Protocol I5Q-MC-CGAQ Pharmacokinetics and Pharmacodynamics of LY2951742 (galcanezumab) in Healthy Subjects Following Subcutaneous Administration of LY2951742 (galcanezumab) Solution in a Prefilled Syringe or an Autoinjector

NCT02836613

Approval Date: 31-May-2016

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Pharmacokinetics and Pharmacodynamics of LY2951742 (galcanezumab) in Healthy Subjects Following Subcutaneous Administration of LY2951742 (galcanezumab) Solution in a Prefilled Syringe or an Autoinjector

galcanezumab (LY2951742)

Eli Lilly and Company
Indianapolis, Indiana USA 46285

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

Approval Date: 31-May-2016 GMT

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1. Protocol Synopsis

Title of Study:
Pharmacokinetics and Pharmacodynamics of LY2951742 (galcanezumab) in Healthy Subjects Following Subcutaneous Administration of LY2951742 (galcanezumab) Solution in a Prefilled Syringe or an Autoinjector

Rationale:
To assess the pharmacokinetics (PK), pharmacodynamics (PD), safety, and tolerability of LY2951742 solution formulation when administered as a subcutaneous dose of 240 mg using a manual prefilled syringe (PFS) or an autoinjector.

Objectives/Endpoints:

Objectives	Endpoints
Primary	
To determine the relative bioavailability of 240 mg LY2951742 after subcutaneous administration of LY2951742 solution as a manual PFS (reference) or autoinjector (test).	The primary endpoints will be the maximum observed concentration (C_{max}) and area under the concentration versus time curve from time zero to infinity (AUC[0-∞]) of LY2951742.
Secondary	
To assess plasma calcitonin gene-related peptide (CGRP) concentrations after subcutaneous administration of 240 mg LY2951742 solution as a PFS or autoinjector.	Maximum observed CGRP concentration ($C_{max, CGRP}$) and area under the concentration versus time curve from zero to time t, where t is the last time point with a measurable concentration of CGRP (AUC[0-$t_{last, CGRP}$]).
To assess the safety and tolerability of LY2951742 in healthy subjects after subcutaneous administration of 240 mg LY2951742 solution as a manual PFS or autoinjector.	Treatment-emergent adverse events (TEAEs).

Summary of Study Design:

Study I5Q-MC-CGAQ is a Phase 1, multi-center, open-label, 2-arm (PFS, autoinjector), randomized, parallel group study where a single dose of 240 mg LY2951742 will be administered to healthy subjects.

Subjects will be admitted to the clinical research unit (CRU) on Day -1. All doses will be administered in the morning of Day 1 as two 1-mL subcutaneous injections of 120 mg/mL solution of LY2951742. Subjects will be stratified to receive injections in the upper arm, abdomen, or thigh. Subjects will remain resident at the CRU until the procedures scheduled at 24 hours postdose have been completed on Day 2, or longer at the discretion of the investigator. All subsequent procedures will be performed on an outpatient basis.

Blood samples will be collected up to 20 weeks postdose to determine serum concentrations of LY2951742 for PK assessments and plasma concentrations of CGRP for PD assessments. Safety and tolerability will be assessed by recording of TEAEs, injection-site reactions (ISR), vital signs, 12-lead electrocardiograms (ECGs), physical examination, clinical chemistry, hematology, immunogenicity, and urinalysis.

Treatment Groups and Duration:
Subjects will be randomized in a 1:1 ratio to 240 mg LY2951742 as a manual PFS (reference) or 240 mg LY2951742 as an autoinjector (test). Each subject will receive a single dose of LY2951742 on a single occasion and have study procedures performed up to 20 weeks after study drug administration. Procedures scheduled for later than Day 2, 24 hours postdose will be performed on an outpatient basis, at the discretion of the investigator.

Number of Subjects:
Up to 160 subjects may be enrolled.

Statistical Analysis:

The AUC(0-∞); area under the concentration versus time curve from zero to time t, where t is the last time point with a measurable concentration (AUC[0-t_{last}]); and C_{max} will be log transformed and analyzed using an analysis of variance (ANOVA) model. The model will include fixed effects for injection device (PFS [reference] or autoinjector [test]), investigative site, and injection site. The least squares means for the PFS and autoinjector and the 90% confidence interval (CI) for the difference in means will be estimated from the ANOVA model and back transformed from the log scale to provide estimates of the geometric means and 90% CIs for the ratio of the geometric means.

Adverse events, product complaints, clinical laboratory parameters, vital signs, and ECG parameters will be assessed. They will be listed, and summarized using standard descriptive statistics.

Log-transformed $C_{max, CGRP}$ and AUC(0-$t_{last, CGRP}$) estimates will be evaluated by an ANOVA with fixed effects for injection device (PFS [reference] or autoinjector [test]), investigative site, and injection site. The least squares means for PFS and autoinjector and the 90% CI for the difference in means will be estimated from the ANOVA model and back transformed from the log scale to provide estimates of the geometric means and 90% CIs for the ratio of the geometric means.

2. Schedule of Activities

Study Schedule Protocol I5Q-MC-CGAQ

Weeks Postdose			0					1			2	3	4	6	8	10	12	16	20
Day	SC[a]	- 1	1	2	3	5	6	8	10	12	15	22	29	43	57	71	85	113	141[b]
Visit Window (days)											±1	±2	±2	±3	±3	±3	±3	±3	±3
CRU admission[c]		X																	
CRU discharge[c]				X															
Outpatient visit[d]	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization			X																
Study drug injection			X[e]																
Informed consent	X																		
Eligibility assessment	X																		
Medical history	X																		
Recording of AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam[f]	X	X	Predose	X				X			X		X	X	X		X	X	X
Body temperature	X	X																	
Height, weight[g]	X		Predose																X
Vital signs (hours)[h]	X	X	Predose, 8	24		X		X			X		X	X	X		X	X	X
Single 12-lead ECG	X	X		24														X	X
Clinical laboratory tests	X	X									X				X			X	X
Serology: HIV, HBV, HCV	X																		
Urine drug screen, ethanol test[i] & pregnancy test[j]	X	X																X	X
LY2951742 PK blood sampling (hours)[k]			8	24	48	96	120	168	216	264	336	504	672	1008	1344	1680	2016	2688	3360
Plasma CGRP sampling for PD (hours)[l]			Predose	24	48	96	120	168	216	264	336	504	672	1008	1344	1680	2016	2688	3360
PGx blood sampling			Predose																
Immunogenicity blood sampling (hours)			Predose								336		672		1344		2016		3360

Abbreviations: AE = adverse event; CRU = clinical research unit; ECG = electrocardiogram; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; PD = pharmacodynamics; PK = pharmacokinetics; PGx = pharmacogenetics; SC = screening.

[a] Screening visit to be conducted within 45 days prior to dosing.

[b] End-of-study visit. Also, procedures for early termination.

[c] Subjects will be admitted to the CRU on Day -1, and may be discharged on Day 2 after the procedures scheduled at 24 hours after dosing have been completed.

[d] Unless otherwise specified, safety monitoring procedures throughout the study should be performed at approximately the same time of day (±2 hours) as dosing was performed on Day 1 (except for procedures scheduled at screening and Day -1).

[e] Each subject will receive a single dose of 240 mg LY2951742 in the morning, administered as 2 × 1-mL (120 mg/mL) subcutaneous injections of solution formulation in either a manual prefilled syringe or an autoinjector device. Injection-site reactions after injection will be assessed as part of AE collection.

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

[g] Height to be measured at screening only.

[h] Vital signs include sitting blood pressure and pulse rate.

[i] Additional urine drug screen and ethanol tests may be performed at the investigator's discretion.

[j] Required for females of child-bearing potential only; however, pregnancy tests carried out in females of non-childbearing potential pending receipt of follicle-stimulating hormone results will not be considered a protocol deviation. Serum pregnancy test will be done on screening, and may be repeated using urine or serum test prior to admission to the clinical research unit and as clinically indicated.

[k] When possible, PK samples on follow-up outpatient visit days should be collected at a time of day close to when dosing occurred on Day 1 (±2 hours). PK sampling times are given as targets to be achieved within reasonable limits. The actual time of PK sampling should be recorded.

[l] Baseline plasma CGRP sample will be taken on Day 1 prior to study drug injection.

3. Introduction

3.1. Study Rationale

This study will assess the pharmacokinetics (PK), pharmacodynamics (PD), safety, and tolerability of LY2951742 solution when administered as a subcutaneous dose of 240 mg using a manual prefilled syringe (PFS) or an autoinjector (synonymous with 'prefilled pen' per the Standard Terms of the European Pharmacopoeia). The study will bridge from the PFS used to administer LY2951742 in Phase 3 migraine prevention trials to the autoinjector that is planned to be available for commercial use.

3.2. Background

LY2951742 is a humanized monoclonal antibody that potently and selectively binds to calcitonin gene-related peptide (CGRP), a peptide that is widely expressed in the central and peripheral nervous system and acts as a local facilitator of inflammatory processes. Therefore, neutralizing CGRP is anticipated to modulate neurogenic inflammation and is considered a therapeutic approach for the treatment of migraine and neuropathic pain. As such, Lilly is currently evaluating LY2951742 for migraine prevention and cluster headache prevention.

Clinical Experience with LY2951742

LY2951742 was administered via the subcutaneous route using a lyophilized formulation in the following completed clinical trials:

In a Phase 1, single ascending-dose and multiple-dose study (I5Q-MC-CGAA), LY2951742 was administered to healthy subjects as single doses from 1 to 600 mg, and 150 mg every 2 weeks (Q2W) for a total of 4 administrations. LY2951742 appeared to be well tolerated and did not result in any serious adverse events (SAEs) or discontinuations due to treatment-emergent adverse events (TEAEs). All TEAEs were mild in severity and the incidence of TEAEs did not increase with higher dose. For the LY2951742-treated subjects, 11 (26%) in the single-dose cohorts, and 4 (57%) in the multiple-dose cohort developed drug-induced anti-drug antibodies (ADA) and there was no apparent effect of these findings on the safety, tolerability, PK, or PD (plasma CGRP concentration) of LY2951742.

In a Phase 1 study (I5Q-MC-CGAE), LY2951742 was administered to Japanese and Caucasian subjects to evaluate the safety, tolerability, PK, and PD of LY2951742 after a single dose of 5 to 300 mg and multiple doses of 300 mg every 4 weeks (Q4W). The data indicated that there are no clinically significant safety findings in these populations, and the PK and PD profiles were comparable.

In a Phase 2a study (I5Q-AR-ART1 [ART-01]), LY2951742 given at a dose of 150 mg Q2W for 12 weeks was effective as compared with placebo in reducing the number of migraine headache days, headache days, headache hours, and the number of migraine attacks in patients with episodic migraines. LY2951742 was well tolerated in migraineurs, with no notable safety findings. No findings of clinical importance on the basis of efficacy, tolerability, PK, and safety were noted with regard to the formation of treatment-emergent ADA.

A Phase 2b, dose-ranging study in patients with episodic migraine (I5Q-MC-CGAB; 273 subjects received LY2951742, 137 subjects received placebo) has completed the double-blind treatment phase and the post-treatment phase. LY2951742 was administered at doses of 5, 50, 120, and 300 mg Q4W for 12 weeks. Preliminary data suggest there are no clinically significant safety findings. Two patients discontinued during the double-blind treatment period due to an adverse event (AE): 1 patient in the 5-mg group due to visual impairment, and 1 patient in the 300-mg group due to abdominal pain (the abdominal pain was a pre-existing condition and not treatment-emergent). Other ongoing trials include two Phase 3 studies which are evaluating the potential of LY2951742 to prevent cluster headache in patients with episodic cluster headache (15Q-MC-CGAL) and patients with chronic cluster headache (15Q-MC-CGAM). A Phase 2, placebo- and active-controlled dose-ranging study (I5Q-MC-CGAF) in patients with mild to moderate osteoarthritis pain of the knee was stopped based on a planned futility analysis; there were no safety events that influenced this decision.

Clinical Pharmacokinetics of LY2951742

In Study CGAA, PK data following single-dose administration indicated that the time to maximum observed concentration (t_{max}) was 7 to 14 days post subcutaneous injection. The maximum observed concentration (C_{max}) and the area under the concentration versus time curve from time zero to infinity (AUC[0-∞]) were generally dose proportional from 1 to 600 mg. The half-life associated with the terminal rate constant in noncompartmental analysis ($t_{1/2}$) of LY2951742 was 25 to 30 days and similar across all dose levels. Pharmacokinetic results from Studies CGAE, ART-01, and CGAB were similar to Study CGAA. In Study CGAE, the PK and PD were generally similar between Japanese and Caucasian subjects.

Clinical Pharmacodynamics of LY2951742

In Study CGAA, PD assessments were performed in healthy subjects following single and multiple doses by evaluating the inhibition in capsaicin-induced dermal blood flow (CIDBF). Dermal blood flow was determined using Laser Doppler Imaging. In general, the 75, 200, and 600 mg doses appeared to elicit a maximum inhibition of CIDBF and this effect was sustained when measured 42 days after a single dose; following repeated doses, the effect on CIDBF was sustained for at least 144 days after the last of four 150-mg subcutaneous injections administered Q2W.

In Studies CGAA and CGAB, total CGRP plasma concentrations were measured following multiple doses of LY2951742. Concentrations of CGRP increased in an LY2951742 dose- and concentration-dependent manner, suggesting binding of LY2951742 to CGRP.

Characteristics of the PFS and Autoinjector

Lilly is evaluating 2 delivery methods for subcutaneous injections of LY2951742, including a glass PFS with a staked (permanently affixed) needle for manual injection, and a glass PFS with a staked needle pre-assembled in an investigational autoinjector. The PFS, including the glass barrel, plunger, and needle, will be identical for the 2 devices and will contain 120 mg LY2951742.

A volume of 1.0 mL containing 120 mg LY2951742 will be filled into a 1.0 mL glass syringe with a 12.7 mm, 27-gauge, thin-wall, stainless steel staked needle. The syringe will be closed at the product contact surface with an elastomeric plunger. The PFS needle will be protected and closed by a rigid needle shield consisting of an elastomeric core with a rigid polypropylene shell. The syringe, needle, and plunger (non-product contact surface) are lubricated. The PFS will be assembled inside the autoinjector, so there will not be a difference in the product contact surfaces.

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

3.3. Benefit/Risk Assessment

No significant adverse effects with LY2951742 have been seen in nonclinical studies (rats, monkeys) with dosing up to 6 months. Additionally, there was no effect of LY2951742 on embryo-fetal development (rats, rabbits) or on male/female fertility (rats).

To date, in Studies CGAA, CGAB, CGAE, and ART-01, more than 450 clinical trial participants (healthy subjects [N=84] and patients with migraine [N=380]) have been exposed to LY2951742 at single doses ranging from 1 to 600 mg and multiple doses up to 300 mg Q4W. Assessment of AEs indicates that LY2951742 has been well tolerated in both populations. The AEs generally have been mild to moderate in severity. Injection-site reactions (for example, injection-site pain and injection-site erythema) in the LY2951742 treatment group were the most frequently reported events in these clinical studies. None of the ISR were considered serious, nor were any serious allergic/hypersensitivity reactions observed. There were no SAEs in the healthy subject studies. In studies with migraine patients, 5 patients treated with LY2951742 experienced 5 SAEs: peripheral vascular disorder, spontaneous abortion, acute appendicitis, Crohn's disease, and suicidal ideation; however, none of the events were judged by the investigator to be related to treatment. In the study of patients with knee pain due to osteoarthritis, one patient treated with LY2951742 reported 3 SAEs: angina pectoris, myocardial infarction (reported as a potential myocardial infarction), and catheter site infection. These events were not considered by the investigator to be related to treatment with LY2951742. Analyses of laboratory values and cardiovascular data from the clinical studies have shown no other clinically important changes in tested parameters.

As LY2951742 is a biologically derived substance, it may be associated with allergic reactions. The investigator should be prepared to treat acute allergic reactions, including acute anaphylaxis. The investigator should also monitor for localized ISR. Because LY2951742 has been administered to only a relatively small number of humans, investigators in clinical studies should monitor for unexpected, off-target, and idiosyncratic adverse effects.

As this study is enrolling healthy subjects, no clinical benefit is anticipated from study participation.

More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of LY2951742 are to be found in the IB.

4. Objectives and Endpoints

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

Table CGAQ.1. Objectives and Endpoints

Objectives	Endpoints
Primary To determine the relative bioavailability of 240 mg LY2951742 after subcutaneous administration of LY2951742 solution as a manual PFS (reference) or autoinjector (test).	The primary endpoints will be the maximum observed concentration (C_{max}) and area under the concentration versus time curve from time zero to infinity (AUC[0-∞]) of LY2951742.
Secondary To assess plasma CGRP concentrations after subcutaneous administration of 240 mg LY2951742 solution as a PFS or autoinjector.	Maximum observed CGRP concentration ($C_{max, CGRP}$) and area under the concentration versus time curve from zero to time t, where t is the last time point with a measurable concentration of CGRP (AUC[0-$t_{last, CGRP}$]).
To assess the safety and tolerability of LY2951742 in healthy subjects after subcutaneous administration of 240 mg LY2951742 solution as a manual PFS or autoinjector.	TEAEs.

5. Study Design

5.1. Overall Design

This will be a Phase 1, multi-center, open-label, 2-arm (PFS, autoinjector), randomized, parallel group study where a single dose of 240 mg LY2951742 will be administered to healthy subjects.

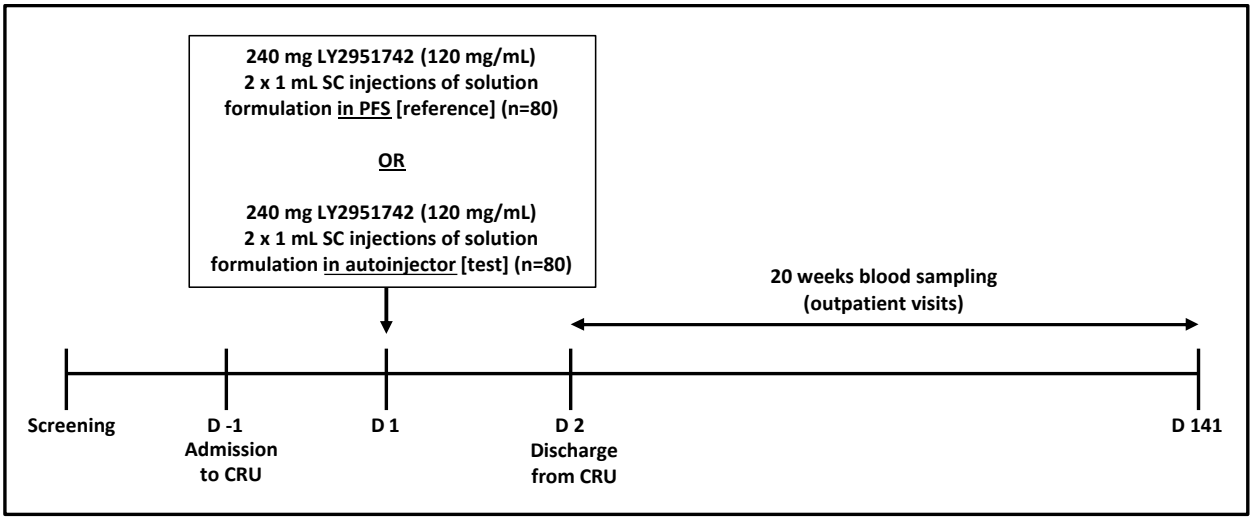
Screening will occur up to 45 days prior to dosing with LY2951742.

Subjects will be admitted to the clinical research unit (CRU) on Day -1. Subjects will be randomized in a 1:1 ratio to 240 mg LY2951742 as a PFS (reference) or 240 mg LY2951742 as an autoinjector (test). All doses will be administered in the morning of Day 1 as two 1-mL subcutaneous injections of 120 mg/mL solution of LY2951742. Subjects will be stratified to receive injections in the upper arm, abdomen, or thigh in each arm of the study, with similar numbers of subjects for each site of injection.

Subjects will remain resident at the CRU until the procedures scheduled at 24 hours postdose have been completed on Day 2, or longer at the discretion of the investigator. All subsequent procedures will be performed on an outpatient basis over a period of approximately 20 weeks (5 half-lives of LY2951742) after study drug administration, including an end-of-study visit (Day 141).

Blood samples will be collected up to 20 weeks postdose to determine serum concentrations of LY2951742 for PK assessments and plasma concentrations of CGRP for PD assessments, and to determine the potential occurrence of ADA and neutralizing antibodies. Safety and tolerability will be assessed by recording of TEAEs, ISR, vital signs (blood pressure and pulse rate), 12-lead electrocardiograms (ECGs), physical examination, clinical chemistry, hematology, and urinalysis.

Figure CGAQ.1 illustrates the study design.



Abbreviations: CRU = clinical research unit; D = day; PFS = prefilled syringe; SC = subcutaneous.

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

5.2. Number of Participants

Up to 160 subjects will be enrolled in this study.

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last subject.

5.4. Scientific Rationale for Study Design

This study is open label because the primary objective for this study is to compare the relative bioavailability of LY2951742 solution as a manual PFS versus autoinjector. Pharmacokinetics is an objective endpoint; therefore, blinding is unnecessary. In addition, the overtly different appearance and operation of the test and reference injection devices (PFS and autoinjector) precludes blinding of subjects or investigators.

LY2951742 is a humanized monoclonal antibody with observed $t_{1/2}$ of approximately 3 to 4 weeks. The planned follow-up period will be 20 weeks after dosing, which enables adequate collection of PK data to assess the relative bioavailability of LY2951742 solution given by a PFS or autoinjector. The $t_{1/2}$ of LY2951742 and the required duration for the wash-out period preclude the use of a cross-over design for this study.

5.5. Justification for Dose

A dose of 240 mg LY2951742 is being evaluated because it is the highest dose in the Phase 3 registration trials for the treatment of migraine prevention. As such, 240 mg will be administered as LY2951742 solution as a PFS or autoinjector.

6. Study Population

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

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

Screening may occur up to 45 days prior to dosing. Subjects who are not dosed within 45 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

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

6.1. Inclusion Criteria

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

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

[1a] male subjects:

agree to use an effective method of contraception and will not donate sperm during the study and for 5 months following dosing

[1b] female subjects:

women of child-bearing potential may participate, and include those who test negative for pregnancy prior to dosing based on a pregnancy test and agree to use one highly effective method of contraception or a combination of 2 effective methods of contraception during the study and for 5 months following dosing. Women may choose to use a double barrier method of contraception. Barrier methods without concomitant use of a spermicide are not reliable or an acceptable method. Thus, each barrier method must include use of a spermicide. It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.

or

women not of child-bearing potential due to surgical sterilization (at least 6 weeks after surgical bilateral oophorectomy with or without hysterectomy, or at least 6 weeks after confirmed tubal occlusion [not tubal ligation]) confirmed by medical history, congenital anomaly such as Müllerian agenesis, or menopause

Postmenopausal is defined as

1) women aged at least 50 years with spontaneous amenorrhea for at least 12 months, not induced by a medical condition such as anorexia nervosa and not taking medications

during the amenorrhea that induced the amenorrhea (for example oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy)

or

2) women aged at least 50 years with spontaneous amenorrhea for 6 to 12 months and a follicle-stimulating hormone level greater than 40 mIU/mL

or

3) women aged at least 55 years not on hormone therapy with spontaneous amenorrhea for at least 6 months

or

4) women aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy (HRT)

[2] are between 18 and 65 years old at the time of screening

[3] have a body mass index (BMI) between 19.0 and 35.0 kg/m^2, inclusive, at screening

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

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

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

[7] are able and willing to give signed informed consent

6.2. Exclusion Criteria

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

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

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

[10] are currently enrolled in a clinical trial involving an 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, in a clinical trial involving an investigational product. If the previous investigational product has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed.

[12] have previously completed or withdrawn from this study or any other study investigating LY2951742, and have previously received LY2951742

[13] have known allergies to LY2951742, related compounds, or any components of the formulation, or history of significant atopy

[14] have received treatment with any monoclonal antibody targeting the CGRP pathway (including LY2951742), or have received other biologic agents (such as monoclonal antibodies) within 4 months or 5 half-lives (whichever is longer) prior to dosing

[15] have a history of multiple (3 or more) or severe allergies or has had an anaphylactic reaction to prescription or non-prescription drugs or food

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

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

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

[19] have a history or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the investigational product; or of interfering with the interpretation of data (appendectomy and cholecystectomy are allowed)

[20] have known or ongoing clinically significant neuropsychiatric disorders. Neuropsychiatric disorders that required active treatment (pharmacological or nonpharmacological) should be considered clinically significant.

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

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

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

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

[25] are women who are lactating

[26] intend to use over-the-counter or prescription medication within 7 days prior to dosing and during the study (especially systemic glucocorticoids, immunomodulatory drugs, drugs with propensity for dermal reactions, drugs with known hepatic toxicity, etc). Stable doses of HRT (including estrogen, estrogen/progesterone combination, and thyroid replacement therapy) are allowed for inclusion. Occasional acetaminophen up to a 2-g dose in a 24-hour period, stool softener, or nasal saline preparations may be allowed for inclusion at the discretion of the investigator.

[27] have donated blood of more than 500 mL or have undergone major surgery within the last month

[28] are unwilling to refrain from consuming xanthine-containing food and drink from 24 hours prior to admission to the CRU, or unwilling to abide by caffeine restrictions as specified in Section 6.3.1

[29] have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females), or are unwilling to stop alcohol consumption 48 hours prior to admission to CRU and during residence in the CRU, and for 48 hours prior to each outpatient visit, or are unwilling to restrict alcohol intake to no more than 21 units per week (males) and 14 units per week (females), with no more than 3 units consumed per day, at all other times during the outpatient period (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits)

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

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

[32] have any other condition which, in the opinion of the investigator and/or Lilly, precludes the subject from providing informed consent, following the protocol procedures and restrictions, or completing the protocol

6.3. Lifestyle and/or Dietary Requirements

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

6.3.1. Xanthines/Caffeine, Alcohol, and Tobacco

Subjects will not be allowed xanthine consumption for 24 hours prior to admission to the CRU. While resident in the CRU, subjects should abide by the CRU caffeine intake guidelines.

Alcohol consumption is not allowed from 48 hours prior to all study visits. While resident in the CRU, subjects should abide by the CRU guidelines. During the outpatient period, alcohol consumption is limited to no more than 21 units per week (males) and 14 units per week

(females), with no more than 3 units to be consumed per day, except for the 48 hours prior to each outpatient visit, during which alcohol consumption is not permitted.

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

6.3.2. Activity

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

6.3.3. Blood or Plasma Donation

Blood or plasma donations are not permitted for 150 days after dosing.

6.4. Screen Failures

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

7. Treatment

7.1. Treatment Administered

This study involves a comparison of the PK of LY2951742 solution formulation administered as a manual PFS versus an investigational autoinjector. Table CGAQ.2 shows the treatment regimens.

Table CGAQ.2. Treatments Administered

Treatment name	LY2951742	LY2951742
Total dose:	240 mg	240 mg
Concentration:	120 mg/mL	120 mg/mL
No. of injections:	2 × 1 mL	2 × 1 mL
Formulation and presentation:	Solution in a prefilled syringe	Solution in an autoinjector

The investigator or designee is responsible for:

- explaining the correct use of the investigational products to the site personnel
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection
- returning all unused medication and autoinjectors to Lilly or its designee at the end of the study
- reporting product quality issues/complaints within the specified time
- and returning any autoinjectors that do not operate correctly to Lilly for further evaluation. A product complaint form must be filed with each device returned.

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

7.1.1. Packaging and Labeling

LY2951742 as a PFS will be supplied as an injectable solution in a 1-mL, single-dose, disposable manual syringe. Each syringe of LY2951742 will be designed to deliver 120 mg of LY2951742. A dose will consist of two 1-mL PFS, with each syringe containing 120 mg of LY2951742, for a total dose of 240 mg LY2951742.

LY2951742 as an investigational autoinjector will be supplied as an injectable solution in a 1-mL, single-dose, disposable autoinjector. Each autoinjector of LY2951742 will be designed to deliver 120 mg of LY2951742. A dose will consist of two 1-mL autoinjectors, with each autoinjector containing 120 mg of LY2951742, for a total dose of 240 mg LY2951742.

Clinical trial materials will be labeled according to the country's regulatory requirements. Autoinjectors will be labeled as "investigational device".

7.1.2. Drug Delivery Devices

A PFS and an investigational autoinjector containing 1 mL of 120 mg/mL LY2951742 solution will be provided for use in the study.

7.2. Method of Treatment Assignment

Subjects will be randomized in a 1:1 ratio to treatment with LY2951742 administered as a PFS or autoinjector. Assignment to the injection device (PFS or autoinjector) and injection site (arm, abdomen, or thigh) will be determined by a computer-generated randomization schedule provided to each site.

7.2.1. Selection and Timing of Doses

Subjects will be allocated to fixed-dose (240 mg LY2951742) treatment according to the randomization schedule.

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

7.3. Blinding

This will be an open-label study.

7.4. Dose Modification

This section is not applicable for this study.

7.5. Preparation/Handling/Storage/Accountability

Only participants enrolled in the study may receive investigational product and only authorized site staff may supply or administer study treatment. All study treatments should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. The syringes of LY2951742 for injection (PFS and autoinjector) should be stored in the refrigerator (2 to 8°C). The syringes should be removed from the refrigerated storage and allowed to equilibrate to room temperature for approximately 30 minutes before administration.

The investigator or designee is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

7.6. Treatment Compliance

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

7.7. Concomitant Therapy

Stable doses of HRT, including estrogen, estrogen/progesterone combination, and thyroid replacement therapy, will be allowed during the study. Over-the-counter medications or other prescription medications are to be avoided within 7 days prior to dosing and during the study (especially systemic glucocorticoids, immunomodulatory drugs, drugs with propensity for dermal reactions, drugs with known hepatic toxicity, etc).

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

7.8. Treatment after the End of the Study

This section is not applicable for this study.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

Not applicable for this single-dose study.

8.1.1. Discontinuation of Inadvertently Enrolled Subjects

If the sponsor or investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly CP or CRP and the investigator to determine if the subject may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly CP or CRP to allow the inadvertently enrolled subject to continue in the study.

8.2. Discontinuation from the Study

Subjects will be discontinued in the following circumstances:

- 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 subject should be discontinued from the study
- Subject Decision
    - the subject requests to be withdrawn from the study

Subjects who discontinue the study early will have end-of-study procedures performed as shown in the Schedule of Activities (Section 2).

8.3. Subjects Lost to Follow-Up

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

9. Study Assessments and Procedures

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

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

Appendix 5 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

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

Investigators must document their review of each laboratory safety report.

9.1. Efficacy Assessments

This section is not applicable for this study.

9.2. Adverse Events

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

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

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

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

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, a study procedure, concomitant treatment or pathologies.

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

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

9.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- events considered significant by the investigator based upon appropriate medical judgment
- when a condition related to the 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.

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.

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

Pregnancy (maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 Code of Federal Regulations (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.

9.2.2. Complaint Handling

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

- Product quality issues/complaints must be reported by site staff within 24 hours of notification to the clinical site/study personnel, or within 24 hours of study/site personnel becoming aware of a product issue, regardless of the availability of the complaint sample.
- Retain the investigational product under appropriate storage conditions, if available or when obtained, until instructed to return it to Lilly.
- Follow the instructions outlined in the Product Complaint Form for other reporting requirements.

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

9.3. Treatment of Overdose

For the purposes of this study, an overdose of LY2951742 is considered to be any dose higher than the dose assigned through randomization.

There is no specific antidote for LY2951742. In the event of an overdose, the subject should receive appropriate supportive care and any AEs should be documented.

9.4. Safety

9.4.1. Laboratory Tests

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

9.4.2. Vital Signs

For each subject, sitting blood pressure and pulse rate measurements should be conducted according to the Schedule of Activities (Section 2) and following the study-specific recommendations included in the Manual of Operations for the study.

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

Additional vital signs may be assessed as clinically indicated as well as at the scheduled times.

Unscheduled orthostatic blood pressure and pulse rate should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured during the study if warranted and agreed upon between the sponsor and investigator.

9.4.3. Electrocardiograms

For each subject, a single 12-lead digital ECG should be collected according to the Schedule of Activities (Section 2) and the study-specific recommendations included in the Manual of Operations for the study.

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the subject receives the dose of the investigational product, should be reported to Lilly, or its designee, as an AE via the eCRF.

Electrocardiograms must be recorded before collecting any blood for safety or PK tests. Subjects 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. All ECGs recorded should be stored at the investigational site.

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

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

9.4.4. Other Tests

9.4.4.1. Injection-Site Assessments

Injection-site reactions that occur as part of the routine AE monitoring will be fully characterized (Appendix 6).

Investigational site staff will be provided with separate instructions/training in how to consistently evaluate ISR and their severity. Photographs of ISR will be taken in a standardized fashion for record-keeping purposes; however, the photographs will not be used to evaluate ISR severity.

9.4.4.2. Physical Examinations

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

9.4.4.3. Body Weight and Height

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

9.4.5. Safety Monitoring

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

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

- trends in safety data
- laboratory analytes
- AEs, including monitoring of ISR and allergic reactions
- product complaints

If a study subject experiences elevated alanine aminotransferase ≥3 × upper limit of normal (ULN), alkaline phosphatase ≥2 × ULN, or elevated total bilirubin ≥2 × 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 subject safety and compliance with regulatory guidance, the investigator is to consult with the Lilly-designated CRP regarding collection of specific recommended clinical information and follow-up laboratory tests (Appendix 4).

9.4.6. Immunogenicity Assessments

Blood samples for immunogenicity testing will be collected to determine antibody production against the investigational products. Additional samples may be collected if there is a possibility that an AE is immunologically mediated. Immunogenicity will be assessed by a validated assay designed to detect ADA in the presence of the investigational products. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the investigational products. Up to 3 additional follow-up visits for immunogenicity analysis may be requested, based on data. These visits may be conducted after the study completion. Adverse events and samples for ADA, LY2951742, and CGRP may be obtained during these visits.

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and Ethical Review Boards (ERBs) allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to LY2951742. Any samples remaining after 15 years will be destroyed.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 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 the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

9.5.1. Bioanalysis

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

Concentrations of LY2951742 will be assayed using a validated method.

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

9.6. Pharmacodynamics

At the visits and times specified in the Schedule of Activities (Section 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 the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

The samples will be stored for up to a maximum of 1 year after the last subject visit for the study at a facility selected by the sponsor.

9.7. Genetics

A blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities, where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to LY2951742 and to investigate genetic variants thought to play a role in migraine and other pain syndromes. Assessment of variable response may include evaluation of AEs or differences in efficacy.

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

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and/or ERBs/institutional review boards impose shorter time limits, for the study at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable res ponse that may not be observed until later in the development of LY2951742 or after LY2951742 is commercially available.

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

9.8. Biomarkers

This section is not applicable for this study.

9.9. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Up to 160 subjects will be enrolled (80 in each arm). The number of subjects was determined on the basis of Study I5Q-MC-CGAO Part B interim data, a Phase 1 single-dose study evaluating 300 mg LY2951742 solution administered as a PFS. The percent coefficient of variation for LY2951742 C_{max} and AUC(0-∞) was approximately 35%. One-hundred sixty (160) subjects (80 per arm) will provide approximately 90% power to demonstrate that the 90% confidence interval (CI) of the ratio of geometric means between test and reference devices for the PK parameter falls within 0.8 to 1.25, assuming the true ratio is 0.95 and 12.5% of subjects will not contribute to the endpoint.

Randomized and dosed subjects with insufficient collection of PK samples may be replaced at the discretion of the sponsor.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

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

10.2.2. Study Participant Characteristics

The subject's age, sex, weight, BMI, height, race/subrace, and smoking habits will be summarized by injection device (LY2951742 as a PFS or autoinjector).

10.3. Statistical Analyses

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

Pharmacokinetic and PD analyses will be conducted using subjects with evaluable PK and PD data. A subject is considered to be evaluable for PK and PD analysis if that subject is compliant with the dosing and PK and PD sampling scheme. Safety analyses will be conducted for all subjects who received at least 1 dose of study drug, whether or not they completed all protocol requirements.

Exploratory analyses of the data will be conducted as deemed appropriate. Study data may be combined with other studies for safety, PK, and/or PD analyses.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

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

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

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

The number of investigational product- or investigational device-related quality issues/complaints will be reported.

10.3.1.2. Statistical Evaluation of Safety

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

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for LY2951742 will be calculated by standard noncompartmental methods of analysis. The primary parameters for analysis will be C_{max} and AUC(0-∞). Other noncompartmental parameters, such as area under the concentration versus time curve from zero to time t, where t is the last time point with a measurable concentration (AUC[0-t_{last}]), t_{max}, $t_{1/2}$, apparent clearance, and apparent volume of distribution may be reported.

10.3.2.2. Pharmacokinetic Statistical Inference

The AUC(0-∞), AUC(0-t_{last}), and C_{max} will be log transformed and analyzed using an analysis of variance (ANOVA) model. The model will include fixed effects for injection device (PFS [reference] or autoinjector [test]), investigative site, and injection site. The least squares means for the PFS and autoinjector and the 90% CI for the difference in means will be estimated from the ANOVA model and back transformed from the log scale to provide estimates of the geometric means and 90% CIs for the ratio of the geometric means.

The t_{max} of LY2951742 between the PFS (reference) and autoinjector (test) will be analyzed using a Wilcoxon rank-sum test. An estimate of the median difference and 90% CI will be calculated.

10.3.3. Pharmacodynamic Analyses

10.3.3.1. Pharmacodynamic Parameter Estimation

Pharmacodynamic parameter estimates for CGRP will be calculated by standard noncompartmental methods of analysis. The primary p arameters for analysis will be $C_{max, CGRP}$ and AUC(0-$t_{last, CGRP}$). The time of $C_{max, CGRP}$ ($t_{max, CGRP}$) will be reported.

10.3.3.2. Pharmacodynamic Statistical Inference

Log-transformed $C_{max, CGRP}$ and AUC(0-$t_{last, CGRP}$) estimates will be evaluated by an ANOVA with fixed effects for injection device (PFS [reference] or autoinjector [test]), investigative site, and injection site. The least squares means for PFS and autoinjector and the 90% CI for the difference in means will be estimated from the ANOVA model and back transformed from the log scale to provide estimates of the geometric means and 90% CIs for the ratio of the geometric means.

The $t_{max, CGRP}$ between injection devices (PFS [reference] or autoinjector [test]) will be analyzed using a Wilcoxon rank-sum test. An estimate of the median difference and 90% CI will be calculated.

10.3.4. Pharmacokinetic/Pharmacodynamic Analyses

If appropriate data are obtained, the serum LY2951742 and plasma CGRP concentrations may be merged with other clinical data, investigated using model-based analyses, and reported separately. Such analyses are not required to be included in this clinical study report.

10.3.5. Evaluation of Immunogenicity

The frequency of antibody formation to LY2951742 will be determined. If a neutralization assay is performed, the frequency of neutralizing antibodies will be determined. The relationship between the presence (or absence) of antibodies and clinical parameters (AEs and so on) may be assessed. If appropriate data are obtained, the relationship between the presence of antibodies and the PK parameters and PD response to LY2951742 may be assessed.

10.3.6. Interim Analyses

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

11. References

None.

Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	anti-drug antibodies
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ANOVA	analysis of variance
AUC(0-∞)	area under the concentration versus time curve from time zero to infinity
AUC(0-t_{last})	area under the concentration versus time curve from zero to time t, where t is the last time point with a measurable concentration
AUC(0-$t_{last, CGRP}$)	area under the concentration versus time curve from zero to time t, where t is the last time point with a measurable concentration of CGRP
BMI	body mass index
CGRP	calcitonin gene-related peptide
CI	confidence interval
CIDBF	capsaicin-induced dermal blood flow
CIOMS	Council for International Organizations of Medical Sciences
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
$C_{max, CGRP}$	maximum observed CGRP concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the 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 Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.

CP	Clinical Pharmacologist
CRP	Clinical Research Physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CRU	clinical research unit
ECG	electrocardiogram
eCRF	electronic case report form
enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the trial are those who have been assigned to a treatment.
enter	Subjects entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	Ethical Review Board
GCP	good clinical practice
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
informed consent	A process by which a subject 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 subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
Investigational product (IP)	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.
investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
ISR	injection-site reaction
Non-investigational product (non-IP)	A product that is not being tested or used as a reference in the clinical trial, but is provided to subjects and used in accordance with the protocol, such as: concomitant or rescue/escape medication for preventative, diagnostic, or therapeutic reasons, medication to ensure adequate medical care, and/or products used to induce a physiological response.

open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participant are aware of the drug therapy received during the study.
PD	pharmacodynamic
PFS	prefilled syringe
PK	pharmacokinetic(s)
Q2W	every 2 weeks
Q4W	every 4 weeks
SAE	serious adverse event
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 trial.
SUSARs	suspected unexpected serious adverse reactions
$t_{1/2}$	half-life associated with the terminal rate constant (λ_z) in noncompartmental analysis
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment
t_{max}	time of maximum observed drug concentration
$t_{max, CGRP}$	time of maximum observed CGRP concentration
ULN	upper limit of normal

Appendix 2. Clinical Laboratory Tests

Laboratory Tests

Hematology[a]	Clinical Chemistry[a]
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Glucose, random
Mean cell volume	Blood urea nitrogen (BUN)
Mean cell hemoglobin	Total protein
Mean cell hemoglobin concentration	Albumin
Leukocytes (WBC)	Total bilirubin
Cell morphology[b]	Alkaline phosphatase (ALP)
Absolute counts of:	Aspartate aminotransferase (AST)
Neutrophils	Alanine aminotransferase (ALT)
Lymphocytes	Creatinine
Monocytes	
Eosinophils	Serology[d]
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B core antibody
	Hepatitis C antibody
Urinalysis[a]	HIV
Specific gravity	
pH	Ethanol testing[e]
Protein	Urine drug screen[e]
Glucose	Serum/urine pregnancy test[f]
Ketones	FSH (females only, to confirm menopausal status)[d]
Bilirubin	
Urobilinogen	
Blood	
Microscopic examination of sediment[c]	

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

a Results will be validated by the laboratory at the time of initial testing.

b To be done as needed.

c Test only if dipstick result is abnormal.

d Performed at screening only.

e Urine drug screen and ethanol level will be performed locally at screening and may be repeated prior to admission to the clinical research unit and as indicated.

f Required for females of child-bearing potential only; however, pregnancy tests carried out in females of non-childbearing pending receipt of FSH results will not be considered a protocol deviation, . Serum pregnancy test will be done at screening, and may be repeated using urine or serum test prior to admission to the clinical research unit and as indicated.

Appendix 3. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for:

- Ensuring that the subject understands the potential risks and benefits of participating in the study.
- Ensuring that informed consent is given by each subject or legal representative. 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 subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject 's willingness to continue his or her participation in the trial.

Ethical Review

The investigator must give assurance that the ERB was properly constituted and convened as required by International Council for 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 before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP.

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

- the current IB and updates during the course of the study
- ICF
- relevant curricula vitae

Regulatory Considerations

This study will be conducted in accordance with:

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
2) applicable ICH GCP Guidelines
3) applicable laws and regulations

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

Protocol Signatures

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

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

Final Report Signature

The final report coordinating investigator or designee will sign the 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 investigator with the most enrolled subjects will serve as the final report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the final report coordinating investigator.

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

Data Quality Assurance

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

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

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

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to the original source documents.

Data Collection Tools/Source Data

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

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 4. 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 subjects in consultation with Lilly Clinical Pharmacology or its designee CRP.

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
Conjugated bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Anti-smooth muscle antibody (or anti-actin antibody)[a]**
CPK	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine 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.

Appendix 5. Blood Sampling Summary

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

Protocol I5Q-MC-CGAQ Sampling Summary

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	45	1	45
Clinical laboratory tests[a]	9	5	45
LY2951742 pharmacokinetics	2.5	20[b]	50
Plasma CGRP	8.5	20[b]	170
Immunogenicity	10	9[b]	90
Pharmacogenetics	10	1	10
Total			410
Total for clinical purposes [rounded up to nearest 10 mL]			410

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

[b] Includes a potential 3 additional samples.

Appendix 6. Injection-Site Reaction Severity Grading Scale

The following table is to be used as a guidance:

Grading[a]/ Symptoms	No or Minimal (Grade 0)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Erythema	0 to <25 mm	25 to 50 mm	51 to 100 mm	>100 mm
Induration	0 to <25 mm	25 to 50 mm and does not interfere with activity	51 to 100 mm or interferes with activity	>100 mm or prevents daily activity
Pain	No to minimal	Mild	Moderate	Severe
Pruritus	No to minimal	Mild	Moderate	Severe

[a] The most severe symptom will drive grading.

Leo Document ID = 88d816ca-1ff0-418d-8bdc-68ce1a04fd94

Approver: PPD
Approval Date & Time: 31-May-2016 13:42:09 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 31-May-2016 15:11:14 GMT
Signature meaning: Approved