I5Q-MC-CGAJ Clinical Protocol

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

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Protocol I5Q-MC-CGAJ
A Phase 3, Long-Term, Open-Label Safety Study of LY2951742 in Patients with Migraine

Confidential Information

LY2951742

A Phase 3, multisite, 12-month, open-label study to assess the safety of LY2951742 (120 mg and 240 mg/month) in patients suffering from migraine headaches, with or without aura. Eligible patients are to be those with episodic or chronic migraine.

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Protocol Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 23-Sep-2015 GMT

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1. Protocol Synopsis

Title of Study:
A Phase 3, Long-Term, Open-Label Safety Study of LY2951742 in Patients with Migraine.

Rationale:
Study I5Q-MC-CGAJ (CGAJ) will enable a comprehensive assessment of the safety of LY2951742 for up to 1 year in patients suffering from migraine, with or without aura.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary To evaluate the long-term safety and tolerability of LY2951742 (120 or 240 mg/month) in patients suffering from migraine, with or without aura, for up to 1 year of treatment.	Analysis of: • treatment-emergent adverse events (TEAEs) • discontinuation rates • vital signs and weight • electrocardiograms (ECGs) • laboratory measures • other safety parameters, including suicidality using the Columbia Suicide Severity Rating Scale (C-SSRS)
Secondary To characterize the long-term pharmacokinetics and pharmacodynamics of LY2951742. To characterize the long-term immunogenicity of LY2951742.	• Assessment of serum concentrations of LY2951742 to enable a pharmacokinetic evaluation. • Assessment of plasma concentrations of calcitonin gene-related peptide (CGRP) to enable a pharmacodynamic evaluation of target engagement of LY2951742. • Development and consequences of anti-drug antibodies and neutralizing antibodies to LY2951742.

Objectives	Endpoints
To evaluate the long-term effectiveness of LY2951742 in the prevention of migraine.	• Mean change from baseline in the number of migraine headache days; • Mean change from baseline in the number of headache days; • Proportion of patients meeting 50% response criteria (reduction of at least 50% in the number of migraine headache days); • Mean change from baseline in the frequency of medication use for the acute treatment of migraines or headaches; • Mean change from baseline in patient's global impression (PGI) of illness as measured by PGI-Severity; • Patient's global impression of improvement as measured by PGI-Improvement
To evaluate the long-term effect of LY2951742 on health outcomes and quality of life.	• Mean change from baseline to endpoint in the evaluation of the Migraine Disability Assessment test (MIDAS) total score and individual items; • Mean change from baseline to endpoint in the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) total score and individual domains; • Change from baseline in health care resource utilization and employment status
To evaluate safety and residual effectiveness during the post-treatment follow-up period.	• Analysis of safety parameters • Time to first loss of response (when patient no longer meets 50% response criteria and/or starts treatment using migraine prevention medication) during the post-treatment follow-up phase

Objectives	Endpoints
To evaluate patient satisfaction with medication and device	• Satisfaction with medication using the Patient Satisfaction with Medication Questionnaire-Modified (PSMQ-M). • Satisfaction with and ease of use of the device for injection using the Subcutaneous Administration Assessment Questionnaire (SQAAQ)
To evaluate results with respect to use of the autoinjector	• Injection-related safety/tolerability and device performance with autoinjector exposures

Summary of Study Design:

Study CGAJ is a multisite, randomized, open-label trial with 3 study periods in patients diagnosed with episodic or chronic migraine headache who are treated with 120 mg/month (with a 240 mg loading dose administered as two injections of 120 mg each) or 240 mg/month of LY2951742. Injections of LY2951742 should be self-administered.

Treatment Arms and Duration:

Two treatment arms: LY2951742 (120 mg/month, administered as 1 injection), and LY2951742 (240 mg/month, administered as 2 injections of 120 mg). Following a 3-to-45-day screening period, eligible patients will be randomized to receive one of two fixed doses of LY2951742 for up to 12 months during an open-label treatment phase, followed by a 4-month, post-treatment phase in which patients are no longer receiving LY2951742.

Number of Patients:

The study will screen an estimated 312 potential study participants and enroll approximately 250 patients to ensure that 100 patients with migraine complete the 12-month treatment phase.

Statistical Analysis:

Effectiveness and safety analyses will be conducted using an intent-to-treat (ITT) population, which is to include all patients who receive at least one dose of investigational product.

Continuous safety and efficacy variables with repeated measures will be analyzed using mixed-model repeated measures (MMRM) which will include the fixed categorical effects of treatment, treatment-by-visit interaction, pooled investigative site, visit, as well as the continuous fixed covariates of baseline and baseline-by-visit interaction. When appropriate, an analysis of variance (ANOVA) or an analysis of covariance (ANCOVA) model with LOCF imputation will be used. Baseline value will be the last available value from Visit 1 to Visit 2.

Categorical safety and efficacy variables with repeated measures will be analyzed using generalized linear mixed model (GLIMMIX) in a similar manner as for mean changes above. Categorical safety variables without repeated measures will be analyzed by Cochran-Mantel-Haenszel (CMH) test controlling for pooled investigative site (Fisher's exact tests, if needed).

Subgroup analyses will be conducted for some of the efficacy and safety measures. No interim analyses are planned for this study. However, an interim analysis may be conducted in support of regulatory submissions if necessary.

2. Introduction

2.1. Background

Migraine is a chronic, debilitating condition found to be one of the top 10 causes of disability expressed as years lived with disability globally (Vos et al. 2012). However, one study estimates that only a small fraction of patients receive preventive treatment, although more than 25% of migraineurs are in need of preventive therapy (Rizzoli 2014). Despite the availability of preventive medications for migraine, significant needs remain for new treatment options with improved efficacy and tolerability.

Calcitonin gene-related peptide (CGRP), a 37-amino acid neuropeptide, is widely expressed throughout the central and peripheral nervous system and acts as a local facilitator of inflammatory processes. Calcitonin gene-related peptide is implicated in the pathophysiology of migraine and is hypothesized to be involved in the release of inflammatory mediators and the transmission of nociceptive (pain) information from intracranial blood vessels to the nervous system (Villalón and Olesen 2009). In migraineurs, serum concentrations of CGRP are significantly elevated during migraine attacks (Goadsby et al. 1990; Goadsby and Edvinsson 1993), and infusion of CGRP to individuals with a history of migraine can trigger migraine attacks (Lassen et al. 1998, Lassen et al. 2002). The neutralization of CGRP with antibodies has been shown to modulate neurogenic inflammation; thus, these antibodies may represent a promising pharmacologic approach for the prevention of migraine (Investigator's Brochure [IB], Section 3.1).

LY2951742 is a humanized monoclonal antibody that potently and selectively binds to CGRP, preventing CGRP-mediated biological effects (IB, Section 3.1). To date, more than 450 clinical trial participants have been exposed to LY2951742 at single doses ranging from 1 to 600 mg and multiple doses up to 300 mg in 5 clinical trials of LY2951742. In studies of patients with migraine (Studies I5Q-MC-ART1 [ART-01] and I5Q-MC-CGAB [CGAB]), efficacy data have demonstrated that LY2951742 had significantly greater mean reductions than placebo in migraine headache days and other efficacy parameters. Across clinical studies of LY2951742, assessment of adverse events (AEs) indicates that LY2951742 has been well tolerated in both healthy subjects and in patients with episodic migraine. The AEs generally have been mild to moderate in severity. In two studies of patients with migraine, the most frequently reported AEs included injection-site pain, upper respiratory tract infection, abdominal pain, dizziness, injection-site erythema, rash, hypertension, and nasopharyngitis. Analyses of laboratory values and cardiovascular monitoring of the clinical studies have shown no other clinically important changes in tested parameters.

2.2. Study Rationale

Study I5Q-MC-CGAJ (CGAJ) will enable a comprehensive safety assessment of LY2951742 in both episodic and chronic migraine patients by including those with a history of at least 4 migraine headache days during a recent 30-day period (Section 5.1) and will build upon preliminary evidence of efficacy and safety from completed studies of LY2951742. This study is intended to provide long-term data that will help support a registration program for patients

with migraine and to provide data in patients who self-inject LY2951742. Study CGAJ will include 12 months on LY2951742 followed by 4 months of post-treatment observation to deepen understanding of the effects of a CGRP antibody in preventing migraines.

3. Objectives and Endpoints

Table CGAJ.1 shows the study objectives and endpoints.

Table CGAJ.1. Objectives and Endpoints

Objectives	Endpoints
Primary To evaluate the long-term safety and tolerability of LY2951742 (120 or 240 mg/month) in patients suffering from migraine, with or without aura, for up to 1 year of treatment	Analysis of: • treatment-emergent adverse events (TEAEs) • discontinuation rates • vital signs and weight • electrocardiograms (ECGs) • laboratory measures • other safety parameters, including suicidality using the Columbia Suicide Severity Rating Scale (C-SSRS)
Secondary To characterize the long-term pharmacokinetics and pharmacodynamics of LY2951742	• Assessment of serum concentrations of LY2951742 to enable a pharmacokinetic evaluation. • Assessment of plasma concentrations of CGRP to enable a pharmacodynamic evaluation of target engagement of LY2951742
To characterize the long-term immunogenicity of LY2951742.	• Development and consequences of anti-drug antibodies and neutralizing antibodies to LY2951742.
To evaluate the long-term effectiveness of LY2951742 in the prevention of migraine	• Mean change from baseline in the number of migraine headache days • Mean change from baseline in the number of headache days • Proportion of patients meeting 50% response criteria (reduction of at least 50% in the number of migraine headache days) • Mean change from baseline in the frequency of medication use for the acute treatment of migraines or headaches • Mean change from baseline in patient's global impression of illness as measured by PGI-Severity; • Patient's global impression of improvement as measured by PGI-Improvement

Objectives and Endpoints

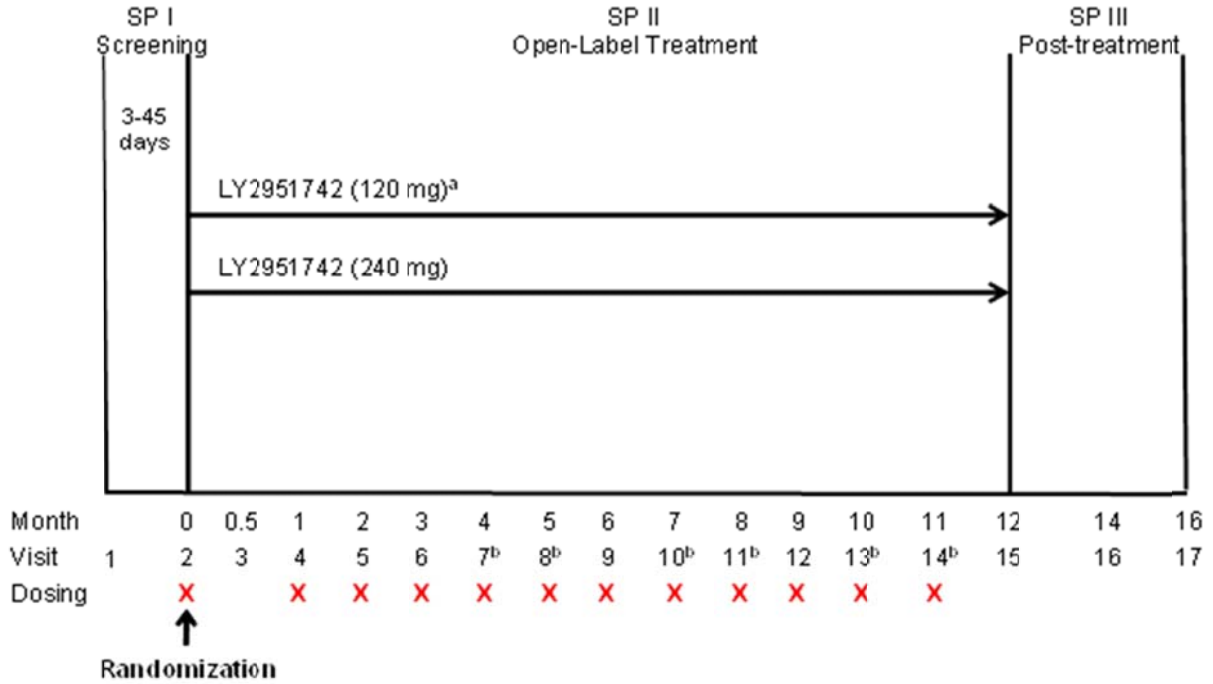
Objectives (cont.)	Endpoints (cont.)
Secondary (cont.)	
To evaluate the long-term effect of LY2951742 on health outcomes and quality of life	• Mean change from baseline to endpoint in the evaluation of the Migraine Disability Assessment test (MIDAS) total score and individual items • Mean change from baseline to endpoint in the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) total score and individual domains • Change from baseline in healthcare resource utilization and employment status
To evaluate safety and residual effectiveness during the post-treatment follow-up period	Analysis of safety parameters • Time to first loss of response (when patient no longer meets 50% response criteria and/or starts treatment using migraine prevention medication) during the post-treatment follow-up phase
To evaluate patient satisfaction with medication and device	• Satisfaction with medication using the PSMQ-M. • Satisfaction (and ease of use) with the device for injection using the Subcutaneous Administration Assessment Questionnaire (SQAAQ)
To evaluate results with respect to use of the autoinjector	• Injection-related safety/tolerability and device performance with autoinjector exposures

4. Study Design

4.1. Overview of Study Design

Study CGAJ is a Phase 3, multisite, randomized, long-term, open-label study to assess the safety of 120 mg/month LY2951742 (with an initial loading dose of 240 mg) and 240 mg/month LY2951742 in patients suffering from migraine, with or without aura. Patients will not be permitted to enroll in Study CGAJ if they previously were treated with LY2951742. As patients will be allowed to self-inject, the study will consist of a mix of office visits and telephone visits.

Figure CGAJ.1 illustrates the study design.



Abbreviation: SP = Study Period.

a Patients randomized to the 120 mg dose will receive a loading dose of 240 mg at the first injection only (Visit 2).

b Telephone visit.

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

Study Period I: The study and potential risks will be explained to the patient at Visit 1. The informed consent form (ICF) must be signed before performing any study procedures. Patients are required to discontinue all excluded medications or migraine prevention treatments at least 30 days prior to Visit 2. Botulinum toxin A or B in the head or neck area must be discontinued at least 4 months prior to Visit 2.

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

Study Period II: If the patient meets all requirements for study eligibility, the patient will be randomized to treatment with one of two doses of LY2951742 (120 mg or 240 mg) at Visit 2 and receive the first dose of LY2951742 at that visit following pretreatment laboratory tests and blood draws. LY2951742 will be administered as subcutaneous injections once monthly at the dosing visits (Visit 2, and Visit 4 through Visit 14) for a total of 12 doses. Patients randomized to 120 mg will receive an initial loading dose of 240 mg (2 injections of 120 mg each) at Visit 2. All injections at subsequent dosing visits will be self-administered as a single injection of 120 mg. Those randomized to 240 mg LY2951742 will receive two injections of 120 mg each at Visit 2 and all subsequent visits. Injections will be delivered via prefilled syringe or by an investigational autoinjector (when the autoinjector device is available for clinical trial use). Patients (and caregivers) will receive training on the use of the prefilled syringe and on the use of the autoinjector when switched to the autoinjector.

At Visit 2 (first dose), the patient must remain at the study site for a 30-minute post-injection observation period. Following appropriate training, all subsequent injections of LY2951742 will be administered by the patient (or caregiver). Injections administered by the patient at Visit 4 and Visit 5 will be done in the office under the supervision of site staff; all subsequent injections will be administered by the patient/caregiver but should be administered unsupervised by the clinical staff. For all office visits, injections will occur after all study procedures have been performed. For all telephone visits at which an injection is scheduled to occur, self-injections must occur on the same day as the scheduled visit, prior to the start of visit procedures. Unscheduled office visits are allowed for safety reasons, assistance with injection administration, or to supply new study drug if needed. If a potentially clinically significant AE is reported by the patient during a telephone visit, the patient should be brought in for appropriate assessment at an unscheduled office visit.

At Visit 2 and all monthly visits, investigators will ask patients about the frequency of headache and migraine headaches experienced in the past 30 days as well as frequency of medication use for migraine or headache. In order to aid recall when answering these questions, patients will be trained to keep track of their migraine and headache days as well as their medication use days using the tracking method of their choice during the study and will be reminded that the site staff will be asking these questions at each visit.

If a patient discontinues early for any reason during the open-label treatment phase, the patient should enter the post-treatment follow-up period (Study Period III); in such cases, patients will be encouraged to complete the follow-up period to assess safety.

Study Period III: During this 4-month follow-up period, patients will no longer receive investigational product. However, patients will continue to track their headache information. Site visits are every 2 months.

4.2. End of Trial Definition

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

4.3. Scientific Rationale for Study Design

The length of the open-label treatment phase (12 months) is considered an appropriate duration to assess the longer-term safety of a migraine prevention medication and is consistent with regulatory feedback. A 4-month post-treatment follow-up phase is included to evaluate patient safety during wash-out of LY2951742. This allows for a total of 5 months of observation from the time of last injection of LY2951742. A 5-month post-treatment observation period allows for a wash-out of approximately 5 elimination half-lives of LY2951742 and should decrease LY2951742 serum concentrations by approximately 97% during this time.

4.4. Justification for Dose

Doses of 120 mg and 240 mg administered once monthly were selected primarily on the basis of clinical efficacy and pharmacokinetic/pharmacodynamic data from the Phase 2 dose-ranging study. Results from the Phase 2 dose-ranging study indicate that 120 mg was statistically significantly superior to placebo at the last 28-day period of the 3-month treatment phase in mean change in migraine headache days, as well as other measures of efficacy and quality of life. The use of a loading dose for the 120 mg arm, and the inclusion of a 240 mg treatment arm, is based on the finding that a higher dose than 120 mg achieved statistically significant separation from placebo as early as Month 1. The planned doses of 120 mg and 240 mg LY2951742 for Study CGAJ also are being studied in three pivotal efficacy studies of LY2951742; two of these studies are in patients with episodic migraine, and one is in patients with chronic migraine.

4.5. Benefit/Risk Assessment

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of LY2951742 are to be found in the Investigator's Brochure (IB).

5. Study Population

All patients must meet the following selection criteria. Eligibility of patients for study enrollment will be based on the results of a screening medical history, physical examination, neurological examination, clinical laboratory tests, electrocardiograms (ECGs), and migraine history during screening, as described in the Inclusion and Exclusion Criteria sections of this protocol. The nature of any comorbid conditions present at the time of the physical examination and any preexisting conditions must be documented. Individuals who do not meet the criteria for participation in this study (screen failure) for specific reasons as outlined may be considered for rescreening once, with approval from Eli Lilly and Company (Lilly) Medical (Section 5.3).

Study participants should be instructed not to donate blood or blood products during the study or for 5 months following the last administration of LY2951742.

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

5.1. Inclusion Criteria

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

Patient and Disease Characteristics

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

[2] Have a diagnosis of migraine as defined by International Headache Society (IHS) International Classification of Headache Disorders (ICHD)-3 beta guidelines (1.1, 1.2, or 1.3) (ICHD-3 2013), with a history of migraine headaches of at least 1 year prior to Visit 1, and migraine onset prior to age 50.

[3] Prior to Visit 1, a history of 4 or more migraine headache days per month on average for the past 3 months.

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

Informed Consent and Patient Agreements

[5] Are able and willing to give signed informed consent.

[6] Are reliable and willing to follow study procedures, including all follow-up visits.

[7] Women of child-bearing potential must test negative for pregnancy at the time of enrollment based on a serum pregnancy test.

[8] All patients, male and female, must agree to use a reliable method of birth control during the study as well as for 5 months after the last dose of investigational product. Acceptable methods of birth control for this study include: oral contraceptives; implantable contraceptives; injectable contraceptives; a contraceptive patch; barrier methods such as diaphragms with contraceptive jelly, cervical caps with contraceptive jelly, condoms with contraceptive foam, or intrauterine devices; a partner with vasectomy. Birth control is not required if the female is infertile due to surgical sterilization (at least 6 weeks after surgical bilateral oophorectomy, hysterectomy, or at least 6 weeks after tubal ligation) confirmed by medical history, or menopause. Menopause is defined as spontaneous amenorrhea for at least 12 months not induced by a medical condition, or spontaneous amenorrhea of 6-12 months and a follicle stimulating hormone level >40 mIU/mL.

[9] 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.

5.2. Exclusion Criteria

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

Prior/Concurrent Clinical Trial Experience

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

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

[12] Current use or prior exposure to LY2951742 or another CGRP antibody, including those who have previously completed or withdrawn from this study or any other study investigating a CGRP antibody.

Prior/Concomitant Therapy

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

[14] Known hypersensitivity to multiple drugs, monoclonal antibodies or other therapeutic proteins, or to LY2951742.

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

[16] Failure to respond to 3 or more adequately dosed migraine preventive treatments from different classes (that is, maximum tolerated dose for at least 2 months). Failure to respond due to tolerability issues is not considered a treatment failure. Migraine preventive treatments are defined as Level A and Level B in Table 1 of the American Academy of Neurology's Evidence-based Guidelines Update: Pharmacologic Treatment for Episodic Migraine Prevention in Adults (Silberstein et al. 2012) as well as botulinum toxin A or B.

Diagnostics Assessments

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

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

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

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

Medical Conditions

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

[22] Patients with a body mass index $\geq$40 kg/m^2

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

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

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

[26] Women who are pregnant or nursing.

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

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

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

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

Other Exclusions

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

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

[33] Are Lilly employees.

5.3. Screen Failures

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

- Inclusion criterion 1. If patients are less than age 18 at the time of informed consent, they may be rescreened if they reach age 18 during the study enrollment period.
- Inclusion criterion 7
- Exclusion criterion 11
- Exclusion criterion 13
- Exclusion criterion 15
- Exclusion criterion 26

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

If rescreening is performed, the individual must sign a new ICF and will be assigned a new identification number.

5.4. Lifestyle and/or Dietary Requirements

No changes in lifestyle or dietary requirements are required during the study. However, patients must be in a fasting state for collection of laboratory samples at selected visits specified in Appendix 2.

6. Treatment

6.1. Treatments Administered

All patients will receive injections of LY2951742 at doses of 120 or 240 mg administered once monthly for up to 12 months during the treatment phase (Section 4.1; Appendix 2). Patients randomized to the 120 mg dose of LY2951742 will receive an initial loading dose of 240 mg (2 injections of 120 mg each) at Visit 2 and 1 injection of 120 mg at each subsequent dosing visit. Patients randomized to the 240 mg dose will receive 2 injections of 120 mg LY2951742 at each dosing visit.

Possible injection sites include the abdomen, thigh, and upper arm. Buttocks may also be used, if needed. If patients are unable to self-inject, they may receive assistance from a caregiver (such as a family member).

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

- training patients and caregivers on the care and use of the prefilled syringe and the investigational autoinjector
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing
- at the end of the study returning all unused medication to Lilly, or its designee, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law.

6.1.1. Medical Devices

The manufactured medical devices provided for use in the study are a disposable manual prefilled syringe and, at some point during the study, an autoinjector. An investigational autoinjector device will be provided during the study when it becomes available.

6.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized to one of two dose groups at Visit 2. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign open-label investigational product to each patient. Site personnel will confirm that they have located the correctly assigned package by entering the confirmation number found on the package into the IWRS.

To achieve between-group comparability for site factor, the randomization will be stratified by site.

6.2.1. Selection and Timing of Doses

The actual time of all dose administrations will be recorded in the patient's electronic case report form (eCRF).

6.3. Blinding

Not applicable.

6.4. Packaging and Labelling

LY2951742 will be supplied as an injectable solution in 1-mL, single-dose, prefilled, disposable manual syringes with study specific labels. Each syringe of LY2951742 is designed to deliver LY2951742 120 mg. Syringes will be supplied in cartons, with the appropriate quantity of syringes specific to the planned dispensing schedule of the investigational product. LY2951742 will be supplied in the investigational autoinjector when the autoinjector becomes available.

Clinical trial materials, including devices, will be labeled according to the country's regulatory requirements.

6.5. Preparation/Handling/Storage

Investigational product will be shipped (as prefilled syringes or autoinjectors) to sites using cold chain transportation. Study drug must be stable and stored in a refrigerator at 2ºC to 8ºC (35.6ºF to 46.4ºF).

Approximately 30 minutes prior to administration, the syringe should be removed from the storage area and allowed to equilibrate at ambient conditions. The drug product should be kept away from direct exposure to bright light (such as sunlight) and hot surfaces until administration.

6.6. Dose Modification

Dose modifications are not permitted in this study.

6.6.1. Special Treatment Considerations

During the post-treatment follow-up period, patients will not receive LY2951742. One month after Visit 15 (2 months after last dose), if clinically warranted due to a worsening of symptoms, patients may start migraine prevention medications at the discretion of the investigator. The list of allowed preventive medications is provided separately.

6.7. Treatment Compliance

Investigators will be required to document the administration of LY2951742 in the eCRF.

LY2951742 must be administered as indicated in the Schedule of Activities (Appendix 2). If the patient is unable to comply with injections in the allowed window, the situation should be discussed with Lilly to determine if the patient may continue.

6.8. Concomitant Therapy

The list of medications allowed or not allowed during the study can be found in the concomitant medications study tool. The concomitant use of acute medications to treat migraine is allowed, with some limitations. Any changes in the list of allowed/not allowed medications will be communicated to investigators and will not constitute a protocol amendment.

6.9. Treatment after Study Completion

6.9.1. Study Extensions

Not applicable.

6.9.2. Continued Access

Investigational product will not be made available to patients after conclusion of this study.

7. Discontinuation Criteria

Patients who discontinue the study or investigational product during open-label treatment (Study Period II) will proceed immediately to Study Period III.

7.1. Discontinuation from Study Treatment

7.1.1. Permanent Discontinuation from Study Treatment

Discontinuation of the investigational product 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 aspartate aminotransferase (AST) >8XULN
- ALT or AST >5X ULN for more than 2 weeks
- ALT or AST >3X ULN and TBL >2X ULN or prothrombin time >1.5X ULN
- ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP >3X ULN
- ALP >2.5X ULN and TBL >2X ULN
- ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Patients who discontinue the investigational product early will have end-of-therapy procedures performed as shown in the Schedule of Activities (Appendix 2) and are requested to proceed into the post-treatment phase.

7.1.2. Temporary Discontinuation from Study Treatment

Not applicable.

7.1.3. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identify a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the sponsor clinical research physician/clinical research scientist (CRP/CRS) and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP/CRS to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product.

7.1.4. Permanent Discontinuation from the Study

Some possible reasons that may lead to permanent discontinuation include:

- 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
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- Investigator Decision
    - the investigator decides that the patient should be discontinued from the study
    - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for the study indication (prevention of migraine) during Study Period II (open-label treatment), discontinuation from the study occurs prior to introduction of the new agent
- Subject Decision
    - the patient asks to be withdrawn from the study

Patients who discontinue the study early will have end-of-study procedures performed as shown in the Schedule of Activities (Appendix 2) and are requested to proceed into the post-treatment phase.

7.1.5. 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. Study Assessments and Procedures

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

Appendix 3 lists the laboratory tests that will be performed for this study.

Appendix 4 lists the tests that may be obtained in the event of a treatment-emergent hepatic abnormality.

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

8.1. Efficacy Assessments

8.1.1. Primary Efficacy Assessments

Not applicable.

8.1.2. Secondary Efficacy Assessments

As this is an uncontrolled study, all efficacy measures represent measures of treatment effectiveness or health outcomes. Migraine and headache frequency as well as abortive medication use will be collected by direct questioning by the investigator or designated site personnel. In addition, the following scales will be used for secondary efficacy assessments as summarized below.

8.1.2.1. Patient Global Impression of Severity

The Patient Global Impression of Severity (PGI-S) scale (Guy 1976) is a patient-rated instrument that measures baseline illness severity. The PGI-S includes a range of possible responses, from 1 ("normal, not at all ill") to 7 ("extremely ill").

8.1.2.2. Patient Global Impression of Improvement

The Patient Global Impression of Improvement (PGI-I) scale (Guy 1976) is a patient-rated instrument that measures the improvement of the patient's symptoms. It is a 7-point scale in which a score of 1 indicates that the patient is "very much better," a score of 4 indicates that the patient has experienced "no change," and a score of 7 indicates that the patient is "very much worse."

8.1.3. Appropriateness of Assessments

All efficacy and safety assessments have been well documented and are generally regarded as reliable, accurate, and relevant in this patient population. This includes health outcomes measures considered to be appropriate for evaluating changes in quality of life, global functioning, and disability (Section 8.9).

8.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

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

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

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

The investigator will decide whether he or she interprets the observed AEs as reasonably possibly related to migraine headache, to the investigational product, investigational study device, study procedure, or other concomitant treatment or pathologies.

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

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

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

8.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (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, based upon appropriate medical judgment.
- when a condition related to the investigational device (for example, prefilled syringe or autoinjector) necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned.

Although all AEs after signing the ICF are recorded in the eCRF, SAE reporting begins after the patient has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, it needs to be reported ONLY if it is considered reasonably possibly related to study procedure.

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

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

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

8.2.1.1. Suspected Unexpected Serious Adverse Reactions

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

8.2.1.2. Adverse Event Monitoring with a Systematic Questionnaire

Suicidality will be assessed as required by the US Food and Drug Administration's Division of Neurology for use in clinical trials involving all drugs for neurological indications. Before administering the C-SSRS (Posner et al. 2011), study site personnel will question the patient

about any change in the pre-existing condition(s) and the occurrence and nature of any AEs. Nonserious AEs obtained through the questionnaire are recorded and analyzed separately. Only *serious* AEs and AEs leading to discontinuation elicited through the C-SSRS are to be recorded as AEs via eCRF. Serious adverse events must be reported to Lilly or its designee within 24 hours as SAEs. Any suicidal behavior, or suicidal ideation per items 4 or 5 (active suicidal ideation with some intent to act, either without specific plan or with specific plan and intent) would prompt referral of the patient to a mental health professional.

8.2.2. Complaint Handling

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

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

8.3. Treatment of Overdose

No data are available at this stage of development.

8.4. Safety Assessments

8.4.1. Electrocardiograms

For each patient, a single, 12-lead digital ECG will be collected at the visits shown in the Schedule of Activities (Appendix 2). Electrocardiograms will have a central overread and should be recorded according to the study-specific recommendations included in an ECG manual.

Any clinically significant findings from ECGs that result in a diagnosis should be reported to Lilly or its designee as an AE via eCRF.

8.4.2. Vital Signs

Vital signs will include body temperature, blood pressure, and pulse. Blood pressure and pulse will be measured in triplicate in the sitting position prior to blood draws and study drug administration (see Study Schedule [Appendix 2]).

Any clinically significant findings from vital signs measurement that result in a diagnosis should be reported to Lilly or its designee as an AE via eCRF.

8.4.3. Laboratory Tests

For each patient, laboratory tests detailed in Appendix 3 should be conducted according to the Schedule of Activities (Appendix 2).

Any clinically significant findings from laboratory tests that result in a diagnosis should be reported to Lilly or its designee as an AE via eCRF.

In addition, an immunogenicity plasma sample will be collected, when possible, for any patient who experiences a potential systemic allergic/hypersensitivity reaction during the study as judged by the investigator. This immunogenicity plasma sample should be collected immediately or as soon as possible, taking into consideration the availability and wellbeing of the patient. Exact date and time of the sample should be recorded on the laboratory requisition form.

8.4.4. Other Tests

Not applicable.

8.4.5. Safety Monitoring

Investigators are responsible for monitoring individual patient safety throughout the trial. If a study patient/subject experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, clinical and laboratory monitoring should be initiated by the investigator. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient/subject safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP/CRS regarding collection of specific recommended clinical information and follow-up laboratory tests. See Appendix 4.

Lilly will periodically review evolving aggregate safety data within the study. In addition, safety data for the trial will also be reviewed periodically by an independent Data Monitoring Committee (DMC; an advisory group for the LY2951742 clinical development program).

8.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Appendix 2), venous blood samples of approximately 2.5 mL each will be collected to determine the serum concentrations of LY2951742. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor.

When a blood sample is collected, the time and date of last dose administration prior to blood sampling should be recorded. The actual date and time (24-hour clock time) of each sampling will be recorded. Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 1 year following last patient visit for the study.

A validated assay will be used to determine serum LY2951742 concentrations. Samples will be analyzed at a laboratory approved by the sponsor.

8.6. Pharmacodynamics

At the visits and times specified in the Schedule of Activities (Appendix 2), venous blood samples will be collected to determine the plasma concentrations of CGRP. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. When a blood sample is collected, the time and

date of last dose administration prior to blood sampling should be recorded. The actual date and time (24-hour clock time) of each sampling will be recorded.

A validated assay will be used to determine plasma drug-tolerant CGRP concentrations. Samples will be analyzed at a laboratory approved by the sponsor.

Bioanalytical samples collected to measure CGRP will be identified by the patient number (coded) and retained for a maximum of 1 year following last patient visit for the study at a facility selected by the sponsor.

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8.8. Biomarkers

Blood samples for non-genetic biomarker research will be collected at the times specified in the Schedule of Activities (Appendix 2), where local regulations and ERBs allow.

Samples will be used for research on the drug target, disease process, pathways associated with migraine headache and/or other pain conditions, mechanism of action of LY2951742, and/or research method or in validating diagnostic tools or assay(s) related to migraine headache and/or other pain conditions.

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

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

8.8.1. Samples for Immunogenicity Research

Where local regulations and ERBs allow, blood samples for immunogenicity testing will be collected to determine antibody production against LY2951742 as specified in the Schedule of Activities (Appendix 2). 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 will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if regulations and ERBs impose shorter time limits, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to LY2951742.

8.9. Health Economics

The self-reported questionnaires will be administered according to the Schedule of Activities (Appendix 2). Health economic, disability and quality of life assessments of LY2951742 in patients with migraine will be based on the following scales:

Migraine Disability Assessment test (MIDAS): The MIDAS was designed to quantify headache-related disability over a 3-month period. This instrument consists of five items that reflect the number of days reported as missing, or with reduced productivity at work or home and social events, are weighted to produce scores in which a higher value is indicative of more disability (Stewart 1999; Stewart 2001). This instrument is considered highly reliable and valid; and is correlated with clinical judgment regarding the need for medical care (Stewart 1999; Stewart 2001).

Migraine Specific Quality of Life questionnaire (MSQ v2.1): The MSQ v2.1 is a self-administered health status instrument, and was developed to address physical and emotional limitations of specific concern to individuals suffering from migraine headaches. The instrument consists of 14 items that address 3 domains: (1) Role Function-Restrictive; (2) Role Function-Preventive; and, (3) Emotional Function (Jhingran 1998). The instrument was designed with a 4-week recall period, and is considered reliable, valid and sensitive to change in migraine (Jhingran 1998; Rendas-Baum 2013). Clinically meaningful differences for each domain have been established and are widely used in the literature.

Patient Satisfaction with Medication Questionnaire Modified (PSMQ-M): The PSMQ-M is a self-rated scale which measures patients' level of satisfaction with study medication (Kalali 1999). The scale has been modified for use in this study, assessing 3 items related to the clinical trial treatment over the past 4 weeks: satisfaction, preference, and side effects. Satisfaction responses range from "very unsatisfied" to "very satisfied" with the current treatment. Preference compares the current study medication to previous medications, with responses from "much rather prefer my previous medication" to "much rather prefer the medication administered to me during the study."

Health Care Resource Utilization (HCRU) and Employment Status: The HCRU will be solicited by study personnel while documenting patient responses. The HCRU consists of 3 questions, asking about hospital emergency room visits, overnight stays in a hospital, and any other visits with a healthcare professional that occurred since their last study visit. Patients are also specifically asked about the number of health care events that are related to migraine headaches, outside of visits associated with their participation in the clinical trial. The baseline visit will include the same questions, however with the frame of reference being over the last 6 months. A question on employment status is also solicited, given the correlation and potential confounding with health outcomes measures.

Subcutaneous Administration Assessment Questionnaire (SQAAQ): The SQAAQ is a self-administered questionnaire that provides an assessment of ease of use and confidence with using a device to administer a subcutaneous injection of investigational product. Patients will respond to questionnaire items using a 7-point Likert scale (from "Strongly Disagree" to "Strongly Agree") shortly after the injection. If a caregiver administers the injection, the patient should be prepared to provide the caregiver's ratings of the questions.

9. Statistical Considerations and Data Analysis

9.1. Determination of Sample Size

Approximately 250 patients will be enrolled in Study CGAJ. This sample size will ensure at least 100 patients with at least 1 year of exposure to fulfill regulatory requirements for registration.

9.2. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. Details of statistical analysis methods will be described in the statistical analysis plan (SAP) document.

Unless otherwise specified, safety and effectiveness analyses will be conducted on an intent-to-treat (ITT) basis, which is to include all patients who receive at least one dose of investigational product. 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.

All statistical tests will be conducted at a 2-sided alpha level of 0.05, and 95% confidence intervals will be provided if appropriate, unless otherwise stated. No adjustments for multiplicity will be applied to any safety or efficacy analyses.

Continuous safety and efficacy variables with repeated measures will be analyzed using mixed-model repeated measures (MMRM) which will include the fixed categorical effects of treatment, treatment-by-visit interaction, pooled investigative site, visit, as well as the continuous fixed covariates of baseline and baseline-by-visit interaction.

The safety and efficacy analyses will be conducted for Study Period II and Study Period III (post-treatment follow-up phase), as well as the two periods combined.

When appropriate, an analysis of variance (ANOVA) or an analysis of covariance (ANCOVA) model with last-observation-carried-forward (LOCF) imputation will be used. Unless otherwise specified, when an ANOVA model is used to analyze a continuous variable, the model will contain the main effect of treatment and pooled investigative site. When an ANCOVA model is used to analyze change from baseline for a continuous variable, the model will include treatment, baseline, and pooled investigative site.

Categorical variables with repeated measures will be summarized and analyzed in a similar manner as for mean changes from a categorical, pseudo likelihood-based repeated measures analysis using a generalized linear mixed model (GLIMMIX) procedure in SAS. Categorical variables without repeated measures will be analyzed by Cochran-Mantel-Haenszel (CMH) test controlling for pooled investigative site (Fisher's exact tests, if needed).

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

9.3. Treatment Group Comparability

9.3.1. Patient Disposition

The number and percentage of ITT patients who complete the study or discontinue early will be summarized for the open-label treatment phase (Study Period II) and post-treatment follow-up phase (Study Period III) both overall and by visit.

9.3.2. Patient Characteristics

The following patient characteristics at baseline will be summarized for all ITT patients.

- Demographic (age, gender, ethnic origin, height, weight, body mass index)
- Migraine headache, headache
- Medical history and pre-existing condition

Medical history and pre-existing conditions will be summarized by preferred term within system organ class (SOC).

9.3.3. Concomitant Therapy

The proportion of patients who received concomitant medication collected via eCRF will be summarized for all ITT patients for the open-label treatment phase and post-treatment follow-up phase separately.

9.3.4. Treatment Compliance

Number of missed injections will be summarized.

9.4. Primary and Secondary Analyses

9.4.1. Primary Analyses

The primary objective of this study is to evaluate the long-term safety and tolerability of LY2951742 (120 or 240 mg/month) in patients suffering from migraine, with or without aura, for up to 1 year of treatment.

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

- adverse events
    - treatment-emergent adverse events
        - by preferred term
        - by SOC
        - by maximum severity
        - considered to be related to investigational product by investigator
    - serious adverse events

  - adverse event leading to discontinuation
- suicidal ideation and behaviors assessed by solicited questioning using the C-SSRS
- vital signs and weight
- electrocardiograms
- laboratory measurements
- anti-LY2951742 antibody

9.4.2. Secondary Analyses

9.4.2.1. Efficacy Analyses

The efficacy objective is to evaluate the effectiveness of LY2951742 in the prevention of migraine, using the following measures:

- mean change from baseline in the number of migraine headache days
- mean change from baseline in the number of headache days
- the proportion of patients meeting criteria for reductions of at least 30%, 50%, 75%, or 100% in the number of migraine headache days
- mean change from baseline in the frequency of medication use for the acute treatment of migraines or headaches
- mean change from baseline in patient's global impression of illness as measured by PGI-Severity
- patient's global impression of improvement as measured by PGI-Improvement post-baseline
- time to first loss of response (when patient no longer meets 50% response criteria and/or starts treatment using migraine prevention medication) during the follow-up phase

For migraine headache and headache day analysis, baseline is the Visit 2 assessment.

9.4.3. Tertiary/Exploratory Analyses

Not applicable.

9.5. Other Safety Analyses

9.5.1. Immunogenicity Analyses

To evaluate the changes in immunogenicity data (anti-drug antibodies, neutralizing anti-drug antibodies) after treatment, the following statistical analyses are planned:

- to summarize the proportions of positive results at each sample collection time point.

- to summarize the incidence of treatment-emergent immunogenicity for the open-label treatment phase. Treatment-emergent immunogenicity will be defined as any of the following:
  - a negative baseline result and a positive postbaseline anti-drug antibody result with a titer ≥20. This is also called treatment-induced ADA.
  - a positive baseline result and a positive postbaseline anti-drug antibody result with a ≥4-fold increase in titers (for example, baseline titer of 10 increasing to ≥40 postbaseline). This is called treatment-boosted ADA.
- to summarize the onset of treatment-induced anti-drug antibody. Anti-drug antibody onset is defined as the time period between the initial administration of the study drug and the first instance of treatment-induced ADA.

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LY2951742 and CGRP concentrations will be illustrated graphically and summarized descriptively. CCI [redacted]

9.7. Other Analyses

9.7.1. Health Outcomes and Economics

The mean change from baseline to each postbaseline visit for open-label treatment phase for MSQ v2.1 (including Role Function-Restrictive, Role Function-Preventive, Emotional Function, and total score) and MIDAS (item scores and total score) (Section 8.9) will be summarized using MMRM as described in Section 9.2.

The HCRU and PSMQ-M will be analyzed with details documented in the SAP.

9.7.2. Device Analyses

Evaluation of autoinjector and prefilled syringe ease of use using the SQAAQ questionnaire will be summarized and analyzed for each individual item and/or domains. In addition, autoinjector exposures will be evaluated with respect to injection-related events and device performance. Further details will be in the SAP.

9.8. Subgroup Analyses

Subgroup analyses will be conducted on key safety measures for the following variables:

- sex (Female versus Male)
- baseline anti-drug antibody status: Any confirmed positive anti-drug antibody at baseline (Yes versus No)

- treatment-emergent anti-drug antibody status: Any treatment-emergent anti-drug antibody (Yes versus No)
- neutralizing anti-drug antibody status: Any positive neutralizing ADA time point (Yes versus No) – note that neutralizing anti-drug antibody assays are performed only on confirmed-positive anti-drug antibodies.
- Region: North American, Europe, Other
- Disease state: episodic migraine versus chronic migraine
- Medication overuse headache: Yes versus No

Subgroup analyses for additional variables will be conducted as deemed appropriate and necessary. Detailed description of the subgroup variables will be provided in the SAP.

9.9. Interim Analyses

No interim analyses are planned for this study. However, an interim analysis may be conducted in support of regulatory submissions if necessary. Interim data snapshots will be provided as supplemental safety data to support external DMC safety reviews across all Phase 3 migraine prevention studies.

10. Study Governance Considerations

10.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

10.1.1. Informed Consent

The investigator is responsible for ensuring:

- that the patient understands the potential risks and benefits of participating in the study
- 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.
- 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.

10.1.2. Ethical Review

The investigator must give assurance that the ERB was properly constituted and convened as required by International Conference on Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on good clinical practice (GCP).

The study site's ERB(s) should be provided with the following:

- the current IB and updates during the course of the study
- informed consent form
- relevant curricula vitae

10.1.3. Regulatory Considerations

This study will be conducted in accordance with:

- 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
- applicable ICH GCP guidelines
- applicable laws and regulations

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

10.1.4. Investigator Information

Investigators in this clinical trial should be neurologists, headache specialists, or other specialists with experience in headache clinical trials and treating migraine headache patients.

10.1.5. 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.

10.1.6. Final Report Signature

The CSR coordinating investigator will sign the final CSR 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.

An investigator selected by the study team will serve as the CSR coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

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

10.2. 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 computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or by 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 according to retention requirements as outlined by the ICH guidelines. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

10.2.1. 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 direct data entry is not used, 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, will be identified and documented by the site in the site's trial file. For data handled by a data management 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-rated scales/questionnaires will be collected at office visits directly via an electronic patient-reported outcome (ePRO) tablet device as part of an ePRO/Clinical Outcome Assessment (COA) system. Data entered into the ePRO/COA system will serve as the source data.

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

10.3. Study and Site Closure

10.3.1. Discontinuation of Study Sites

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

10.3.2. 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.

11. References

Goadsby PJ, Edvinsson L. The trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. *Ann Neurol*. 1993;33(1):48-56.

Goadsby PJ, Edvinsson L, Ekman R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. *Ann Neurol*. 1990;28(2):183-187.

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 27 July 2015.

[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.

Jhingran P, Osterhaus JT, Miller DW, Lee JT, Kirchdoerfer L. Development and validation of the Migraine-Specific Quality of Life Questionnaire. *Headache.* 1998;38(4):295-302.

Kalali A. Patient satisfaction with, and acceptability of, atypical antipsychotics. *Curr Med Res Opin.* 1999;15(2):135-137.

Lassen LH, Haderslev PA, Jacobsen VB, Iversen HK, Sperling B, Olesen J. CGRP may play a causative role in migraine. *Cephalalgia.* 2002;22(1):54-61.

Lassen LH, Jacobsen VB, Pedersen PA, Sperling B, Iversen HK, Olesen J. Human calcitonin gene-related peptide (hCGRP)-induced headache in migraineurs. *Eur J Neurol*. 1998;5(suppl 3):S63.

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.

Rendas-Baum R, Bloudek LM, Maglinte GA, Varon SF. The psychometric properties of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ) in chronic migraine patients. *Qual Life Res.* 2013;22(5):1123–1133.

Rizzoli P. Preventive pharmacotherapy in migraine. *Headache*. 2014;54(2):364-369.

Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2012;78(17):1337-1345.

Stewart WF, Lipton RB, Dowson AJ, Sawyer J. Development and testing of the Migraine Disability Assessment (MIDAS) Questionnaire to assess headache-related disability. *Neurology.* 2001;56 (6 Suppl 1):S20-S28.

Stewart WF, Lipton RB, Kolodner K, Liberman J, Sawyer J. Reliability of the migraine disability assessment score in a population-based sample of headache sufferers. *Cephalalgia.* 1999;19(2):107-114.

Villalón CM, Olesen J. The role of CGRP in the pathophysiology of migraine and efficacy of CGRP receptor antagonists as acute antimigraine drugs. *Pharmacol Ther*. 2009;124(3):309-323.

Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012;380(9859): 2163-2196.

Appendix 1. 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.
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.
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.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
ITT	intent to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
SAE	serious adverse event
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.

Appendix 2. Schedule of Activities

Schedule of Activities Protocol I5Q-MC-CGAJ

Study Period (SP)	SP I	SP II														SP III		
Description	Screen-ing	Treatment														Post-treatment		
Interval (days) since previous visit, days		3-45	14	16	30	30	30	30	30	30	30	30	30	30	30	60	60	ET
Interval allowance (days)			+/- 3	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 5	+/- 5	
Visit	1	2	3[a]	4	5	6	7 (Phone visit)	8 (Phone visit)	9	10 (Phone visit)	11 (Phone visit)	12	13 (Phone visit)	14 (Phone visit)	15	16	17	
Month		0	0.5	1	2	3	4	5	6	7	8	9	10	11	12	14	16	
Assessments and Procedures																		
Informed consent	X																	
Inclusion/exclusion	X	X																
Demographics	X																	
Physical examination[b]	X																	
Height	X																	
Weight	X								X						X		X	X
Waist/hip circumference	X																	
Medical history	X																	
Pre-specified migraine history		X																
Substance use	X																	
ECG[c]	X	X							X						X		X	X
Vital signs[d]	X	X		X	X	X			X			X			X	X	X	X
Adverse events and product complaints	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LY2951742 treatment[e]		X		X	X	X	X	X	X	X	X	X	X	X				
Concomitant medications	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period (SP)	SP I	SP II														SP III		
Description	Screen-ing	Treatment														Post-treatment		
Interval (days) since previous visit, days		3-45	14	16	30	30	30	30	30	30	30	30	30	30	30	60	60	ET
Interval allowance (days)			+/- 3	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 5	+/- 5	
Visit	1	2	3[a]	4	5	6	7 (Phone visit)	8 (Phone visit)	9	10 (Phone visit)	11 (Phone visit)	12	13 (Phone visit)	14 (Phone visit)	15	16	17	
Month		0	0.5	1	2	3	4	5	6	7	8	9	10	11	12	14	16	
Clinical Laboratory Tests and Sampling Schedule																		
Hematology	X	X				X			X			X			X		X	X
Clinical chemistry	X	X[f]				X			X[f]			X			X[f]		X	X[f]
HDL	X	X[f]				X			X[f]			X			X[f]		X	X[f]
Urinalysis [g]	X	X							X						X		X	X
HbA1c		X							X						X		X	X
Fasting insulin/ fasting C-peptide		X[f]													X[f]			X[f]
Serum pregnancy (for women of childbearing potential) or FSH (Visit 1 only; all other female patients)	X														X		X	X
Urine pregnancy [h]		X		X	X	X	X	X	X	X	X	X	X	X				
Urine drug screen	X																	
Immunogenicity[i]		X	X	X	X	X			X						X		X	X
PK blood sample[i]			X	X	X	X			X						X		X	X
CCI																		
Biomarker storage sample [i]	X	X				X			X						X		X	X
CCI																		

Scales, Questionnaires, and Outcomes Measures																		
Assessment of migraine and headache days		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MIDAS		X				X			X			X			X		X	X
MSQ (v2.1)		X		X	X	X			X			X			X	X	X	X
HCRU and Employment Status		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PSMQ-M				X					X						X			X
PGI-Severity		X																
PGI-Improvement				X	X	X			X			X			X			X
Nonmigraine chronic pain assessment [j]		X							X						X			X
SQAAQ				X	X	X	X	X	X	X	X	X	X	X	X			X
C-SSRS/SHSF, SHFU[k]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Schedule of Activities Protocol I5Q-MC-CGAJ (abbreviations and footnotes)

Abbreviations: AE = adverse event; CGRP = Calcitonin-gene related peptide; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ET = early termination; FSH = follicle stimulating hormone; HbA1c = hemoglobin A1c; HCRU = Health Care Resource Utilization; HDL = High-density lipoprotein; MIDAS = Migraine Disability Assessment test; MSQ (v2.1) = Migraine Specific Quality of Life Questionnaire Version 2.1; PGI = Patient Global Impression; PK = pharmacokinetics; PSMQ-M = Patient Satisfaction with Medication Questionnaire-Modified; SHSF = self-harm supplement form; SHFU = self-harm follow-up form; SQAAQ = Subcutaneous Administration Assessment Questionnaire.

Note: 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. If the patient has discontinued the trial and returns for hepatic follow-up, the site should use the 800 series as the visit designation.

a Visit 3 will be for collection of PK, immunogenicity, and CGRP plasma samples and spontaneously reported AEs.

b Physical examinations at screening must include a neurological exam.

c Electrocardiograms (ECGs) will be performed at Visit 1, Visit 2, Visit 9, Visit 15 and Visit 17 or early termination. Note: the Visit 2 ECG should be collected prior to blood draws and dosing. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

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

e Patients will receive injections of LY2951742 after all other visit procedures are completed. Following the first dose at Visit 2, patients will be observed for at least 30 minutes in the office. Injections administered by the patient at Visit 4 and Visit 5 will be done in the office under the supervision of the staff; all subsequent injections will be administered by the patient/caregiver and should be unsupervised by the clinical staff.

f Fasting laboratory samples (such as chemistry) will be collected at baseline (Visit 2), 6 months (Visit 9), and study endpoint (Visit 15 or early study termination). Fasting status is defined as no food or caloric beverage 8 hours prior to testing. All other samples may be collected on a nonfasting basis.

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

h A positive urine test must be followed by a serum pregnancy test for confirmation. Patients will be provided with a home pregnancy kit for testing (prior to injection) at each home visit.

i Immunogenicity, CCI and biomarker storage samples, as well as PK blood sampling to be performed at the indicated visits and prior to dose administration if the visit is a dosing visit. Samples will be taken in the event of early termination. Immunogenicity samples also will be collected in the event of a potential systemic allergic/hypersensitivity reaction (see Section 8.4.3). The exact date and time of the sample should be recorded.

j Questionnaire administered by clinician to assess other chronic pain conditions.

k The C-SSRS, and SHSF (and SHFU when applicable) will be completed at scheduled and unscheduled office visits.

Appendix 3. Clinical Laboratory Tests

Clinical Laboratory Tests

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

Abbreviations: CGRP = calcitonin gene-related peptide; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HDL = high density lipoprotein; PK = pharmacokinetic; RBC = red blood cells; WBC = white blood cells.

Clinical Laboratory Tests (footnotes)

[a] A positive urine leukocyte esterase result will require a follow-up sample with microscopic analysis and possibly a urine culture.

[b] Fasting laboratory samples will be collected as shown in the Schedule of Activities (Appendix 2). Fasting is defined as no food or drink, except water, for at least 8 hours prior to testing. All other samples may be collected on a nonfasting basis.

[c] May be repeated during the study at the discretion of the investigator.

[d] May be repeated during the study at the discretion of the investigator.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

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

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

a Assayed by Lilly-designated or local laboratory.

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

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