Protocol I6T-MC-AMAE

# Relative Bioavailability of LY3074828 Solution Formulation in Pre-Filled Syringes Compared to Lyophilized Formulation After Single Subcutaneous Administration

NCT03188510

Approval Date: 05-Apr-2017

# Protocol I6T-MC-AMAE
# Relative Bioavailability of LY3074828 Solution Formulation in Pre-Filled Syringes Compared to Lyophilized Formulation After Single Subcutaneous Administration



LY3074828


Eli Lilly and Company
Indianapolis, Indiana USA 46285


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

Approval Date: 05-Apr-2017 GMT

# Table of Contents

## Relative Bioavailability of LY3074828 Solution Formulation in Pre-Filled Syringes Compared to Lyophilized Formulation After Single Subcutaneous Administration

**Section** **Page**

## List of Tables

**Table** **Page**

## List of Appendices

# 1. Protocol Synopsis

**Title of Study:**
Relative Bioavailability of LY3074828 Solution Formulation in Pre-Filled Syringes Compared to Lyophilized Formulation After Single Subcutaneous Administration

**Rationale:**
Study I6T-MC-AMAE (AMAE) is a Phase 1 study conducted in healthy subjects to determine the relative bioavailability of LY3074828 solution formulations supplied in pre-filled syringes (PFSs) compared to lyophilized formulation supplied in a vial, after single subcutaneous administration. The lyophilized formulation was used in completed and ongoing Phase 1 and 2 clinical trials. The solution formulation supplied in PFSs is being developed as the commercial formulation of LY3074828 for the treatment of autoimmune and inflammatory diseases to offer a more convenient method of administration.

**Objectives/Endpoints:**

| Objectives | Endpoints |
|---|---|
| **Primary**<br>To evaluate the relative bioavailability of LY3074828 solution formulation in PFSs and lyophilized formulation. | The ratio of geometric least square means between the CCI LY3074828 solution formulation supplied in the PFSs and the CCI LY3074828 lyophilized formulation for area under the concentration-time curve from time 0 extrapolated to infinity (AUC[0-∞]), and area under the concentration-time curve from time 0 to the time of last measurable concentration (AUC[0-$t_{last}$]). |
| **Secondary**<br>To evaluate the relative bioavailability of CCI and CCI LY3074828 solution formulations, and CCI LY3074828 solution formulations in PFSs and CCI LY3074828 lyophilized formulation. | The ratio of geometric least square means between the CCI and CCI LY3074828 solution formulations supplied in PFSs, and between the CCI LY3074828 solutions formulation supplied in PFSs and the CCI LY3074828 lyophilized formulation, for AUC(0-∞) and AUC(0-$t_{last}$). |
| To assess the tolerability of LY3074828 in healthy subjects. | Incidence of treatment-emergent adverse events (TEAEs).<br>Incidence of treatment-emergent anti-drug antibodies (TE-ADAs). |

**Summary of Study Design:**
Study AMAE is a single-center, randomized, parallel-treatment, open-label, Phase 1 single-dose study evaluating LY3074828 in healthy subjects.

Subjects will report to the clinical research unit (CRU) on Day -1 and will remain at the CRU until the scheduled procedures have been completed on Day 2. After randomization, study drug will be administered by subcutaneous (SC) injection in the morning of Day 1 after an overnight fast. Subjects will be followed for 12 weeks following dose administration to assess the tolerability and pharmacokinetics (PK) of LY3074828.

Safety and tolerability will be explored by clinical laboratory tests, vital sign measurements, 12-lead electrocardiograms (ECGs), recording of adverse events (AEs), physical examinations/medical assessments, immunogenicity, and injection-site assessments.

**Treatment Arms and Duration:**
Subjects will each receive a single SC dose of LY3074828 and will be randomized to 1 of 3 treatment arms:

- Reference: CCI LY3074828 lyophilized formulation, as three SC injections
- Test 1: CCI LY3074828 solution formulation in two PFSs, as SC injections
- Test 2: CCI LY3074828 solution formulation in four PFSs, as SC injections

**Number of Subjects:**
Approximately 54 subjects (18 per treatment arm) may be enrolled in this study to allow evaluable data from 16 subjects per treatment arm to be obtained. A subject's study participation is considered as complete if he/she received the study drug and completes all activities up to and including at least Day 57. A maximum of 6 subjects may be replaced if pharmacokinetic (PK) and anti-drug antibody (ADA) samples are not collected up to and including Day 57.

**Statistical Analysis:**
Pharmacokinetic parameter estimates will be evaluated to delineate effects of formulation. Log-transformed dose-normalized (DN)-AUC(0-$\infty$), DN-AUC(0-$t_{last}$), and DN-maximum drug concentration ($C_{max}$) will be evaluated in a linear fixed-effects model with a fixed effect for formulation. For the primary endpoint, a model comparing the differences between the CCI LY3074828 solution formulation and the CCI LY3074828 lyophilized formulation will be used. For the secondary endpoints, a model comparing the differences between the CCI LY3074828 solution formulation and the CCI LY3074828 lyophilized formulation, and between the CCI and CCI LY3074828 solution formations will be used. Differences will be back-transformed to present the ratios of geometric least squares means and the corresponding 90% confidence interval (CI). If leakage occurs frequently, whether injection-site leakage occurred (yes/no) may also be included as a covariate in the model. Furthermore, if leakage is found to be significant, the amount of leakage will also be added to the model.

Time of $C_{max}$ ($t_{max}$) will be analyzed using a Wilcoxon rank sum test. Estimates of the median difference, 90% CIs, and p-values from the Wilcoxon rank sum test will be calculated.

Additional PK analyses may be conducted if deemed appropriate.

Safety parameters will be listed, and summarized using standard descriptive statistics. The 0 hour (post-injection) pain score will be evaluated in a linear fixed-effects model with a fixed effect for treatment. The distribution of the data will be explored prior to analysis to determine whether data transformation is required. The differences between the CCI and CCI injections for the lyophilized formulation will be back-transformed (if applicable) to present the ratios of geometric least squares means and the corresponding 90% CI.

Additional safety and tolerability analyses will be performed if warranted upon review of the data.

# 2. Schedule of Activities

**Study Schedule Protocol I6T-MC-AMAE**

| | **Screening** | **Days** | | | | | | | | | | | | **Comments** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | ≤ 28 days | **-1** | **1** | **2** | **4** ±1d | **8** ±1d | **11** ±1d | **15** ±2d | **22** ±2d | **29** ±2d | **43** ±2d | **57** ±3d | **71** ±3d | **85/ED** ±3d | |
| Informed consent | X | | | | | | | | | | | | | | |
| Review / confirm inclusion/exclusion criteria | X | X | | | | | | | | | | | | | Any time prior to dosing. |
| Subject admission to CRU | | X | | | | | | | | | | | | | |
| Subject discharge from CRU | | | | X | | | | | | | | | | | |
| Outpatient visit | X | | | | X | X | X | X | X | X | X | X | X | X | |
| LY3074828 dose | | | X | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | |
| Weight, height, and BMI | X | | | | | | | | | | | | | | |
| Vital signs: blood pressure, pulse rate, temperature (hour) | X | X | Predose, 2, 6 | 24 | 72 | 168 | 240 | 336 | 504 | 672 | 1008 | 1344 | | X | Times with respect to start of dosing. Single ECGs to be collected. Time allowance for 2, 6, and 24 hour timepoints: ±15, ±30, and ±90 minutes, respectively. |
| 12-lead ECG (hour) | X | | Predose, 2, 6 | 24 | 72 | 168 | | 336 | | 672 | | 1344 | | X | |
| Physical examination / medical assessment | | X | | X | | | | | | | | X | | X | Full physical examination/medical assessment at Day -1 and ED. Symptom directed physical examination/ medical assessment at all other timepoints, and as deemed necessary by the investigator. |
| AE review | X | X | X | X | X | X | X | X | X | X | X | X | X | X | AE only after signing ICF. |
| QuantiFERON®-TB Gold test | X | | | | | | | | | | | | | | |
| Serology | X | | | | | | | | | | | | | | |
| Ethanol test and urine drug screen | X | X | | | | | | | | | | | | | May be repeated at the discretion of the investigator. |
| FSH / Serum pregnancy test | X | X | | | | | | | | X | | X | | X | Serum pregnancy tests for female subjects of childbearing potential only. For women who are considered to be postmenopausal, FSH should be drawn at screening to confirm postmenopausal status as defined in inclusion |

| | Screening | Days | | | | | | | | | | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | ≤ 28 days | **-1** | **1** | **2** | **4** ±1d | **8** ±1d | **11** ±1d | **15** ±2d | **22** ±2d | **29** ±2d | **43** ±2d | **57** ±3d | **71** ±3d | **85/ED** ±3d | |
| | | | | | | | | | | | | | | | criterion [1b]; women with confirmed postmenopausal status can be exempted from further pregnancy tests during the study. |
| Clinical chemistry, hematology, and urinalysis | X | X | | | | X | | | | X | | X | | X | |
| Injection-site assessment for erythema, induration, categorical pain, pruritus, and edema (hour) | | | 0, 0.25 | 24 | | 168 | | 336 | | | | | | | Times with respect to start of dosing. 0 hour assessments within 5 minutes following injection. Time allowance for 0.25-hour assessment is ±5 minutes. Additional assessments performed if deemed necessary by the investigator. |
| Injection-site pain based on VAS (hour) | | | 0, 0.5, 1, 3, 6 | 24 | | | | | | | | | | | Performed for both injections of lyophilized formulation into the lower quadrants (ie, first 2 injections), and for the first injection of solution formulation (administered to a lower quadrant). 0 hour assessments to be performed within 1 minute following injection. Time allowance for 0.5 and 1 hour will be ±5 minutes and all other time allowances will be ±15 minutes. |
| Injection-site leakage and bleeding assessment (hour) | | | 0 | | | | | | | | | | | | Performed for both injections of lyophilized formulation into the lower quadrants (ie, first 2 injections), and for the first injection of solution formulation (administered to a lower quadrant). 0 hour assessments to be performed within 1 minute following injection. |
| LY3074828 pharmacokinetic sampling (hour) | | | 0, 2, 6 | 24 | 72 | 168 | 240 | 336 | 504 | 672 | 1008 | 1344 | 1680 | 2016 | Times with respect to start of dosing. 0 hour collection immediately (within 15 minutes) before dosing. Time allowance for 2, 6, and 24 hour timepoints: ±15, ±30, and ±90 |

| | Screening | Days | | | | | | | | | | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | ≤ 28 days | **-1** | **1** | **2** | **4** ±1d | **8** ±1d | **11** ±1d | **15** ±2d | **22** ±2d | **29** ±2d | **43** ±2d | **57** ±3d | **71** ±3d | **85/ED** ±3d | |
| | | | | | | | | | | | | | | | minutes respectively. |
| Immunogenicity sample | | | Predose | | | | | X | | X | | X | | X | LY3074828 antibody sample. |
| Pharmacogenetics sample | | X | | | | | | | | | | | | | |

Abbreviations: AE = adverse event; BMI = body mass index; CRU = clinical research unit; d = day; ECG = electrocardiogram; ED = early discontinuation; FSH = follicle-stimulating hormone; ICF = informed consent form; TB = tuberculosis; VAS = visual analog scale.

Site should schedule activities as appropriate. In cases where several study procedures are scheduled at the same time, follow this order of priority for procedures: pharmacokinetic samples, ECG, vital signs, clinical laboratory tests, VAS, injection-site leakage assessment, injection-site assessment, immunogenicity sample, stored sample, such that PK sample collection occurs as close to the nominal collection time as possible. Procedures specified as predose may be performed within 2 hours from planned dosing.

.

# 3. Introduction

## 3.1. Study Rationale

Study I6T-MC-AMAE (AMAE) is a Phase 1 study conducted in healthy subjects to determine the relative bioavailability of LY3074828 solution formulations supplied in pre-filled syringes (PFSs) compared to lyophilized formulation supplied in a vial, after single subcutaneous (SC) administration. The lyophilized formulation was used in completed and ongoing Phase 1 and 2 clinical trials. The solution formulation supplied in PFSs is being developed as the commercial formulation of LY3074828 for the treatment of autoimmune and inflammatory diseases to offer a more convenient method of administration.

## 3.2. Background

LY3074828 is a humanized immunoglobulin G4-variant monoclonal antibody that is directed against the p19 subunit of interleukin-23 (IL-23) and does not bind interleukin-12 (IL-12). LY3074828 is being developed for the treatment of autoimmune diseases in which the IL-23 pathway is thought to have a significant pathogenic role. Neutralization of IL-23 with an anti-mouse IL-23 surrogate antibody (directed against the p19 subunit) significantly reduced the development of arthritis and inhibited ileal inflammation in a mouse model of spondyloarthropathy with bowel inflammation (Ruutu et al. 2012), and additionally, neutralization of IL-23 significantly reduced the disease score in the relapsing-remitting experimental autoimmune encephalomyelitis (multiple sclerosis-like) model in mice. Anti-IL-23 antibody also demonstrated some efficacy in preclinical arthritis models, depending on the timing of intervention (Cornelissen et al. 2013).

LY3074828 has been evaluated in 5 healthy volunteers (single CCI SC doses) and in 33 subjects with plaque psoriasis (single ascending IV doses of CCI or CCI mg) in Study I6T-MC-AMAA (AMAA). Furthermore, 43 healthy Japanese and Caucasian subjects were administered single intravenous (IV) doses of CCI or CCI mg LY3074828, or placebo, or single SC doses of CCI mg LY3074828, or placebo, in Study I6T-MC-AMAD (AMAD).

No serious adverse events (SAEs) were reported in either study. There were no drug-related treatment-emergent adverse events (TEAEs) of Grade 2 or higher reported in Study AMAA, and no infusion reactions or injection-site reactions, or AEs considered related to study drug, were reported in Study AMAD. There were no dose-dependent trends in adverse events (AEs), or clinically important changes in vital signs, electrocardiograms (ECGs), or clinical laboratory results across both studies that were considered to be related to the study drug. CCI

Treatment-emergent anti-drug antibodies (TE-ADAs) developed in 3 subjects after administration of single IV doses of LY3074828 in Study AMAA; however, there was no correlation between TE-ADA titers and the doses of LY3074828. The earliest timepoint at which TE-ADAs were detected was Day 22, which was the first postdose timepoint at which immunogenicity was assessed. Treatment-emergent ADAs developed in 2 subjects following single SC doses of CCI mg LY3074828 in Study AMAD; however, titers were ≤1:160.

LY3074828 is currently being evaluated in three Phase 2 studies:

- Study I6T-MC-AMAC is being conducted in approximately 240 subjects with ulcerative colitis. Three IV doses of CCI, CCI, or CCI mg LY3074828 (or placebo) are administered every 4 weeks (Q4W) during the induction period. Subjects with a clinical response are subsequently administered SC doses of CCI mg LY3074828 (or placebo) CCI or CCI mg LY3074828 CCI during the 92-week maintenance period. CCI
- Study I6T-MC-AMAF is being conducted in approximately 200 subjects with plaque psoriasis. Two SC doses of CCI, CCI, or CCI mg LY3074828 (or placebo) are administered CCI during the induction period, followed by CCI during the 88-week maintenance period.
- Study I6T-MC-AMAG is to be conducted in approximately 180 subjects with Crohn's disease (CD). CCI LY3074828 treated subjects with an improvement in CD score will either continue with this dose regimen, CCI

## 3.3. Benefit/Risk Assessment

Based on LY3074828 nonclinical and preliminary clinical data, there are no anticipated risks requiring monitoring beyond those for a typical humanized monoclonal antibody in human studies. As with other immunomodulatory therapies, LY3074828 may increase the risk of developing an infection or may exacerbate an existing serious infection. These may include opportunistic infections and reactivation of latent infections, such as tuberculosis (TB) and hepatitis B. Subjects will therefore be screened for hepatitis B/C, human immunodeficiency virus (HIV), and TB.

Treatment-emergent ADAs have been observed in 2 of the 11 healthy subjects that have been administered SC doses of LY3074828; however, titers were ≤1:160. No clinically significant safety or tolerability concerns have been identified in patients or subjects to date for LY3074828 up to the highest dose given CCI

Healthy subjects are not expected to derive any benefit from participating in studies of LY3074828.

More information about the known and expected benefits, risks, SAEs and reasonably anticipated AEs of LY3074828 are to be found in the Investigator's Brochure (IB).

# 4. Objectives and Endpoints

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

**Table AMAE.1. Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary**<br>To evaluate the relative bioavailability of LY3074828 solution formulation in PFSs and lyophilized formulation. | The ratio of geometric least square means between the CCI LY3074828 solution formulation supplied in the PFSs and the CCI LY3074828 lyophilized formulation for area under the concentration-time curve from time 0 extrapolated to infinity (AUC[0-∞]), and area under the concentration-time curve from time 0 to the time of last measurable concentration (AUC[0-$t_{last}$]). |
| **Secondary**<br>To evaluate the relative bioavailability of CCI and CCI LY3074828 solution formulations, and CCI LY3074828 solution formulation in PFSs and CCI LY3074828 lyophilized formulation.<br><br>To assess the tolerability of LY3074828 in healthy subjects. | The ratio of geometric least square means between the CCI and CCI LY3074828 solution formulations supplied in PFSs, and between the CCI LY3074828 solutions formulation supplied in PFSs and the CCI LY3074828 lyophilized formulation, for AUC(0-∞) and AUC(0-$t_{last}$).<br><br>Incidence of treatment-emergent adverse events (TEAEs).<br>Incidence of treatment-emergent anti-drug antibodies (TE-ADAs). |
| **Exploratory**<br>To assess local tolerability and leakage of a LY3074828 lyophilized formulation and solution formulations supplied in PFSs at injection-sites. | Assessments of pain (using a visual analog scale).<br>Incidence of erythema, induration, categorical pain, pruritus, edema, and leakage at injection-sites. |

# 5. Study Design

## 5.1. Overall Design

Study AMAE is a single-center, randomized, parallel-treatment, open-label, Phase 1 single-dose study evaluating LY3074828 healthy subjects.

**Screening Period (≤28 days):** Subjects should be evaluated for study eligibility ≤28 days prior to enrollment.

**Residential Period (2 days):** Fifty-four subjects who fulfill the eligibility criteria will be randomized to 1 of 3 treatment arms, with 18 subjects randomized to each arm:

- Reference: CCI LY3074828 lyophilized formulation, as three SC injections
- Test 1: CCI LY3074828 solution formulation in two PFSs, as SC injections
- Test 2: CCI LY3074828 solution formulation in four PFSs, as SC injections

Subjects will report to the clinical research unit (CRU) on Day -1 and will remain at the CRU until the scheduled procedures have been completed on Day 2, as defined in the Schedule of Activities (Section 2). After randomization, study drug will be administered by SC injection in the morning of Day 1 after an overnight fast. Subjects within the same enrollment group may be dosed across several days if required by the site for logistical or other purposes.

**Outpatient Follow-up Period (12 weeks):** The follow-up period will include outpatient visits for a total of 12 weeks following dose administration on Day 1 to assess tolerability and PK of LY3074828.

## 5.2. Number of Participants

Approximately 54 subjects (18 per treatment arm) may be enrolled in this study to allow evaluable data from 16 subjects from each treatment arm to be obtained. A subject's study participation is considered as complete if he/she received the study drug and completes all activities up to and including at least Day 57. A maximum of 6 subjects may be replaced if PK and anti-drug antibody (ADA) samples are not collected up to and including Day 57.

## 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

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications in patients. Healthy subjects are frequently used in the assessment of bioavailability of both small and large molecules.

Single doses of LY3074828 and the PK sampling timepoints have been selected to generate PK profiles sufficient to fulfill the study objectives. As the primary endpoints of this study are

PK-related and are not subject to bias, it is not considered necessary for this study to be blinded. Subjects and site staff will be aware of the administration route.

A parallel-group design was chosen because a crossover design is impractical for compounds that have long half-lives, such as monoclonal antibodies. Additionally, a crossover study design could confound PK data if subjects develop neutralizing ADAs.

Monoclonal antibody therapy has been associated with hypersensitivity reactions, including injection-site reactions. Follow-up details on injection-site reactions will be collected by the investigative site regarding the severity, duration, type, and timing of the start of the event in relation to the start of study drug administration in order to further characterize these events.

## 5.5. Justification for Dose

CCI [redacted]

CCI [redacted]

# 6. Study Population

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

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

Screening should occur up to 28 days prior to enrollment. Subjects who are not enrolled within 28 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 female subjects, as determined by medical history and physical examination.

[1a] male subjects:

a) male subjects with non-pregnant partners of childbearing potential must use a male condom with spermicide, or agree that a sponge with spermicide will be used by the female partner, for the duration of the study, and for 24 weeks following dosing with the study drug. Barrier protection methods without concomitant use of spermicide are not an effective or acceptable method of contraception. The combined use of male and female condoms as a method of contraception is not acceptable

b) male subjects with pregnant partners must use condoms during intercourse for the duration of the study, and for 24 weeks following dosing with the study drug

c) for male subjects with female partners of non-childbearing potential, contraceptive requirements do not apply

d) for male subjects who are exclusively in same sex relationships, as their preferred and usual lifestyle, contraceptive requirements do not apply

e) male subjects should refrain from sperm donation for the duration of the study, and for 24 weeks following dosing with the study drug

[1b] female subjects:

women of non-childbearing potential may participate, and include those who are:

a) infertile due to surgical sterilization (at least 6 weeks following hysterectomy, bilateral oophorectomy) with verbal confirmation of surgical success, or congenital anomaly such as mullerian agenesis

b) postmenopausal, defined as:

   a. a women at least 50 years of age, not on hormone therapy, with an intact uterus, and who has had:

      - cessation of menses for at least 1 year, or
      - at least 6 months of spontaneous amenorrhea, without an alternative medical cause, and confirmed with a follicle-stimulating hormone >40 mIU/mL, or

   b. a woman of at least 55 years of age, not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea, without an alternative medical cause, or

   c. a woman of at least 55 years of age, with a diagnosis of menopause prior to starting hormone-replacement therapy

women of childbearing potential may participate, and must agree to use a highly effective method of contraception (ie, a contraceptive measure with a failure rate of <1% per year), in addition to the use of a male condom with spermicide by the male partner, for the duration of the study, and for 12 weeks following dosing with the study drug

Highly effective methods of contraception include:

- placement of a hormonal or non-hormonal intrauterine device, or
- established use of oral, injected, or implanted hormonal contraception associated with inhibition of ovulation, or
- male partner sterilized, with verbal confirmation of surgical success (the vasectomized male partner must be the sole partner of that subject), or
- bilateral tubal ligation

Additionally:

a) women of childbearing potential must test negative for pregnancy prior to initiation of treatment based on a serum pregnancy test at the screening visit and on Day -1

b) for female subjects who are exclusively in same sex relationships, as their preferred and usual lifestyle, contraceptive requirements do not apply

[2] are 18 to 65 years of age, inclusive, at time of screening

[3] have a body mass index (BMI) of 18.0 to 32.0 kg/$m^2$, inclusive, at time of 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 and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling.

[9] are Lilly employees or employees of Covance

[10] are currently enrolled in a clinical study 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 in a clinical trial involving an investigational product within 30 days or 5 half-lives (whichever is longer) prior to screening. If the clinical trial involved treatment with biologic agents (such as monoclonal antibodies, including marketed drugs), at least 3 months or 5 half-lives (whichever is longer) should have elapsed prior to Day 1

[12] have previously completed or withdrawn from this study or any other study investigating LY3074828, and have previously received the investigational product

[13] have known allergies to LY3074828, related compounds or any components of the formulation, or history of significant atopy

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

[15] have an abnormal blood pressure as determined by the investigator

[16] have a history or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological (including thalassemia and serious glucose-6-phosphate dehydrogenase deficiency), 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

[17] have known or ongoing psychiatric disorders deemed clinically significant by the investigator

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

[19] show evidence of HIV infection and/or positive human HIV antibodies

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

[21] show evidence of hepatitis B, and/or positive hepatitis B surface antigen, and/or hepatitis B core antibody

[22] are women who are lactating

[23] have used or intend to use over-the-counter or prescription medications, including herbal medications, within 14 days prior to dosing and for the duration of the study. Stable doses of oral contraceptive or hormone-replacement therapy are permitted, at the discretion of the investigator

[24] have donated blood of more than 500 mL within the month prior to screening

[25] have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females), have a positive test for ethanol, or are unwilling to abide by the alcohol restrictions described in Section 6.3.2 (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)

[26] have a tobacco consumption of more than 10 cigarettes per day (or equivalent), are unwilling to refrain from smoking for approximately 1 hour prior to each ECG and vital sign measurements during the study, or who are unwilling to abide by the CRU smoking guidelines described in Section 6.3.2

[27] have had symptomatic herpes zoster within 3 months of screening

[28] show evidence of active or latent TB, as documented by medical history, examination, and TB testing (negative [not indeterminate] QuantiFERON®-TB Gold test); or have had household contact with a person with active TB, unless appropriate and documented prophylaxis treatment has been given

[29] have received live vaccine(s), including attenuated live vaccines, and those administered intranasally, within 8 weeks of screening, or intend to during the study

[30] have been treated with steroids within 1 month of screening, or intend to during the study

[31] are immunocompromised

[32] have received treatment with biologic agents (such as monoclonal antibodies) for a medical condition within 3 months or 5 half-lives (whichever is longer) prior to Day 1

[33] have significant allergies to humanized monoclonal antibodies

[34] have clinically significant multiple or severe drug allergies, or intolerance to topical corticosteroids, or severe post treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis)

[35] 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

[36] have had breast cancer within the past 10 years

[37] in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study

## 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. Meals and Dietary Restrictions*

Subjects should fast overnight for at least 8 hours before dosing (water is permitted). Standard meals will be provided at all other times while subjects are resident at the CRU, as per the CRU's policy.

### *6.3.2. Caffeine, Alcohol, and Tobacco*

Subjects should not consume caffeine while at the CRU, and for 12 hours prior to admission to the CRU. At other times during the outpatient period, subjects will be allowed to maintain their regular caffeine consumption.

Alcohol consumption is not permitted while at the CRU, and for 12 hours prior to each study visit. At other times, alcohol consumption should be limited to 2 units per day (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).

Subjects who smoke will be advised to not increase their consumption of tobacco products during the study. Subjects will be asked to refrain from smoking for approximately 1 hour prior to each ECG and vital sign measurements, and to abide by the CRU smoking guidelines.

### *6.3.3. Activity*

Subjects will be advised to maintain their regular levels of physical activity/exercise during the study, but to refrain from vigorous exercise. Strenuous activity should be avoided from 24 hours prior to admission until discharge from the CRU. While certain study procedures are in progress at the site, subjects may be required to remain recumbent or sitting.

## 6.4. Screen Failures

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

# 7. Treatment

## 7.1. Treatment Administered

The LY3074828 lyophilized formulation will be supplied in a sterile vial to be reconstituted prior to injection as detailed in the pharmacy instructions.

The LY3074828 solution formulations will be supplied in CCI containing CCI LY3074828. The CCI dose will comprise two CCI and the CCI CCI

The actual date and time of all dose preparation and administration will be documented, and drug accountability records will be maintained by the site pharmacy.

This study involves a comparison of CCI SC doses of LY3074828 that will be prepared from a lyophilized product with CCI and CCI SC doses of LY3074828 that will supplied as a solution in PFSs. Table AMAE.2 shows the treatment regimens.

**Table AMAE.2. Treatments Administered**

| Treatment arm | Lyophilized formulation CCI | Pre-filled syringes CCI | Pre-filled syringes CCI |
|---|---|---|---|
| Reference/test | Reference | Test 1 | Test 2 |
| Product | LY3074828 | LY3074828 | LY3074828 |
| Dose | [redacted] | CCI | CCI |
| Concentration | CCI | CCI | CCI |
| Injection volumes | CCI CCI CCI | CCI CCI | CCI CCI |
| Number of injections | 3 | 2 | 4 |
| Formulation and presentation | Lyophilized powder for reconstitution | Solution in a PFS | Solution in a PFS |

Abbreviations: PFS = pre-filled syringe.
a Theoretical total dose = 252 mg

Injection-sites selected for SC administration should be in the abdominal region approximately 5 cm from the umbilicus, and treatment should be administered with the needle applied at approximately 45 degrees with pinching the skin. Subcutaneous administration of LY3074828 should be given by a limited number of individuals for consistency. The same type of syringe and needle (27-gauge, half-inch needle) should be used for all subjects to ensure all injections are delivered to a consistent depth target into the SC space. Subsequent injection(s) should be given immediately following the previous injection.

For the lyophilized formulation (Reference), the CCI injection and the first of the CCI injections will be given into lower quadrants of the abdomen. The remaining CCI injection will be administered into an upper quadrant. The order and location of the first 2 injections will be randomized (see Section 7.2).

For administration of the CCI solution formulation in PFSs (Test 1), injections will be given into separate lower quadrants of the abdomen. For administration of the CCI solution formulation in PFSs (Test 2), the first 2 injections will be given into separate lower quadrants of the abdomen, and the final 2 injections will be given into separate upper quadrants of the abdomen.

Further information around SC administration will be in pharmacy handling instructions.

Investigational products will be prepared at the site by pharmacists or other trained personnel. Investigational products will only be administered to subjects on-site by nurses or other appropriately trained personnel.

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 to Lilly or its designee at the end of the study

**Note:** In some cases, the site 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*

LY3074828 lyophilized formulation and solution formulation in PFSs will be supplied to the investigator by Lilly. Clinical trial materials are manufactured in accordance with good manufacturing practices. All investigational products will be stored, inventoried, reconciled, and destroyed according to applicable regulations.

LY3074828 lyophilized formulation will be supplied for clinical trial use as a powder in a glass vial and should be stored refrigerated (2°C to 8°C). Each vial is manufactured to deliver CCI LY3074828 and will be reconstituted with sterile water to a concentration of CCI Contents from multiple vials will be pooled for each injection, as required.

LY3074828 solution formulation will be supplied as an injectable solution in a 1-mL, single-dose, disposable manual syringe. Each syringe of LY3074828 will be designed to deliver CCI LY3074828 and therefore two or four PFSs will be required to administer doses of CCI LY3074828 or CCI LY3074828, respectively. The PFSs should be stored refrigerated, and should be removed from refrigerated storage and allowed to equilibrate to room temperature for approximately 30 minutes prior to dose administration.

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

## 7.2. Method of Treatment Assignment

Subjects will be randomized to 1 of 3 treatment arms (CCI LY3074828 lyophilized formulation [Reference], CCI LY3074828 solution formulation [Test 1], or 500 mg LY3074828 solution formulation [Test 2]). Those that are randomized to receive the lyophilized formulation will be further randomized to 1 of 4 treatment sequences:

| Sequence | First Injection | Second Injection |
|---|---|---|
| 1 | CCI administered into left lower quadrant | CCI administered into right lower quadrant |
| 2 | CCI administered into right lower quadrant | CCI administered into left lower quadrant |
| 3 | CCI administered into left lower quadrant | CCI administered into right lower quadrant |
| 4 | CCI administered into right lower quadrant | CCI administered into left lower quadrant |

For all sequences, the third injection will comprise a 1.0 mL injection administered into an upper quadrant.

Randomization will be performed using a computer-generated randomization schedule.

### *7.2.1. Selection and Timing of Doses*

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

## 7.3. Blinding

This is an open-label study.

## 7.4. Dose Modification

Dose adjustments are not permitted in this study.

## 7.5. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained, as communicated by the sponsor, during transit for all investigational product received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive investigational products 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 (see Section 7.1.1) with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation and final disposition records).

## 7.6. Treatment Compliance

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

## 7.7. Concomitant Therapy

Over-the-counter or prescription medication, including herbal medication, are not permitted within 14 days prior to dosing and throughout the study. However, stable doses of oral contraceptive or hormone-replacement therapy are permitted at the discretion of the investigator.

Paracetamol/acetaminophen (up to 2 g/day) is permitted at the discretion of the investigator. Additional drugs are to be avoided during the study, unless required to treat an AE.

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 or clinical research physician. 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

Randomized subjects who discontinue the study prematurely for any reason should complete the AE and early discontinuation (ED) procedures performed as shown in the Schedule of Activities (Section 2). The reason for, and the date of discontinuation, will be collected for all subjects.

### *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 clinical pharmacologist or clinical research physician 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 clinical pharmacologist or clinical research physician to allow the inadvertently enrolled subject to continue in the study without continued treatment with investigational product.

## 8.2. Discontinuation from the Study

Subjects will be discontinued in the following circumstances:

- Enrollment in any other clinical study 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)
- The investigator decides that the subject should be discontinued from the study
- The subject requests to be withdrawn from the study

Subjects who discontinue the study early will have ED 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 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.

The specifications in this protocol for the timings of safety and sample collection are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based upon merging clinical information. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the eCRF. Late collection outside the stipulated time allowances or failure to obtain samples due to clinical issues, such as problems with equipment, venous access, or subject defaulting on a scheduled procedure, will not be considered as protocol deviations but the site will still be required to notify the sponsor in writing via a file-note.

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.

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 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 preexisting 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, or a study procedure, taking into account concomitant treatment or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between the investigational product 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
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above

Study site personnel must alert the Lilly clinical research physician/clinical pharmacologist, or its designee, of any SAE as soon as practically possible.

Additionally, study site personnel must alert Lilly Global Patient Safety, 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.

Although all AEs are recorded in the eCRF after signing informed consent, SAE reporting to the sponsor begins after the subject has signed informed consent and has received investigational product. However, if an SAE occurs after signing informed consent, but prior to receiving investigational product, AND is considered reasonably possibly related to a study procedure then it MUST be reported.

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. 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.

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 so that the situation can be assessed.

## 9.3. Treatment of Overdose

For the purposes of this study, an overdose of LY3074828 is considered any dose higher than the dose assigned through randomization.

There is no specific antidote for LY3074828. In the event of an overdose, the subject should receive appropriate supportive care and any AEs should be documented.

Refer to the IB for further details.

## 9.4. Safety

### *9.4.1. Laboratory Tests*

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

Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the study.

### *9.4.2. Vital Signs*

For each subject, vital signs measurements (blood pressure, pulse rate, and temperature) 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. Additional vital signs may be measured during the study if warranted.

Blood pressure and pulse rate should be measured after at least 5 minutes supine.

Unscheduled orthostatic vital signs should be assessed where considered appropriate by the investigator. If orthostatic measurements are required, subjects should be supine for at least 5 minutes and stand for at least 3 minutes. If the subject feels unable to stand, supine vital signs only will be recorded.

### 9.4.3. Electrocardiograms

For each subject, a single 12-lead digital ECG will be collected according to the Schedule of Activities (Section 2). Electrocardiograms must be recorded before collecting any blood for safety or PK tests. Subjects must be supine for at least 5 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary by the investigator. All ECGs recorded should be stored at the investigational site.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the 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 (including, but not limited to, changes in QT/corrected QT [QTc] interval from baseline) 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.

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

### 9.4.4. Tuberculosis Testing

Subjects will be tested as indicated in the Schedule of Activities (Section 2) for evidence of active or latent TB using the QuantiFERON-TB Gold test. If the test is indeterminate, 1 retest is allowed. If the retest is indeterminate, the subject will be excluded from the study.

Subjects who have had household contact with a person with active TB must be excluded unless appropriate and documented prophylaxis treatment for TB has been given.

Subjects with any history of active TB are excluded from the study, regardless of previous or current TB treatments.

### 9.4.5. Safety Monitoring

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

Lilly will review SAEs within time frames mandated by company procedures. The Lilly clinical pharmacologist or clinical research physician will periodically review the following data:

- trends in safety data
- laboratory analytes
- AEs including monitoring of incidence of any nature of any infections, and injection-site reactions

When appropriate, the Lilly clinical pharmacologist or clinical research physician will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist.

#### 9.4.5.1. Hepatic Safety

If a study subject experiences elevated alanine aminotransferase (ALT) ≥3× upper limit of normal (ULN), alkaline phosphatase (ALP) ≥2× ULN, or elevated total bilirubin (TBL) ≥2× ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, aspartate aminotransferase (AST), ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatinine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator based on consultation with the Lilly clinical pharmacologist or clinical research physician. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

Additional safety data should be collected if 1 or more of the following conditions occur:

- elevation of serum ALT to ≥5× ULN on 2 or more consecutive blood tests
- elevated serum TBL to ≥2× ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2× ULN on 2 or more consecutive blood tests
- hepatic event considered to be a SAE.

#### 9.4.5.2. Monitoring of Hypersensitivity Reactions

There is a risk of systemic hypersensitivity reactions with any biological agent, including acute anaphylaxis and delayed hypersensitivities to LY3074828. Symptoms and signs that may occur as part of these hypersensitivity reactions include, but are not limited to: fever, chills, joint and muscle pain, rash, itching, urticaria, dizziness, headache, throat irritation, and shortness of breath. Less commonly, life-threatening anaphylactic reactions may occur, which may include vascular collapse and/or respiratory compromise.

All subjects will be closely monitored for signs and symptoms of hypersensitivity reactions following administration of the study drug, and appropriate medical care should be provided. Hypersensitivity reactions will be evaluated by examination of TEAEs and SAEs, and through the use of a follow-up form which will be completed by the investigator. Potential hypersensitivity events will be evaluated by a Lilly clinical research physician based on accepted criteria (Sampson et al. 2006).

### *9.4.6. Injection-Site Assessments*

Injection-site reactions will be evaluated through the collection and review of TEAEs and through the use of an Injection-Site Reaction Follow-up Form completed by the investigator. Local tolerability at the injection-sites will be examined by evaluation of erythema, induration, categorical pain, pruritus, and edema as indicated in Section 2. For each event, the severity, duration, and timing of the event in relation to the administration of study drug will be recorded. If one or more symptom(s) of an injection-site reaction is reported during the assessment, a single AE for injection-site reaction will be recorded on the AE page of the eCRF.

Pain assessments will help to determine if injection volume (1.0 mL versus 1.5 mL) is a contributing factor. For the lyophilized formulation, injection-site assessments of pain and leakage will be performed for the 2 injections in the lower quadrants of the abdomen (1.0 mL and 1.5 mL injections). For both dose levels of solution formulation in PFSs, injection-site assessments of pain and leakage will be performed for the first injection, which will be administered into a lower quadrant of the abdomen.

Pain measurements will be quantified using a 100-mm validated visual analog scale (VAS). The VAS is a well-validated tool (Williamson and Hoggart 2005) for the assessment of injection-site pain, and is presented as a 10-cm (100-mm) line, anchored by verbal descriptors, usually "no pain" and "worst imaginable pain." The subject will be asked to rate any pain on a scale of 0 to 100 mm on the line immediately (within 1 minute) following the start of the injection and at time points according to the Schedule of Activities (Section 2).

Injection-site leakage will be assessed using pre-weighed filter paper, blotting the injection-site immediately after the injection to absorb any post-injection leakage and placing the filter paper back on the tared analytical balance in a similar manner as previously described (Ignaut and Fu 2012). The amount of leakage will be calculated by subtracting the pre-weighed filter paper measurement from the post-injection-site blot filter paper measurement. Any bleeding from the injection-site will also be documented.

## 9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 2 mL each will be collected to determine the serum concentrations of LY3074828. 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. 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 LY3074828 will be assayed using a validated enzyme-linked immunosorbent assay.

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

### *9.6.1. Immunogenicity Assessments*

Blood samples for immunogenicity testing will be collected to determine antibody production against the investigational products, as specified in the Schedule of Activities (Section 2). 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 ADAs 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 product(s).

A risk-based approach will be used to monitor subjects who develop TE-ADAs during and following treatment with LY3074828. TE-ADAs are defined as either 2-fold increase in titer (ie, 1:20) above the minimum required dilution (1:10) if no ADAs were detected at baseline (predose), or a 4-fold or greater increase in titer over baseline for subjects that are ADA-positive at baseline. LY3074828 is a monoclonal antibody that binds to p19 of IL-23, and there is no unique/non-redundant endogenous protein counterpart, greatly minimizing the risk of cross-reactive ADA. Any potential risks of ADA development following this single-dose trial would be dependent on LY3074828 exposure outside of this clinical trial. The largest potential risk would be reaction upon subsequent drug exposure that could range in severity from mild local injection-site reactions to systemic anaphylaxis and/or systemic immune complex disease (Arthus-reaction). These potential risks would likely be associated with higher serum concentrations of ADA.

Given that the subjects have only a single exposure to LY3074828, any ADA response is anticipated to peak and then diminish due to lack of additional exposures. Subjects will have ADA sampling at baseline (predose), Day 15, Day 29, Day 57, and Day 85. Subjects that are observed to have significant (ie, greater than 1:1000 titer) and non-decreasing titers that meet the definition of TE-ADA, will be requested to return every 3 months after the last sample to have follow-up ADA samples tested until the titer has returned to within 1 titer of their baseline or is clearly trending back to the baseline titer. The rationale for the definitions of both TE-ADA and return to baseline is based on the premise that a 1-titer change may result from expected assay variability.

Subjects followed for at least 1 year since last dose who have not returned to baseline, as defined above, will be assessed for safety concerns and, if no clinical sequelae are recognized by the clinical team, no further follow-up will be required. Subjects who have clinical sequelae that are considered potentially related to the presence of TE-ADA may also be asked to return for additional follow-up testing.

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

## 9.7. Genetics

A blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities (Section 2), 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 exposure or response to LY3074828 and to investigate genetic variants thought to play a role in autoimmune and inflammatory diseases. 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 IRB 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 response that may not be observed until later in the development of LY3074828 or after LY3074828 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

Approximately 54 subjects (18 per treatment arm) may be enrolled to allow evaluable data from 16 subjects from each treatment arm to be obtained. The estimated total variability (coefficient of variation) in AUC(0-$\infty$), AUC(0-$t_{last}$), and maximum observed drug concentration ($C_{max}$) was 49%, 49%, and 23%, respectively, in Study AMAA following a single SC dose of 120 mg LY3074828. The coefficient of variation of 49% was used for precision estimates and is assumed for all treatment arms. A sample size of 48 subjects will provide a precision, in log scale, of approximately 0.32 for the geometric means ratio in AUC(0-$\infty$), AUC(0-$t_{last}$), and $C_{max}$ of lyophilized to solution formulation in log scale. That is, there is a 90% probability that the half-length of the 90% confidence interval (CI) of the geometric means ratio in log scale is not larger than 0.32. Subjects who are randomized but not administered treatment, or subjects (maximum of 6) that are administered treatment but do not have PK and ADA samples collected up to and including Day 57, may be replaced to ensure that approximately 16 subjects from each treatment arm may complete the study.

## 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 other demographic data will be summarized by treatment and overall.

## 10.3. Statistical Analyses

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

Pharmacokinetic analyses will be conducted on the full analysis set. This set includes all data from all randomized subjects receiving the dose of LY3074828 with evaluable PK data, according to the treatment the subjects actually received. Safety analyses will be conducted for all subjects receiving a dose of LY3074828, whether or not they completed all protocol requirements.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for population PK analysis purposes to avoid issues with post-hoc analyses and incomplete disclosures of analyses.

No adjustments for multiple comparisons will be made.

## *10.3.1. Safety Analyses*

### 10.3.1.1. Clinical Evaluation of Safety

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

The incidence of symptoms for each treatment will be presented by severity and by association with investigational product as perceived by the investigator. Symptoms reported to occur prior to study entry 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.

### 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, and changes from baseline (predose) where appropriate, 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 LY3074828 will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be AUC(0-$\infty$) and AUC(0-$t_{last}$) for LY3074828. The secondary parameters for analysis will be $C_{max}$ and time of $C_{max}$ ($t_{max}$) of LY3074828. Dose-normalized (DN)-AUC(0-$\infty$), DN-AUC(0-$t_{last}$), and DN-$C_{max}$ will be calculated. Other noncompartmental parameters, such as $t_{1/2}$, apparent total body clearance of drug calculated after extra-vascular administration (CL/F), and apparent volume of distribution during the terminal phase after extra-vascular administration ($V_Z$/F) may be reported.

### 10.3.2.2. Pharmacokinetic Statistical Inference

Pharmacokinetic parameter estimates will be evaluated to delineate effects of formulation. Log-transformed DN-AUC(0-$\infty$), DN-AUC(0-$t_{last}$), and DN-$C_{max}$ will be evaluated in a linear fixed-effects model with a fixed effect for formulation. For the primary endpoint, a model comparing the differences between the CCI LY3074828 solution formulation and the CCI LY3074828 lyophilized formulation will be used. For the secondary endpoints, a model comparing the differences between the CCI LY3074828 solution formulation and the CCI LY3074828 lyophilized formulation, and between the CCI and CCI LY3074828 solution formulations will be used. Differences will be back-transformed to present the ratios of geometric least squares means and the corresponding 90% CI. If leakage occurs frequently, whether injection-site leakage occurred (yes/no) may also be included as a covariate in the model. Furthermore, if leakage is found to be significant, the amount of leakage will also be added to the model.

The $t_{max}$ will be analyzed using a Wilcoxon rank sum test. Estimates of the median difference, 90% CIs, and p-values from the Wilcoxon rank sum test will be calculated.

Additional PK analyses may be conducted if deemed appropriate.

### *10.3.3. Pharmacodynamic Analyses*

This section is not applicable for this study.

### *10.3.4. Pharmacokinetic/Pharmacodynamic Analyses*

This section is not applicable for this study.

### *10.3.5. Evaluation of Immunogenicity*

The frequency of formation of antibodies to LY3074828 will be determined. Treatment-emergent ADAs are those that are induced or boosted by exposure to study drug, with a 4-fold increase in titer compared to baseline if ADAs were detected at baseline, or a titer 2-fold greater than the minimum required dilution (1:10) if no ADAs were detected at baseline.

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) will be assessed. Likewise, the relationship between the presence of antibodies and the PK parameters to LY3074828 will be assessed.

### *10.3.6. Exploratory Analysis*

Incidence of erythema, induration, categorical pain, pruritus and edema will be listed and summarized by treatment.

The 0 hour (post-injection) pain score will be evaluated in a linear fixed-effects model with a fixed effect for treatment. The distribution of the data will be explored prior to analysis to determine whether data transformation is required. The differences between the 1.5 mL and 1.0 mL injections for the lyophilized formulation will be back-transformed (if applicable) to present the ratios of geometric least squares means and the corresponding 90% CI. It is possible that the pain scores will be 0 so if the distribution of the data implies that a log-transformation is required then the score may be updated to log(VAS+1) to allow for the inclusion of the 0 values in the analysis.

Leakage data will be summarized by treatment using descriptive statistics and may be used as a covariate in the PK analyses.

### *10.3.7. Data Review During the Study*

Data may be accessed and analyzed while the trial is ongoing, but no changes to the study design are planned. An assessment committee will not be formed.

Data review is scheduled to occur when safety and PK data through approximately Day 57 (8 weeks postdose) become available from at least 12 subjects from each treatment group. The

purpose of the data review is to trigger Chemistry, Manufacturing, and Control processes with respect to LY3074828 formulation, and to inform dose selection for Phase 3 first registration.

### *10.3.8. Interim Analyses*

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

# 11. References

Cornelissen F, Asmawidjaja PS, Mus AM, Corneth O, Kikly K, Lubberts E. IL-23 dependent and independent stages of experimental arthritis: no clinical effect of therapeutic IL-23p19 inhibition in collagen-induced arthritis. *PLoS One*. 2013;8(2):e57553.

Ignaut DA, Fu H. Comparison of insulin diluent leakage postinjection using two different needle lengths and injection volumes in obese patients with type 1 or type 2 diabetes mellitus. *J Diabetes Sci Technol.* 2012 Mar 1;6(2):389-93.

Ruutu M, Thomas G, Steck R, Degli-Esposti MA, Zinkernagel MS, Alexander K, Velasco J, Strutton G, Tran A, Benham H, Rehaume L, Wilson RJ, Kikly K, Davies J, Pettit AR, Brown MA, McGuckin MA, Thomas R. β-glucan triggers spondylarthritis and Crohn's disease-like ileitis in SKG mice. *Arthritis Rheum*. 2012;64(7):2211-2222.

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, Brown SG, Camargo CA Jr, Cydulka R, Galli SJ, Gidudu J, Gruchalla RS, Harlor AD Jr, Hepner DL, Lewis LM, Lieberman PL, Metcalfe DD, O'Connor R, Muraro A, Rudman A, Schmitt C, Scherrer D, Simons FE, Thomas S, Wood JP, Decker WW. Second symposium on the definition and management of anaphylaxis: summary report - Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006;117(2):391-7.

Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. *J Clin Nurs*. 2005;14(7):798-804.

# Appendix 1. Abbreviations and Definitions

| Term | Definition |
|---|---|
| **ADA** | anti-drug antibody |
| **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. |
| **ALP** | alkaline phosphatase |
| **ALT** | alanine aminotransferase |
| **AUC** | area under the concentration versus time curve |
| **AUC(0-∞)** | area under the concentration versus time curve from time zero to infinity |
| **$AUC_{0-168}$** | area under the concentration versus time curve during the dosing interval |
| **AUC(0-$t_{last}$)** | area under the concentration versus time curve from time zero to time t, where t is the last sample with a measurable concentration |
| **BMI** | body mass index |
| **CD** | Crohn's disease |
| **CI** | confidence interval |
| **$C_{max}$** | maximum observed drug 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 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. |
| **CRU** | clinical research unit |
| **DN** | dose normalized |
| **ECG** | electrocardiogram |
| **eCRF** | electronic case report form |
| **ED** | early discontinuation |

| | |
|---|---|
| **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. |
| **GCP** | good clinical practice |
| **HIV** | human immunodeficiency virus |
| **IB** | Investigator's Brochure |
| **ICF** | informed consent form |
| **ICH** | International Council for Harmonisation |
| **IL-12** | interleukin-12 |
| **IL-23** | interleukin-23 |
| **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. |
| **interim analysis** | An interim analysis is an analysis of clinical trial data, separated into treatment groups, that is conducted before the final reporting database is created/locked. |
| **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. |
| **IRB** | institutional review board |
| **IV** | intravenous |
| **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. |
| **PFS** | pre-filled syringe |
| **PK** | pharmacokinetic(s) |
| **Q1W** | once every week |
| **QTc** | corrected QT |
| **SAE** | serious adverse event |

| | |
|---|---|
| **SC** | subcutaneous |
| **screen** | The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial. |
| **SUSARs** | suspected unexpected serious adverse reactions |
| **$t_{1/2}$** | half-life associated with the terminal rate constant |
| **TB** | tuberculosis |
| **TBL** | total bilirubin |
| **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. |
| **TE-ADA** | treatment-emergent anti-drug antibody |
| **$t_{max}$** | time to maximum observed drug concentration |
| **ULN** | upper limit of normal |
| **VAS** | visual analog scale |

# Appendix 2. Clinical Laboratory Tests

## Laboratory Tests

| | |
|---|---|
| Hematology[a] | Clinical Chemistry[a] |
| Hematocrit | Sodium |
| Hemoglobin | Potassium |
| Erythrocyte count (RBC) | Calcium |
| Mean cell volume | Phosphorus |
| Mean cell hemoglobin | Glucose (random) |
| Mean cell hemoglobin concentration | Blood urea nitrogen (BUN) |
| Leukocytes (WBC) | Uric acid |
| Cell Morphology | Total cholesterol |
| Absolute counts of: | Total protein |
| Neutrophils | Albumin |
| Lymphocytes | Total bilirubin[c] |
| Monocytes | Alkaline phosphatase (ALP) |
| Eosinophils | Aspartate aminotransferase (AST) |
| Basophils | Alanine aminotransferase (ALT) |
| Platelets | Creatinine |
| | |
| Urinalysis[a] | Ethanol testing[d] |
| Specific gravity | Urine drug screen[d] |
| pH | QuantiFERON-TB Gold test[a,e] |
| Protein | |
| Glucose | Serology[e] |
| Ketones | Hepatitis B surface antigen |
| Bilirubin | Hepatitis B core antibody |
| Urobilinogen | Hepatitis C antibody |
| Blood | HIV antibodies |
| Nitrite | Serum Pregnancy test[f,g] |
| Microscopic examination of sediment[b] | |
| | Hormone Panel |
| | Follicle-stimulating hormone [e,h] |

Abbreviations: HIV = human immunodeficiency virus; RBC = red blood cells; WBC = white blood cells.

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

b If clinically indicated, per investigator's discretion.

c If total bilirubin is elevated, direct bilirubin and indirect bilirubin may be measured.

d Urine drug screen and ethanol level will be performed locally at screening and on Day -1 during admission to the clinical research unit. May be repeated at the discretion of the investigator.

e Performed at screening only.

f Women of childbearing potential only.

g Refer to Section 2 for specific sampling timing.

h To be done for women only when needed to confirm postmenopausal status.

# Appendix 3. Study Governance, Regulatory and Ethical Considerations

## *Informed Consent*

The investigator is responsible for:

- ensuring that the subject understands the nature of the study, potential risks and benefits of participating in the study, and that their participation is voluntary.
- 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.
- providing a copy of the ICF to the participant or the participant's legal representative and retaining a copy on file.

## *Recruitment*

Lilly, or its designee, is responsible for the central recruitment strategy for subjects. Individual investigators may have additional local requirements or processes. Study-specific recruitment material should be approved by Lilly.

## *Ethical Review*

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

Documentation of IRB 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 IRB 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, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

## *Final Report Signature*

The investigator or designee will sign the clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

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 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/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 IRBs 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 site 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.

## *Data Protection*

Data systems used for the study will have controls and requirements in accordance with local data protection law.

The purpose and use of subject personal information collected will be provided in a written document to the subject by the sponsor.

## *Study and Site Closure*

## *Discontinuation of Study Sites*

Study site participation may be discontinued if Lilly or its designee, the investigator, or the IRB 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 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 | |
| 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 | |
| Alanine aminotransferase (ALT) | **Anti-nuclear antibody[a]** |
| Aspartate aminotransferase (AST) | **Alkaline Phosphatase Isoenzymes[a]** |
| Gamma-glutamyl transferase (GGT) | **Anti-smooth muscle antibody (or anti-actin antibody)[a]** |
| Creatinine kinase (CPK) | |

Abbreviations: 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 I6T-MC-AMAE Sampling Summary**

| Purpose | Maximum Blood Volume per Sample (mL) | Maximum Number of Blood Samples | Maximum Total Volume (mL) |
|---|---|---|---|
| Screening tests[a] | 14 | 1 | 14 |
| Clinical laboratory tests[a] | 7.5 | 5 | 37.5 |
| Pharmacokinetics[b] | 2 | 17 | 34 |
| Immunogenicity[a] | 10 | 5 | 50 |
| Pregnancy tests | 3.5 | 4 | 14 |
| Pharmacogenetics | 10 | 1 | 10 |
| Total | | | 159.5 |
| Total for clinical purposes [rounded up to nearest 10 mL] | | | 160 |

[a] Additional samples may be drawn if needed for safety purposes.
[b] Includes a potential 3 additional sample.

Leo Document ID = f2710a55-46cb-479f-ac8c-02791f209472

Approver: PPD
Approval Date & Time: 04-Apr-2017 20:30:35 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 05-Apr-2017 14:28:47 GMT
Signature meaning: Approved