attacks fulfilling criteria for **Cluster Headache** and occurring in bouts (cluster periods)
- B. At least two cluster periods lasting from 7 days to 1 year (when untreated) and separated by pain-free remission periods of ≥ 1 month.

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:
 - a. 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 an MOH of some other headache type.
 - b. 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.
 - c. Are taking indomethacin and/or are suspected of having another distinct trigeminal autonomic cephalgina such as hemicrania continua, paroxysmal hemicrania, or short-lasting unilateral neuralgiform headache attacks (SUNCT or SUNA).
 - d. 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 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) history of 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:

- a. 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).
- b. 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.
- c. 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.
- d. Clinical evidence of peripheral vascular disease (e.g., Buerger's Disease) or a diagnosis of Raynaud's Phenomenon.
- e. Have any history of intracranial or carotid aneurysm, intracranial hemorrhage, or stroke.
- f. 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:

- a. Have a lifetime history of seizures (except for childhood febrile seizures).
- b. 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.
- c. Prior to Visit 3, patients with an elevation of $\geq 2X$ the upper limit of normal (ULN) for alanine aminotransferase (ALT), or $\geq 1.5X$ ULN for 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.
- d. 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:

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

- b. History of drug, alcohol, opioid, or barbiturate abuse/dependence within 1 year prior to SP II (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 medication in a manner that the Investigator considers indicative of abuse/dependence. This exclusion criterion does not apply to tobacco and caffeine.
- c. History of use of psilocybin (mushrooms), LSD, or 2-bromo-LSD within 2 months prior to SP II.
- d. 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 during the baseline assessment (defined in Statistical Methods, Section 12) as evidence of inadequate compliance.

26. Employees of Lilly 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) $\geq 40 \text{ kg/m}^2$.

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 4
- Inclusion Criterion 5; 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 during their next cluster headache period. Rescreening during the current cluster headache period is not allowed.
- Inclusion Criterion 5b; If a patient fails eligibility due to the occurrence of >8 cluster headache attacks per day, the patient may be considered for rescreen during their current cluster headache period, if, in the opinion of the investigator, the patient would be expected to continue in the current period for at least another 6 weeks based on previous cluster period history. If the patient is not expected to continue in the current period for another 6 weeks, the patient may be considered for rescreen during their next cluster headache period.
- Inclusion Criterion 5 “Note” section only; a patient with 2 or more consecutive days without an attack during the baseline assessment may be considered for rescreen during their next cluster headache period. Rescreening during the current cluster headache period is not allowed.
- 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 during their current cluster headache period, if, in the opinion of the investigator, the patient would be expected to continue in the current period for at least another 6 weeks based on previous cluster period history. If the patient is not expected to continue in the current period for another 6 weeks, the patient may be considered for rescreen during their next cluster headache period.
- Exclusion Criterion 28

- Patients using a concomitant medication that requires a stable dose for a specific duration prior to SPII per study requirements, may be rescreened if additional time is needed to meet the duration requirement.
- Patients using concomitant medication(s) that require a wash-out prior to SPII, may be rescreened once an adequate wash-out (e.g. 5 half-lives) has occurred.

Additionally, if a patient enters SP I while in remission and does not enter a cluster period during the maximum duration of SP I (12 months), they are considered a screen failure and must be discontinued from the study. If they still wish to participate in the study and the study is still actively enrolling new patients, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number and complete Visit 1 again. If a patient enters SP I while in remission and the study completes full enrollment while the patient is still in SP I, the patient will be discontinued from the study.

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 one of the following conditions after consultation with the Lilly designated medical monitor:

- ALT or AST $>8\times$ ULN
- ALT or AST $>5\times$ ULN for more than 2 weeks
- ALT or AST $>3\times$ ULN and either TBL level $>2\times$ ULN or international normalized ratio (INR) $>1.5\times$ ULN

- ALT or AST $>3\times$ 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 $>3\times$ ULN
- ALP $>2.5\times$ ULN and TBL $>2\times$ ULN
- ALP $>2.5\times$ 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 discontinue from SP III and enter SP IV, 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:

- If a patient remains within the screening phase when study enrollment is complete, the patient will be discontinued.
- Enrollment in any other clinical trial involving an investigational product 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 therapeutic agent, between 30 days prior to SP II through SP III, 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 should enter the post-treatment period; those patients who discontinue the study early during SP IV 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: placebo or LY2951742 300 mg. Each treatment group will be administered three 1 ml SC injections, by qualified site personnel, every 30 days for a total of 2 administrations during SP III. 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 investigational product dispensing and collection, and
- returning all unused medication to Lilly or its designee at the end of the study.

Note: In some cases, sites may destroy the material if, during the 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. The drug product is composed of the active ingredient, LY2951742, in citrate buffer in addition to other inactive ingredients.

Details for the requirements for preparation of the LY2951742 doses and placebo solutions will be provided to the unblinded site personnel in the Pharmacy Binder Dosing Instructions for LY2951742, 75 mg.

Storage and Stability

Unreconstituted glass vials of LY2951742 for Injection, 75 mg, are stable and must be stored in a refrigerator at 2°C to 8°C (35.6°F to 46.4°F).

Approximately 20 minutes prior to preparing for administration to patients, the vials should be removed from the 2°C to 8°C storage area and allowed to equilibrate at ambient conditions. After dose preparation, immediate transfer to the syringe is recommended for administration. Drug product must be administered within 6 hours when stored at room temperature.

Investigational Product Dose Preparation

The designated unblinded site personnel is responsible for preparing LY2951742 and placebo injections according to the CGAL Pharmacy Binder Dosing Instructions for LY2951742, 75 mg, and each dose will be identified as study drug without identification of the drug or dose.

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

Following dose preparation, 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.

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 investigational product to each patient. The Unblinded Site Personnel should confirm the assigned packages in IWRS prior to preparation and administration.

The IWRS system will be programmed 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) and investigative site. The purpose of the algorithm is to maintain approximately the same proportion of gender 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 study of LY2951742 in cluster headache is 300 mg administered approximately 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 Q2W, 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 three 1-mL SC injections every 30 days for a total of 2 administrations during SP III. 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 acute/abortive treatments for their cluster headache attacks: high-flow oxygen; oral triptans, sumatriptan SC injections; sumatriptan nasal spray; zolmitriptan nasal spray; acetaminophen; NSAIDs. No medications, treatments, procedures, or other interventions for the preventive treatment of cluster headache are permitted during SP II and SP III. In SP IV, if the investigator deems it necessary to resume a preventive medication for a patient, the patient is allowed to resume only the following medications for prevention of cluster headache: verapamil (maximum daily dosage: 480 mg), lithium, melatonin, valproate, gabapentin, and topiramate. Patients will be asked to record use of their allowed standard abortive treatments in their daily ePRO diary.

A list of allowed/not allowed medications will be provided separately. 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, over-the-counter (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/CRS or delegate.

10. Efficacy, 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. 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 investigational product 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 informed consent form (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 eCRF into the Lilly designated electronic data capture system (EDC).

In addition, all AEs occurring after the patient receives the first dose of investigational product 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 investigational product. If a patient experiences an SAE after signing informed consent, but prior to receiving investigational product, 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 adverse events 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 investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the 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 ([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 patient 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 patient 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 at every scheduled and unscheduled office visit as specified in the Study Schedule ([Attachment 1](#)). 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) at every scheduled and unscheduled office visit as specified in the Study Schedule ([Attachment 1](#)). 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-Help 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 clinical research physician 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 (GPS) 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 experiences elevated ALT $\geq 3X$ ULN, ALP $\geq 2X$ ULN or elevated TBL $\geq 2X$ 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 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 ([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 (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 investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

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 meet Inclusion/Exclusion criteria and to monitor patient 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, pharmacodynamics, 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.



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 (storage sample) will be collected at the times specified in the Study Schedule ([Attachment 1](#)) and in the amounts specified ([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 episodic cluster headache, mechanism of action of LY2951742, and/or research method or in validating diagnostic tools or assay(s) related to episodic 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 (with or without pre-existing antibodies) against LY2951742. Immunogenicity will be assessed by a validated assay designed to detect anti-drug antibodies 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.



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

Some or all of a patient'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 patient'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 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/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 during SP III will be conducted on an intent-to-treat (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 during SP III will be conducted on the safety population, which also includes all patients who were randomized and receive at least 1 dose of study drug. However, patients will be analyzed by actual study treatment received most often (modal treatment) during the double-blind treatment phase. When change from baseline is assessed, the patient will be included in the analysis only if he/she has a baseline and a post-baseline measurement.

For analyses of the post-treatment phase, the post-treatment population will be used. Post-treatment population will be defined as all patients who entered the post-treatment phase (SP IV) as indicated by entering any post-treatment visit.

Details related to handling of missing data will be described 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 unless otherwise stated. The 95% confidence intervals (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.

Categorical comparisons between treatment groups will be performed using Fisher's exact tests, where appropriate.

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 changes, will be described in the statistical analysis plan (SAP) and/or 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 Eli Lilly and Company 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 and SP IV 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.

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 of Visit 1.

Comparisons between treatment groups will be performed using Fisher's exact tests for categorical data and ANOVA with treatment and pooled investigative site 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 collected from eCRF as well as abortive medications for cluster headache attack collected through ePRO will be summarized separately for all ITT patients for both SP III and SP IV. Treatment group comparisons will be done using Fisher's exact test for SP III with the ITT population. Descriptive statistics only will be presented for the treatment groups in SP IV.

12.2.5. Treatment Compliance

Treatment compliance will be calculated for SP III 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

ePRO diary compliance at each weekly interval (including baseline, Week 1, 2, 3, 4, 5, 6, 7 and 8) 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 entries 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 is 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 weekly 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 restricted maximum likelihood-based (REML-based), mixed-effects repeated measures (MMRM) analysis using all the longitudinal observations from Week 1 to Week 3. The analysis of the primary outcome will be the main effect of treatment between LY2951742 300 mg and placebo across Weeks 1 to 3 of the treatment phase from a repeated measures analysis on mean change from baseline in the weekly attack frequency. This provides the average treatment effect over the 3-week period. Baseline is defined as the last 7 days in the eligibility report (pre-randomization diary phase).

The model for the primary analysis will include the fixed, categorical effects of treatment, gender, 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-patient and within-patient portions by the DDFM=BETWITHIN option in SAS®.

12.2.7.2. Gated Secondary

The gated secondary outcome, 50% response, is the proportion of patients meeting the response criteria at Week 3 and will be assessed using Koch's Nonparametric Randomization-Based Analysis of Covariance method (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 Week 3, for any reason, will be considered a non-responder at all missing assessments.

12.2.8. Other Efficacy Analyses

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

For the continuous secondary and exploratory efficacy measures, the change from baseline to each weekly interval post-baseline measure will be analyzed from repeated measures analyses.

For 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 efficacy measures including 30% response, 50%, and 75% response and 100% response, the percentage of patients meeting response criteria at each weekly 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®.



12.2.10. Safety Analyses

The safety analyses will be conducted for SP III and SP IV.

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

- AEs
 - TEAEs
 - By preferred term
 - By system organ class
 - By maximum severity
 - Considered to be related to IP by investigator
 - SAEs
 - AE leading to discontinuation
- Suicidal ideation and behaviors assessed by solicited questioning using the C-SSRS
- Vital signs and weight
- ECGs
- Laboratory measurements
- Anti-drug antibody.

12.2.10.1. Categorical Safety Variables

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 the safety population. Descriptive statistics only will be presented for the treatment groups in SP IV with the post-treatment population.

12.2.10.2. Adverse Events

Treatment-emergent adverse events (TEAEs) 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 (Preferred Term [PT], High Level Term, or System Organ Class [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 and SP IV 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.

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 for analysis.

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 corrected QT (QTc) and QTcF (measured in milliseconds [msec]) will be calculated with Fridericia's formula as $QT/RR^{1/2}$. The number and percent of patients meeting criteria for treatment-emergent abnormalities in ECG intervals (pulse rate [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 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 Data Monitoring Committee (DMC) Charter. However, this interim analysis for sample size re-estimation will not happen due to enrollment infeasibility. The DMC will still independently monitor patient safety during this trial.

The other 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.

Unblinding details are specified in the unblinding plan section of the statistical analysis plan (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 investigational product.

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 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.

14. References

de Hoon J, Montieth D, Vermeersch S, Van Hecken A, Abu-Raddad E, Collins E, Schuetz T, Scherer J, Grayzel D. Safety, pharmacokinetics, and pharmacodynamics of LY2951742: a monoclonal antibody targeting CGRP [abstract]. In: Abstracts of the 2013 International Headache Congress, 27–30 June 2013, John B. Hynes Veterans Memorial, Convention Center, Boston, MA, USA. *Cephalalgia*. 2013;33(Suppl 8):247. Abstract P367.

Diggle P, Kenward MG. Informative drop-out in longitudinal data analysis. *J Royal Statist Soc Series C: Appl Statist*. 1994;43(1):49-93.

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*. 2014;13(9):885-892.

Edvinsson L, Goadsby PJ. Neuropeptides in migraine and cluster headache. *Cephalalgia*. 1994;14(5):320-327.

Fanciullacci M, Alessandri M, Figini M, Geppetti P, Michelacci S. Increase in plasma calcitonin gene-related peptide from the extracerebral circulation during nitroglycerine-induced cluster headache attack. *Pain*. 1995;60(2):119-123.

Fanciullacci M, Alessandri M, Sicuteri R, Marabini S. Responsiveness of the trigeminovascular system to nitroglycerine in cluster headache patients. *Brain*. 1997;120(2):283-288.

Guy W. ECDEU assessment manual for psychopharmacology, revised 1976. Rockville, MD: National Institute of Mental Health, Psychopharmacology Research Branch. p 217-222. Available at: <https://archive.org/details/ecdeuassessmentm1933guyw>. Accessed December 16, 2014.

[ICHD-3] Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*. 2013;33(9):629-808.

[IHS] International Headache Society. Guidelines for controlled trials of drugs in cluster headache. 1995. Available at: <http://www.ihc-headache.org/ichd-guidelines>. Accessed December 16, 2014.

Karst M, Halpern JH, Bernateck M, Passie T. The non-hallucinogen 2-bromo-lysergic acid diethylamide as preventative treatment for cluster headache: an open, non-randomized case series. *Cephalalgia*. 2010;30(9):1140-1144.

Kenward MJ, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. *Biometrics*. 1997;53(3):983-997.

Koch GG, Tangen CM, Jung JW, Amara IA. Issues for covariance analysis of dichotomous and ordered categorical data from randomized clinical trials and non-parametric strategies for addressing them. *Stat Med*. 1998;17(15-16):1863-1892.

Manzoni GC, Terzano MG, Bono G, Micieli G, Martucci N, Nappi G. Cluster headache—clinical findings in 180 patients. *Cephalalgia*. 1983;3(1):21-30.

Matharu MS, Goadsby PJ. Trigeminal Autonomic Cephalgias. *J Neurol Neurosurg Psychiatry*. 2002;72(Suppl 2):ii19-ii26.

McCarthy PW, Lawson SN. Cell type and conduction velocity of rat primary sensory neurons with calcitonin gene-related peptide-like immunoreactivity. *Neuroscience*. 1990;34(3):623-632.

McGeeney BE. Hallucinogens and cannabinoids for headache. *Headache*. 2012;52(Suppl 2):94-97.

Pocock S, Simon R. Sequential treatment assignment with balancing of prognostic factors in controlled clinical trial. *Biometrics*. 1975;31(1):103-115.

Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, Currier GW, Melvin GA, Greenhill L, Shen S, Mann JJ. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*. 2011;168(12):1266-1277.

Rozen TD, Fishman RS. Cluster headache in the United States of America: demographics, clinical characteristics, triggers, suicidality, and personal burden. *Headache*. 2012;52(1):99-113.

Tepper SJ, Stillman MJ. Cluster headache: potential options for medically refractory patients (when all else fails). *Headache*. 2013;53(7):1183-1190.

The Sumatriptan Cluster Headache Study Group. Treatment of Acute Cluster Headache with Sumatriptan. *N Engl J Med*. 1991;325:322-326.

Torelli P, Manzoni GC. Pain and behaviour in cluster headache. A prospective study and review of the literature. *Funct Neurol*. 2003;18(4):205-210.

van Vliet JA, Eekers PJ, Haan J, Ferrari M. Features involved in the diagnostic delay of cluster headache. *J Neurol Neurosurg Psychiatry*. 2003;74(8):1123-1125.

Attachment 1. Protocol CGAL Study Schedule

Study Schedule, Protocol I5Q-MC-CGAL, SP I - SP III

Patient Status	Entering in active cluster period	Entering in Remission		SP III					Comments
		SP I	SP II	Treatment					
Study Phase (SP)	Screening/ Pre-Rand. Diary	Screening	Pre-Rand. Diary	3	4 (Ph. visit)	5	6 (Ph. visit)	7	Comments
Description	1 (Note: V1 and V2 procedures are combined into V1)	1	2	3	4 (Ph. visit)	5	6 (Ph. visit)	7	
Visit	Min range: SP I/II-10 to 15d	Allowable range b/w V1 and V2: 0 d to 1 yr	Min range: SPII-10 to 15d; V2 to V3-5d	3	4 (Ph. visit)	5	6 (Ph. visit)	7	Phone visits (V4 and V6) are contacts between office visits to collect any spontaneously reported AE
Visit Day									For flow of patients through SP I and SP II, please refer to the study design Section 7.1.
Month				Day 1	Day 7	Day 30	Day 37	Day 60	
Interval (days) since previous office visit						1		2	
Interval allowance (days)					7	30	7	30	The interval from V3 to V5 and the interval from V5 to V7 should be no less than 28 days .
					+/-1	+5/-2	+/-1	+5/-2	
Informed consent	X	X							Patients who have an extended period between V1 and V2 may need to be re-consented according to local regulations. Sites will be encouraged to stay in contact with patients during SP I who enter in remission.
Inclusion and exclusion criteria	X	X	X	X					
Dispense ePRO diary	X	X							
Demographics	X		X						
Med history and pre-existing conditions	X	X							

Study Schedule, Protocol I5Q-MC-CGAL, SP I - SP III

Patient Status	Entering in active cluster period	Entering in Remission		SP III Treatment					Comments
		SP I	SP II						
Study Phase (SP)	Screening/ Pre-Rand. Diary	Screening	Pre-Rand. Diary						
	1 (Note: V1 and V2 procedures are combined into V1)	1	2	3	4 (Ph. visit)	5	6 (Ph. visit)	7	
Visit									
Treatment				X		X			IP injections are to occur after all other visit procedures are completed. Following the first dose at V3 , patients will be observed for 30 min in the office
Prior cluster headache attack history	X	X							
ECG	X		X					X	All ECGs should be collected prior to blood draws and dosing. Patients must be supine for approx. 5-10 min before ECG collection and remain supine but awake during ECG collection
Physical examination	X	X	X						Must include a brief neurological exam
Caffeine use	X		X						
Tobacco use (smoking and non-smoking)	X		X						
Nicotine use	X		X						
Alcohol use	X		X						
Height	X	X	X						
Weight	X	X	X					X	

Study Schedule, Protocol I5Q-MC-CGAL, SP I - SP III

Patient Status	Entering in active cluster period SP I/II Screening/ Pre-Rand. Diary	Entering in Remission		SP III Treatment					Comments	
		SP I Screening	SP II Pre-Rand. Diary							
Visit		1 (Note: V1 and V2 procedures are combined into V1)	2	3	4 (Ph. visit)	5	6 (Ph. visit)	7	Phone visits (V4 and V6) are contacts between office visits to collect any spontaneously reported AE	
		X		X						
Waist and Hip Circumference										
Vital signs		X		X		X		X	Vital signs will be taken at scheduled and unscheduled office visits and 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*	*Fasting chemistry labs (no food or drink, except water, for at least 8 hrs) to be performed at this visit.	
Urinalysis		X		X				X		
HbA1C		X		X				X		
Serum Pregnancy or FSH		X		X					Female patients	
Urine drug screen		X		X						
Randomization										

Study Schedule, Protocol I5Q-MC-CGAL, SP I - SP III

Patient Status	Entering in active cluster period SP I/II Screening/ Pre-Rand. Diary	Entering in Remission		SP III Treatment					Comments	
		SP I Screening	SP II Pre-Rand. Diary							
Visit		1 (Note: V1 and V2 procedures are combined into V1)	2	3	4 (Ph. visit)	5	6 (Ph. visit)	7		
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.	
Plasma Storage Sample (K+/EDTA)		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 blood sampling					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.	

Study Schedule, Protocol I5Q-MC-CGAL, SP I - SP III

Patient Status	Entering in active cluster period SP I/II Screening/ Pre-Rand. Diary	Entering in Remission		SP III Treatment					Comments
		SP I Screening	SP II Pre-Rand. Diary						
Visit		1 (Note: V1 and V2 procedures are combined into V1)	2	3	4 (Ph. visit)	5	6 (Ph. visit)	7	
									Phone visits (V4 and V6) are contacts between office visits to collect any spontaneously reported AE

CCI

RNA storage sample	X	X	X		X		X		Sample must be collected in a Tempus tube
PGI-I					X			X	
C-SSRS/SHSF, SHFU	X	X	X	X		X		X	To be completed at scheduled and unscheduled office visits
Recording of AEs	X	X	X	X	X	X	X	X	
Review Diary data				X		X		X	Following Informed Consent, patients are required to complete their diaries daily beginning on the day of their next cluster headache attack. Sites should review the diary compliance with the patient during office visits.
Concomitant medications	X	X	X	X	X	X	X	X	

Abbreviations: AE = adverse event; approx. = approximately; b/w = between; CGRP = calcitonin-gene related peptide; C-SSRS = Columbia-Suicide Severity Rating Scale; d = day; ECG = electrocardiogram; ePRO = electronic patient-reported outcome; ET = early termination; FSH = follicle stimulating hormone; hrs = hours; IP = investigational product; min = minute; PGI-I = Patient Global Impression of Improvement; Ph = phone; Pre-Rand. = pre-randomization; PK = pharmacokinetics; SHSF = Self-Harm Supplement Form; SHFU = Self-Harm Follow-Up Form; SP = Study Phase; V = visit; yr = year.

^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, I5Q-MC-CGAL, SP IV-ET

Study Phase (SP)	SP IV		ET	<u>Comments</u>
Description	Post-treatment			
Interval (days) since previous office visit	60	60		
Interval allowance (days)	+/- 8	+/- 8		
Visit	8	9		
Visit Day	Day 120	Day 180	ET	
Month	4	6		
ECG		X	X	All ECGs should be collected prior to blood draws and dosing. Patients must be supine for approx. 5-10 min before ECG collection and remain supine but awake during ECG collection
Weight		X	X	
Vital signs	X	X	X	Vital signs will be taken at scheduled and unscheduled office visits and 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*	*Fasting chemistry labs (no food or drink, except water, for at least 8 hrs) to be performed at this visit.
Urinalysis		X	X	
HbA1C		X	X	
Serum Pregnancy		X	X	Females only
Immunogenicity		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.
Plasma Storage Sample (K+/EDTA)		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 blood 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	Sample must be collected in a Tempus tube

Study Schedule, I5Q-MC-CGAL, SP IV-ET

Study Phase (SP)	SP IV		ET	<u>Comments</u>
Description	Post-treatment			
Interval (days) since previous office visit	60	60		
Interval allowance (days)	+/- 8	+/- 8		
Visit	8	9		
PGI-I		X	X	
C-SSRS/SHSF, SHFU	X	X	X	To be completed at scheduled and unscheduled office visits
Recording of AEs	X	X	X	
Concomitant medications	X	X	X	

Abbreviations: AE = adverse event; approx. = approximately; b/w = between; CGRP = calcitonin-gene related peptide; C-SSRS = Columbia-Suicide Severity Rating Scale; d = day; ECG = electrocardiogram; ePRO = electronic patient-reported outcome; ET = early termination; FSH = follicle stimulating hormone; hrs = hours; IP = investigational product; min = minute; PGI-I = Patient Global Impression of Improvement; Ph = phone; Pre-Rand. = pre-randomization; PK = pharmacokinetics; SHSF = Self-Harm Supplement Form; SHFU = Self-Harm Follow-Up Form; SP = Study Phase; V = visit; yr = year.

^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 CGAL Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology:

Hemoglobin
Hematocrit
Erythrocyte count (RBC)
Mean cell volume
Mean cell hemoglobin concentration
Leukocytes (WBC)
Neutrophils, segmented
Lymphocytes
Monocytes
Eosinophils
Basophils
Platelets
HbA_{1c}

Urinalysis:

Specific gravity
pH
Protein
Glucose
Ketones
Blood
Urine leukocyte esterase

Clinical Chemistry:

Serum Concentrations of:
Sodium
Potassium
Total bilirubin
Direct bilirubin
Alkaline phosphatase
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Blood urea nitrogen (BUN)
Creatinine
Uric acid
Calcium
Glucose (fasting)^a

Albumin

Creatine kinase (CK)
Total cholesterol^a
HDL^a

Other

PK Sample (LY2951742 serum concentration determination)
Immunogenicity
Urine Drug Screen^b

Pregnancy Test (females only)^c

Serum pregnancy or FSH

Stored Samples

Plasma Storage (K+/EDTA **CCl**)

CCl

RNA

Abbreviations: FSH = follicle-stimulating hormone; HDL = high density lipoprotein; PK = pharmacokinetic; RBC = red blood cells; RNA = ribonucleic acid; WBC = white blood cells.

^a Fasting at Visit V3, V7, V9 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 V9 or 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
	Hepatitis C antibody
	Hepatitis E antibody, IgG
	Hepatitis E antibody, IgM
Hepatic Chemistry^a	Anti-nuclear antibody^a
Total bilirubin	Alkaline phosphatase isoenzymes^a
Direct bilirubin	Anti-Actin antibody^a
Alkaline phosphatase	Anti-smooth muscle antibody^a
ALT	
AST	
GGT	
CPK	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate 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 CGAL 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-CGAL 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	6	21 mL
CCI				
PK sample (determination of LY2951742 serum concentration)	Blood	2.5 mL	4	10 mL
CCI				
Plasma storage sample (K+/EDTA)	Blood	5 mL	6	30 mL
Immunogenicity samples	Blood	10 mL	4	40 mL
RNA storage sample	Blood	3 mL	5	15 mL
Total	Blood			196 mL
Hepatic monitoring ^c	Blood	3 - 30 mL	-	-

Abbreviation: CGRP = calcitonin gene related peptide; PK = pharmacokinetic; RNA = ribonucleic acid.

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

^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-CGAL(d)

Overview

Protocol I5Q-MC-CGAL (c), A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 in Patients with Episodic 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:

- Updated the primary endpoint to be the overall treatment effect across Weeks 1 to 3 in weekly cluster headache attack frequency rather than the treatment effect at a single time point (Week 3) in that treatment period to enable evaluation of treatment effect over a 3-week period.
- 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 randomization algorithm.
- Safety population and modal treatment description were added for safety analyses since it is more appropriate to present safety results by the actual treatments patients received.
- 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.
- 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.
- Updated the protocol to reflect that the interim analysis for sample size re-estimation will not occur.
- Minor editorial changes throughout the protocol as found.

Revised Protocol Sections

Note:	Deletions have been identified by strike-throughs .
	Additions have been identified by the use of <u>underline</u> .

Header

I5Q-MC-CGAL(ed) Clinical Protocol

Title

Protocol I5Q-MC-CGAL(ed)

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) and has been identified for clinical development in pain conditions relevant to the CGRP pathway such as migraine and cluster headache.

Primary Objective: The primary objective of this study is to assess the efficacy of LY2951742 300 mg every 30 days compared with placebo in reducing the frequency of weekly cluster headache attacks in patients with episodic cluster headache. The primary outcome measure will be the weekly cluster headache attack frequency. The primary endpoint will be the overall mean change from baseline in weekly cluster headache attack frequency from baseline to across Weeks 1 to Week 3 with LY2951742 compared with placebo. Baseline is defined as the last 7 days in the eligibility report (pre-randomization diary phase).

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 (NAbBs) ~~upon availability of the validated assay~~.

Exploratory Objectives:

- Change in percentage of times using oxygen ~~or triptan~~ from baseline for each weekly interval through Week 8 comparing LY2951742 with placebo.
- Change in percentage of times using triptan from baseline for each weekly interval through Week 8 comparing LY2951742 with placebo.

Statistical Methods:

Unless otherwise specified, efficacy analyses during SP III will be conducted on an intent-to-treat (ITT) population, which includes all patients who are randomized and receive at least ~~one~~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 during SP III will be conducted on the safety population, which also includes all patients who were randomized and receive at least 1 dose of study drug. However, patients will be analyzed by actual study treatment received most often (modal treatment) during the double-blind treatment phase.~~ When change from baseline is assessed, the patient will be included in the analysis only if he/she has a baseline and a post-baseline measurement.

For ~~some of the~~ analyses of the post-treatment phase, the post-treatment population will be used. Post-treatment population will be defined as all patients who entered the post-treatment phase (SP IV) as indicated by entering ~~the first~~any post-treatment visit. ~~Patients in the post-treatment population will be analyzed according to the treatment that they were randomized to at their randomization visit for analyses by treatment.~~ Details related to handling of missing data will be described 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 unless otherwise stated. The 95% confidence intervals (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.

~~Unless otherwise specified, when an analysis of variance (ANOVA) model is used to analyze a continuous efficacy variable, the model will contain the main effects of treatment, gender and pooled investigative site. Similar logic is applied to an analysis of covariance (ANCOVA) model, which in general, refers to the ANOVA model with baseline values added as a covariate. Categorical comparisons between treatment groups will be performed using Cochran-Mantel-Haenszel (CMH) controlling for pooled investigative site and Fisher's exact tests, where appropriate.~~

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 from Week 1 to Week 3. The analysis of the primary outcome will be the ~~contrast main effect of treatment~~ between LY2951742 300 mg and placebo ~~at across~~ Weeks 1 to 3 of the treatment phase from a repeated measures analysis on mean change from baseline in the weekly attack frequency. This provides the average treatment effect over the 3-week period. Baseline is defined as the last 7 days in the eligibility report (pre-randomization diary phase).

~~If the sample size is increased as a result of the interim analysis, the Cui, Hung, and Wang (CHW) procedure (Cui et al. 1999) will be applied to the primary endpoint to control the type I error at a one-sided $\alpha=0.025$ 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, Mehta, and Posch (2009) to assess sensitivity of the point estimate.~~

Efficacy – Gated Secondary:

~~If the sample size is increased, the CHW test statistic will be calculated for the gated secondary outcome. The analysis of the secondary gatekeeper objective will be performed if the placebo versus LY2951742 comparison is significant for the primary efficacy analysis at a one sided $\alpha=0.025$ significance level using the methodology described in the SAP.~~

Safety: The safety analyses will be conducted for SP III and SP IV as well as SP III and SP IV combined. For SP III and SP IV 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
 - o TEAEs
 - by PT
 - by SOC
 - by maximum severity
 - ~~by outcome~~
 - considered to be related to IP by investigator
 - o SAEs
 - o AE leading to discontinuation
- Suicidal ideation and behaviors assessed by solicited questioning using the C-SSRS
- Vital signs and weight
- Electrocardiograms
- Laboratory measurements
- Anti-LY2951742 drug antibody

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 the ITT-safety population

4. Abbreviations and Definitions

CHW	Cui, Hung, and Wang procedure
NABs	NAb

5. Introduction

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

6. Objectives

6.1. Primary Objective

The primary objective is to assess the efficacy of LY2951742 300 mg every 30 days compared with placebo in reducing the frequency of weekly cluster headache attacks in patients with episodic cluster headache. The primary outcome measure will be the weekly cluster headache attack frequency. The primary endpoint will be the overall mean change from baseline in weekly cluster headache attack frequency from baseline across Weeks 1 to Week 3 with LY2951742 compared with placebo. Baseline is defined as the last 7 days in the eligibility report (pre-randomization diary phase).

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 (NABsNAb) upon availability of the validated assay.

6.3. Exploratory Objectives

To assess whether galcanezumabLY2951742 is superior to placebo as measured by:

- Change in percentage of times using oxygen or triptan from baseline for each weekly interval through Week 8 comparing LY2951742 with placebo.
- Change in percentage of times using triptan from baseline for each weekly interval through Week 8 comparing LY2951742 with placebo.

7.2. Discussion of Design and Control

The proposed duration of the double-blind treatment phase is 8 weeks, with the primary endpoint assessed across~~during~~ Weeks 1 to 3 after the first IP dose.

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 during SP III will be conducted on an intent-to-treat (ITT) population, which includes all patients who are randomized and receive at least ~~one~~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 during SP III will be conducted on the safety population, which also includes all patients who were randomized and receive at least 1 dose of study drug. However, patients will be analyzed by actual study treatment received most often (modal treatment) during the double-blind treatment phase.~~ When change from baseline is assessed, the patient will be included in the analysis only if he/she has a baseline and a post-baseline measurement.

For ~~some of the~~ analyses of the post-treatment phase, the post-treatment population will be used. Post-treatment population will be defined as all patients who entered the post-treatment phase (SP IV) as indicated by entering ~~the first any~~ post-treatment visit. ~~Patients in the post-treatment population will be analyzed according to the treatment that they were randomized to at their randomization visit for analyses by treatment.~~

Details related to handling of missing data will be described 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 unless otherwise stated. The 95% confidence intervals (CIs) for the difference in least-square means (LSMeans) between treatment¹ 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.

~~Unless otherwise specified, when an analysis of variance (ANOVA) model is used to analyze a continuous efficacy variable, the model will contain the main effects of treatment, gender and pooled investigative site. Similar logic is applied to an analysis of covariance (ANCOVA) model, which in general, refers to the ANOVA model with baseline values added as a covariate.~~

Categorical comparisons between treatment groups will be performed using ~~Cochran Mantel-Haenszel (CMH) controlling for pooled investigative site and~~ Fisher's exact tests, where appropriate.

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:
 - o Number of weekly cluster headache attacks
 - o Number of times an abortive medication was taken
 - o Mean Average severity of cluster headache pain
 - o Mean Average cluster headache attack minutesduration
 - o Number of times an abortive medication was taken per cluster headache
 - o Number of times of using the oxygen or triptan
 - o Number of times of using acetaminophen/paracetamol or NSAIDs
 - o Percentage of times of using oxygen or triptan
 - o Percentage of times of using acetaminophen/paracetamol or NSAIDs

12.2.5. Treatment Compliance

Treatment compliance will be calculated for SP III 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 weekly interval (including baseline, Week 1, 2, 3, 4, 5, 6, 7 and 8) 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 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. 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 all the cluster headache attack ePRO questions.

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-weekly 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 restricted maximum likelihood-based (REML-based), mixed-effects repeated measures (MMRM) analysis using all the longitudinal observations from Week 1 to Week 3. The analysis of the primary outcome will be the contrast main effect of treatment between LY2951742 300 mg and placebo at across Weeks 1 to 3 of the treatment phase from a repeated measures analysis on mean change from baseline in the weekly attack frequency. This provides the average treatment effect over the 3-week period. Baseline is defined as the last 7 days in the eligibility report (pre-randomization diary phase).

If the sample size is increased as a result of the interim analysis, the Cui, Hung, and Wang (CHW) procedure (Cui et al. 1999) will be applied to the primary endpoint to control the type I error at a one sided $\alpha=0.025$ significance level. The CHW method ensures strong control of type I 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, Mehta, and Posch (2009) to assess sensitivity of the point estimate.

12.2.7.2. Gated Secondary

If the sample size is increased, the CHW test statistic will be calculated for the gated secondary outcome. The analysis of the secondary gatekeeper objective will be performed if the placebo versus LY2951742 comparison is significant for the primary efficacy analysis at a one sided $\alpha=0.025$ significance level using the methodology described in the SAP.

12.2.8. Other Efficacy Analyses

For the continuous secondary and exploratory efficacy measures, the change from baseline to each weekly interval post-baseline measure will be analyzed from repeated measures analyses.

For 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 and SP IV ~~as well as SP III and SP IV combined. For SP III and SP IV 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
 - o TEAEs
 - by PT
 - by SOC
 - by maximum severity
 - ~~by outcome~~
 - considered to be related to IP by investigator
 - o SAEs
 - o AE leading to discontinuation
- Suicidal ideation and behaviors assessed by solicited questioning using the C-SSRS
- Vital signs and weight
- Electrocardiograms
- Laboratory measurements
- Anti-LY2951742 drug antibody

12.2.10.1. Categorical Safety Variables

Comparisons between treatment groups for all categorical safety measures will be made using Fisher's exact test for SP III with the ITT safety population. Descriptive statistics only will be presented for the treatment groups in SP IV with the post-treatment 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 corrected QT (QTc) ~~interval will be calculated using two correction formulas. The and QTcF~~ (measured in milliseconds [msec]) will be calculated with Fridericia's formula as $QT/RR^{1/3}$. ~~The Large Clinical Trial Population Based QT Correction (QTeLCTPB) (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 (pulse rate [PR], QRS, ~~and QTcF, and QTeLCTPB~~) 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.

12.2.12 Interim Analyses

Up to ~~two~~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 Data Monitoring Committee (DMC) Charter. ~~However, this interim analysis for sample size re-estimation will not happen due to enrollment infeasibility. The DMC will still independently monitor patient safety during this trial.~~

The ~~other~~^{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 operational and statistical bias that results 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.~~

14. References

~~Brannath W, Mehta CR, Posch M. Exact confidence bounds following adaptive group sequential tests. Biometrics. 2009;65(2):539-546.~~

~~Cui L, Hung HM, Wang SJ. Modification of sample size in group sequential clinical trials. Biometrics. 1999;55(3):853-857.~~

Leo Document ID = fae6126b-0387-4e12-8507-dc69d70e4a66

Approver: PPD

Approval Date & Time: 29-Mar-2018 21:38:08 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 29-Mar-2018 21:38:08 GMT

Signature meaning: Approved