Protocol 05 I6T-MC-AMAL

# A Phase 1, Single-Dose Study to Assess the Relative Bioavailability, Absolute Bioavailability, and Tolerability of LY3074828 Formulations in Healthy Subjects

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# A Phase 1, Single-Dose Study to Assess the Relative Bioavailability, Absolute Bioavailability, and Tolerability of LY3074828 Formulations in Healthy Subjects



LY3074828


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

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# 1. Protocol Synopsis

**Title of Study:**

A Phase 1, Single-Dose Study to Assess the Relative Bioavailability, Absolute Bioavailability, and Tolerability of LY3074828 Formulations in Healthy Subjects

**Rationale:**

Study I6T-MC-AMAL (AMAL) is a Phase 1 study designed to compare the formulation of LY3074828 previously used in Phase 1 and 2 studies with the formulation proposed for Phase 3 studies. Study AMAL will determine whether the pharmacokinetics (PK) and tolerability of LY3074828 are affected following changes to the investigational product, when administered subcutaneously to healthy subjects. The potential effect of administering the same volume as a single injection (1 × 2-mL) or as 2 injections (2 × 1-mL) on PK and tolerability will also be investigated during subcutaneous (SC) administration. In addition, the absolute bioavailability of LY3074828 Drug Product produced by the new process will be investigated by inclusion of an intravenous (IV) LY3074828 treatment.

**Objective(s)/Endpoints:**

| Objectives | Endpoints |
|---|---|
| **Primary**<br>To evaluate the relative bioavailability of the LY3074828 lyophilized formulation prepared by reconstitution (Reference) and the extemporaneously prepared formulation (SC 2 × 1- mL) when administered to healthy subjects by SC injection. | Reference versus SC 2 × 1-mL.<br>The ratio of geometric least squares means between the test and reference formulations will be calculated for key PK parameters of LY3074828. Primary endpoints will be area under the concentration versus time curve (AUC) from time zero to infinity (AUC[0-∞]) and AUC from time zero to time t, where t is the last sample with a measurable concentration (AUC[0-$t_{last}$]). The secondary endpoints will be maximum observed drug concentration ($C_{max}$) and time to $C_{max}$ ($t_{max}$). |
| **Secondary**<br>To evaluate the relative bioavailability of LY3074828 extemporaneously prepared as the test formulation when the same volume is administered to healthy subjects by SC injection using a single injection (1 × 2-mL) and 2 injections (2 × 1-mL). | SC 2 × 1-mL versus SC 1 × 2-mL of test formulation.<br>The ratio of geometric least squares means between the SC 2 × 1-mL and SC 1 × 2-mL injections will be calculated for key PK parameters of LY3074828. Primary endpoints will be AUC(0-∞) and AUC(0-$t_{last}$). The secondary endpoints will be $C_{max}$ and $t_{max}$. |
| To evaluate the absolute bioavailability of LY3074828 extemporaneously prepared as the test formulation when administered to healthy subjects by SC injection compared to IV infusion. | SC 2 × 1-mL versus IV and SC 1 × 2-mL versus IV.<br>The ratio of geometric least squares means of the formulations (SC/IV) will be calculated for AUC(0-∞). |
| To assess the impact of Drug Product formulation changes and number of injections on tolerability of LY3074828. | All treatments.<br>Incidence of treatment-emergent adverse events (TEAEs)<br>Incidence of treatment-emergent anti-drug antibodies (TE-ADAs) |

**Summary of Study Design:**

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

Subjects will report to the clinical research unit (CRU) on Day –1 and remain at the CRU until after the scheduled procedures have been completed on Day 2. After randomization, study drug will be administered by either IV or SC injection in the morning of Day 1 after an overnight fast.

Safety will be explored by clinical laboratory tests, vital signs measurements, 12-lead electrocardiograms (ECGs), recording of adverse events (AEs), and immunogenicity assessments.

**Treatment Arms and Duration:**
Subjects will each receive a single dose of LY3074828 and will be randomized to 1 of 4 treatments as follows:

- **Reference:** 250 mg LY3074828; lyophilized formulation with 2 × 1-mL + 1 × 1.5-mL SC injections;
- **Test SC 2 × 1 mL:** 250 mg LY3074828; test formulation with 2 × 1-mL SC injections;
- **Test SC 1 × 2 mL:** 250 mg LY3074828; test formulation with 1 × 2-mL SC injection;
- **Test IV:** 250 mg LY3074828; test formulation by IV infusion over at least 30 minutes.

**Number of Subjects:**
A total of 72 subjects will be enrolled to ensure that approximately 64 subjects complete the study (16 completers per treatment). Study completion is defined as completing all activities up to and including at least Study Day 29.

**Statistical Analysis:**

Pharmacokinetic parameter estimates will be evaluated to delineate effects of LY3074828 formulation when administered to healthy subjects by SC injection (Reference and SC 2 × 1-mL). Log-transformed $C_{max}$, AUC(0-∞), and AUC(0-$t_{last}$) estimates will be evaluated in a linear fixed-effect model with a fixed effect for formulation. The differences between the test (SC 2 × 1-mL) compared to the reference formulation will be back-transformed to present the ratios of geometric least squares means and the corresponding 90% confidence interval (CI).

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.

Similar analyses to those described above will be conducted to delineate the effect of administering the same volume as a single injection (SC 1 × 2-mL) or as 2 injections (SC 2 × 1-mL).

In order to evaluate absolute bioavailability, a fixed-effect model will be used to analyze the log-transformed AUC(0-∞) and AUC(0-$t_{last}$) of LY3074828. The model will contain formulation (SC or IV) as a fixed effect. The absolute bioavailability will be estimated for the ratio of the least-squares geometric means of the formulations (SC/IV). The corresponding 90% CI of the ratios will also be estimated. Data from Test IV will be used for the IV formulation (reference). If the number of injections is not observed to have an effect based on the analyses described above, data from SC 2 × 1-mL and SC 1 × 2-mL will be combined and used for the SC formulation (and will be considered the primary analysis). If the number of injections is observed to have an effect (SC 2 × 1-mL versus SC 1 × 2-mL comparison), analyses to evaluate absolute bioavailability will be done separately

(ie, SC 2 × 1-mL versus IV and SC 1 × 2-mL versus IV). The primary analysis will be considered as that including SC 1 × 2-mL.

Where possible, a single linear model with contrasts to test the different objectives will be used.

Additional analyses may be conducted if they are deemed appropriate.

# 2. Schedule of Activities

**Study Schedule Protocol I6T-MC-AMAL**

| **Study Day** | **Screening ≤ 28 days** | **-1** | **1** | **2** | **4** ±1d | **8** ±1d | **11**[a] ±2d | **15** ±2d | **22** ±2d | **29** ±2d | **43** ±2d | **57** ±3d | **71** ±3d | **85** ±3d | **FU/ED**[d] | **Comment** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Informed consent (written) | X | | | | | | | | | | | | | | | |
| Review / confirm inclusion/exclusion criteria | X | X | | | | | | | | | | | | | | Any time prior to dosing |
| Admission to CRU | | X | | | | | | | | | | | | | | |
| Discharge from CRU | | | | X | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | |
| Outpatient visit | X | | | | X | X | X | X | X | X | X | X | X | X | X | |
| Weight / height | X | | | | | | | | | X | | | | X | X | Height at screening only. |
| Vital signs: blood pressure, pulse rate, temperature (hour) | X | | Predose, end of infusion[b], 2, 6 | 24 | 72 | 168 | 240 | 336 | 504 | 672 | 1008 | | | 2016 | X | Times are referenced to start of dosing. Single ECGs will be collected. Time allowance for 2, 6, and 24 hour time points will be ±15 minutes, ±30 minutes and ±90 minutes respectively. End of infusion vital signs and ECG should be taken 5 to 15 minutes after the end of infusion. |
| 12-lead ECG (hour) | X | | Predose, end of infusion[b], 2, 6 | 24 | 72 | 168 | | 336 | | 672 | | | | 2016 | X | |
| Physical examination / Medical assessment | X | X | | X | | | | | | | | | | X | X | Full physical examination/ medical assessment at screening, Day -1, ED. Symptom directed physical examination/ medical assessment at all other time points, and as deemed necessary by the investigator. |
| AE review | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | AE only after signing ICF |
| QuantiFERON®-TB Gold test | X | | | | | | | | | | | | | | | |
| Pregnancy test[c] | X | X | | | | | | | | X | | X | | X | X | Women of childbearing potential only. Serum pregnancy test at screening, urine at other times. A positive urine pregnancy test will be confirmed with a serum pregnancy test. |
| Clinical laboratory tests | X | X | | | | X | | | | X | | X | | X | X | Urine ethanol and drug screen performed at screening and Day -1 during CRU |

| Study Day | Screening ≤ 28 days | -1 | 1 | 2 | 4 ±1d | 8 ±1d | 11[a] ±2d | 15 ±2d | 22 ±2d | 29 ±2d | 43 ±2d | 57 ±3d | 71 ±3d | 85 ±3d | FU/ED[d] | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | | admission, and may be repeated at the discretion of the investigator. |
| LY3074828 dose | | | X | | | | | | | | | | | | | |
| Injection / infusion-site assessment for erythema, induration, categorical pain, pruritus, and edema (hour) | | | 0, 0.25[e], end of infusion[b] | 24 | | 168 | | 336 | | | | | | | | Times are referenced to start of dosing. 0 hour assessments should be performed within 5 minutes after giving all SC injections or start of IV infusion. End of infusion assessments should be completed within 5 minutes after infusion. Additional assessments may be performed if deemed necessary by the investigator. |
| Injection site pain based on Visual analog scale (VAS) (hour) | | | 0, 0.5, 1, 3, 6 | 24 | | | | | | | | | | | | Performed only on subjects randomized to Test SC 2 x 1 mL (assessed for the first of 2 injections) and Test SC 1 x 2 mL only. 0 hour assessments should be performed within 1 minute after injection. Time allowance for 0.5 and 1 hour will be ±5 minutes and all other time allowance will be ±15 minutes. |
| Injection site leakage and bleeding assessment (hour) | | | 0 | | | | | | | | | | | | | Performed only on subjects randomized to Test SC 2 x 1 mL and Test SC 1 x 2 mL only. 0 hour assessments should be performed within 1 minute after injection. |
| LY3074828 PK sampling (hour) | | | 0, end of infusion[b], 2, 6 | 24 | 72 | 168 | 240 | 336 | 504 | 672 | 1008 | 1344 | 1680 | 2016 | X | Times are referenced to start of dosing. 0 hour collection should be taken immediately (within 15 minutes) before dosing. The end of infusion sampling should be taken at the end of IV infusion. Time allowance for 2, 6, and 24 hour time points will be ±15, ±30, and ±90 minutes respectively. |

| Study Day | Screening ≤ 28 days | -1 | 1 | 2 | 4 ±1d | 8 ±1d | 11[a] ±2d | 15 ±2d | 22 ±2d | 29 ±2d | 43 ±2d | 57 ±3d | 71 ±3d | 85 ±3d | FU/ED[d] | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Immunogenicity sample | | | Predose | | | | | X | | X | | | | X | X | LY3074828 antibody sample |
| Pharmacogenetics sample | | X | | | | | | | | | | | | | | For storage only. |

Abbreviations: AE = adverse event; CRU = clinical research unit; d = day; ECG = electrocardiogram; ED = early discontinuation; FU = follow-up visit; ICF = informed consent form; IV = intravenous; PK = pharmacokinetic; 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: PK samples, ECG, vital signs, clinical laboratory tests, VAS, injection site leakage assessment, injection / infusion site assessment, immunogenicity sample, stored sample. Procedures specified as predose may be performed within 2 hours from planned dosing.

a Day 11 required for subjects receiving subcutaneous treatments only.

b Required for subjects receiving IV treatments only.

c All female subjects of childbearing potential will have serum pregnancy test at screening. For women who are considered to be postmenopausal, follicle-stimulating hormone should be drawn to confirm postmenopausal status as defined in inclusion criterion [1b]; women with confirmed postmenopausal status can be exempted from further pregnancy tests during the study.

d Within 7 to 14 days after the last procedure or upon ED.

e Required for subjects receiving SC treatments only – time allowance of ±5 minutes.

# 3. Introduction

## 3.1. Study Rationale

CCI

Study I6T-MC-AMAL (AMAL) is a Phase 1 study designed to determine whether the pharmacokinetics (PK) and tolerability of LY3074828 are affected following these changes to the investigational product, when administered subcutaneously to healthy subjects. The potential effect of administering the same volume as a single injection (1 × 2-mL) or as 2 injections (2 × 1-mL) on PK and tolerability will also be investigated during subcutaneous (SC) administration (see Section 5.4 for rationale for study design). In addition, the absolute bioavailability of LY3074828 Drug Product produced by the new process will be investigated by inclusion of an intravenous (IV) LY3074828 treatment.

## 3.2. Background

Interleukin-23 (IL-23), a member of the interleukin-12 (IL-12) family of cytokines, is a heterodimeric protein composed of 2 subunits: the p40 subunit, which IL-23 shares with IL-12, and the p19 subunit, which is believed to be specific to IL-23. Interleukin-23 is produced by antigen-presenting cells, such as dendritic cells and macrophages (Oppmann et al. 2000; Andersson et al. 2004). Interleukin-23 is critically involved in the maintenance and amplification of T helper 17 (Th17) cells. In addition to Th17 cells, many innate immune cells respond to IL-23 and are important both in resistance to infection and in mediating pathology in many autoimmune or inflammatory diseases including ulcerative colitis and Crohn's disease (CD) (Croxford et al. 2014).

Treatment of autoimmune or inflammatory diseases with IL-23–targeted therapy is being pursued by many companies. The first such biologic to demonstrate clinical benefit in autoimmune disease was ustekinumab, which is now an approved medicine for the treatment of patients with psoriasis and psoriatic arthritis (Stelara® package insert, 2015) and is being evaluated in Phase 3 trials for treatment of CD (Toussirot et al. 2013). Ustekinumab is a monoclonal antibody that recognizes the common p40 subunit of IL-12 and IL-23; therefore, it does not target IL-23 specifically. Blockade of the IL-12 pathway may prevent Th1 cell-induced interferon blockade of Th17 cell development, thus potentially limiting the clinical activity of p40 targeting antibodies. Experimental studies suggest that blocking the

IL-23/Th17/interleukin-17 immune axis (and not IL-12) is sufficient to treat autoimmune inflammation (Monteleone et al. 2009). Interleukin-23-specific medicines targeted to the IL-23 p19 subunit have demonstrated clinical activity in psoriasis and CD (Kopp et al. 2015; Sofen et al. 2014; Krueger et al. 2015; Sands et al. 2015). Although clinical evaluation of an IL-23-targeted therapy in ulcerative colitis has yet to occur, the IL-23/Th17 pathway is suggested to have a significant role in patients with ulcerative colitis (Gheita et al. 2014; Globig et al. 2014; El-Bassat et al. 2014).

LY3074828 is a humanized immunoglobulin G4-variant monoclonal antibody that is directed against the p19 subunit of IL-23 and does not bind 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. LY3074828 does not bind rodent IL-23, so a surrogate molecule was developed to neutralize mouse IL-23 for use in preclinical studies. Neutralization of IL-23 with this surrogate antibody significantly reduced the development of arthritis and inhibited ileal inflammation in a mouse model of spondyloarthropathy with bowel inflammation (Ruutu et al. 2012). In addition, 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).

Study I6T-MC-AMAA (AMAA), has been completed to date evaluating LY3074828 in healthy volunteers and in subjects with plaque psoriasis. Seven cohorts of subjects with active psoriasis received single doses of IV LY3074828 (up to 600 mg) or placebo. A single cohort of 5 healthy subjects received single SC doses of LY3074828 (120 mg). A total of 33 subjects with psoriasis and 5 healthy subjects were administered LY3074828. Seven subjects with psoriasis received placebo.

- No serious adverse events (SAEs) were reported. Treatment-emergent adverse events (TEAEs) reported as related to investigational product included one Grade 1 event of diarrhea experienced by a single subject in the 5-mg IV cohort, 2 Grade 1 events of nausea experienced by 2 subjects in the 20-mg IV cohort, one Grade 1 event of headache experienced by a single subject in the 200-mg IV cohort, and five Grade 1 events of injection site pain experienced by 3 subjects in the 120-mg SC cohort. No LY3074828 TEAEs of Grade 2 or higher were reported. No dose-dependent trends in adverse events (AEs) were seen. No clinically important changes in vital signs, electrocardiograms (ECGs), or clinical laboratory results were observed.
- Pharmacokinetic results from Study AMAA indicate that serum exposure of LY3074828 increases in a dose-proportional manner. The mean half-life associated with the terminal rate constant ($t_{1/2}$) was 10.5 days and did not appear to be dependent on dose. The overall mean clearance following IV administration was approximately 0.526 L/day and is within the range expected for human monoclonal antibodies. Maximum concentrations were observed 3 days postdose following SC administration. Based on the area under the concentration versus time curve (AUC), the SC bioavailability was 40%.

- Treatment-emergent anti-drug antibodies (TE-ADAs) developed in 3 subjects after administration of single IV doses of LY3074828, (120 mg, 2 subjects; 350 mg, 1 subject). No subject had TE-ADAs after SC administration. There was no correlation between TE-ADA titers and the doses of LY3074828.

The clinical phase of Study I6T-MC-AMAD (AMAD) has been completed. A total of 43 healthy Japanese and Caucasian subjects were administered LY3074828 or placebo via either IV infusion (60 to 1200 mg) or SC injection (200 mg) in a Phase 1, single-site, subject- and investigator-blind, randomized, placebo-controlled, single-dose study. Subjects were followed-up for up to 12 weeks following the single dose of study drug.

- No SAEs and no AEs considered related to study drug were reported. The reported TEAEs were not dose dependent. There were no infusion reactions or injection site reactions. There were no clinically significant findings in vital signs, ECGs, or clinical laboratory tests, except for 1 subject having an abnormal ECG finding that was mild and not considered to be related to study drug.
- Preliminary PK data available from Study AMAD indicate that the PK of LY3074828 are similar in Japanese and Caucasian subjects.

## 3.3. Benefit/Risk Assessment

Based on LY3074828 nonclinical and preliminary clinical data, there are no anticipated risks requiring monitoring beyond those of a typical humanized monoclonal antibody in human studies. No clinically significant safety or tolerability concerns have been identified in patients or subjects to date for LY3074828 up to the highest dose given (1200 mg IV, single dose).

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 AMAL.1 shows the objectives and endpoints of the study.

**Table AMAL.1. Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary**<br>To evaluate the relative bioavailability of the LY3074828 lyophilized formulation prepared by reconstitution (Reference) and the extemporaneously prepared formulation (subcutaneous [SC] 2 × 1-mL) when administered to healthy subjects by SC injection. | Reference versus SC 2 × 1-mL.<br>The ratio of geometric least squares means between the test and reference formulations will be calculated for key pharmacokinetic (PK) parameters of LY3074828. Primary endpoints will be area under the concentration versus time curve (AUC) from time zero to infinity (AUC[0-∞]), and AUC from time zero to time t, where t is the last sample with a measurable concentration (AUC[0-$t_{last}$]). The secondary endpoints will be maximum observed drug concentration ($C_{max}$) and time to $C_{max}$ ($t_{max}$). |
| **Secondary**<br>To evaluate the relative bioavailability of LY3074828 extemporaneously prepared as the test formulation when the same volume is administered to healthy subjects by SC injection using a single injection (1 × 2-mL) and 2 injections (2 × 1-mL). | SC 2 × 1-mL versus SC 1 × 2-mL of test formulation.<br>The ratio of geometric least squares means between the SC 2 × 1-mL and SC 1 × 2-mL injections will be calculated for key PK parameters of LY3074828. Primary endpoints will be AUC(0-∞) and AUC(0-$t_{last}$). The secondary endpoints will be $C_{max}$ and $t_{max}$. |
| To evaluate the absolute bioavailability of LY3074828 extemporaneously prepared as the test formulation when administered to healthy subjects by SC injection compared to intravenous (IV) infusion. | SC 2 × 1-mL versus IV; SC 1 × 2-mL versus IV.<br>The ratio of geometric least squares means of the formulations (SC/IV) will be calculated for AUC(0-∞). |
| To assess the impact of Drug Product formulation changes and number of injections on tolerability of LY3074828. | All treatments.<br>Incidence of treatment-emergent adverse events (TEAEs).<br>Incidence of treatment-emergent anti-drug antibodies (TE-ADAs). |

# 5. Study Design

## 5.1. Overall Design

Study AMAL is a single-center, randomized, parallel-treatment, open-label, Phase 1 single-dose administration study evaluating LY3074828 in 72 healthy subjects.

**Screening Period (≤4 weeks):** Subjects will be evaluated for study eligibility ≤28 days prior to enrollment.

**Residential Period (2 days):** Subjects who fulfill the eligibility criteria will be randomized to 1 of 4 treatments, with 18 subjects randomized to each treatment, as shown below:

- **Reference:** 250 mg LY3074828; lyophilized reference formulation with 2 × 1-mL + 1 × 1.5-mL SC injections;
- **Test SC 2 × 1-mL:** 250 mg LY3074828; test formulation with 2 × 1-mL SC injections;
- **Test SC 1 × 2-mL:** 250 mg LY3074828; test formulation with 1 × 2-mL SC injection;
- **Test IV:** 250 mg LY3074828; test formulation by IV infusion over at least 30 minutes.

Subjects will report to the clinical research unit (CRU) on Day –1 and remain at the CRU until after 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 either IV infusion or 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 (approximately 14 weeks):** The follow-up period will include outpatient visits for a total of 12 weeks following Day 1 dose administration to assess tolerability and PK of LY3074828. An end-of-study follow-up visit will be scheduled within 7 to 14 days after the last procedure or upon early discontinuation (ED).

## 5.2. Number of Participants

A total of 72 subjects will be enrolled to ensure that approximately 64 subjects complete the study (16 completers per treatment). From a data standpoint, 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 Study Day 29.

## 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

Single doses of 250 mg LY3074828 and the PK sampling timepoints have been selected to generate PK profiles sufficient to fulfill the study objectives.

As the primary endpoints are PK-related and therefore considered to be objective in nature, it is not considered appropriate to include a placebo control during this study. Furthermore, the secondary objective relating to tolerability is a comparison between formulations and therefore addition of a placebo control will not contribute to the scientific validity of the study. As only a single dose level (250 mg) of LY3074828 will be administered during this study, and subjects and site staff will be aware of the administration route (eg, number of SC injections, IV dosing), an unblinded study design has been selected.

Due to the maximum achievable concentration of the lyophilized reference formulation being 72 mg/mL, it is not possible to administer 250 mg with a total injection volume of 2 mL for consistency with the other SC treatments. The total injection volume for the reference formulation was therefore increased to 3.5 mL to ensure a comparable total dose to the test formulation. Although the theoretical total dose for this treatment is 252 mg, the dose levels for all treatments are referred to as 250 mg for the purposes of this protocol.

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

## 5.5. Justification for Dose

CCI [redacted] Doses up to 1200 mg were found to be safe when administered by IV infusion in healthy subjects in the single-dose Study AMAD. Subcutaneous bioavailability was approximately 40% in Study AMAA.

The margin of safety for the dose of 250 mg IV relative to the no-observed-adverse-effect level observed in the 6-month nonclinical toxicology study in cynomolgus monkeys is 26.3 based on dose and 7.5 based on AUC (Table AMAL.2). Margins of safety for the 250 mg SC treatments are expected to be higher than the 250mg IV dose.

**Table AMAL.2. Margin of Safety for Intravenous Administration of LY3074828 Based on Administered Dose and Predicted Exposure**

| | Dose (mg/kg) | Dose Multiple [a] | $AUC_{0\text{-}672h,ss}$ (µg•h/mL) | Margin of Safety [b] |
|---|---|---|---|---|
| **Human dose (250 mg IV) [c]** | 3.8 (IV) | | 11400 | |
| **Monkey NOAEL [d] 6-month study** | 100 Q1W (SC) | 26.3 | 85800 [e] | 7.5 |
| **Monkey NOAEL [f] 4-week study** | 100 Q1W (IV) | 26.3 | 204000 [g] | 17.9 |

Abbreviations: AUC = area under the plasma concentration versus time curve; $AUC_{0\text{-}168}$ = AUC during the dosing interval; $AUC_{0\text{-}672h,ss}$ = AUC over 672 hours at steady state; IV = intravenous; NOAEL = no observed-adverse-effect level; SC = subcutaneous; Q1W = once every week.

a Dose multiple is the dose in animals divided by dose in humans.

b Margin of safety is the calculated AUC in animals divided by predicted AUC in humans.

c Highest proposed dose in this study; a body weight of 65 kg is assumed. Phase 2 studies with LY3074828 are primarily using a dosing interval of 4 weeks (672 hours). Human $AUC_{0\text{-}672h,ss}$ is equivalent to the expected $AUC_{0\text{-}\infty}$ following a single dose in this study. Human $AUC_{0\text{-}672h,ss}$ at 250 mg IV is predicted based on the average IV clearance observed in Study I6T-MC-AMAA (0.526 L/day).

d NOAEL was determined in a 6-month repeat dose toxicity study using a Q1W dosing interval (Study 20043324).

e Monkey AUC value was based on average of male and female Day 176 means of $AUC_{0\text{-}168}$ and has been multiplied by 4 to align with the 4-week AUC interval projected for humans.

f NOAEL was determined in a 1-month repeat-dose toxicity study using a Q1W dosing interval (Study 20029153).

g Monkey AUC value was based on average of male and female Day 29 means of $AUC_{0\text{-}168}$ and has been multiplied by 4 to align with the 4-week AUC interval projected for humans.

# 6. Study Population

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

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

Screening may 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 females, as determined by medical history and physical examination

[1a] male subjects:

agree to not donate sperm for the duration of the study and for 3 months following dosing and to use at least 1 effective method of contraception for the duration of the study or for 3 months following dosing, whichever is longer, as follows:

a) Male subjects with non-pregnant partners of childbearing potential must use a male condom with spermicide in addition to another acceptable method of contraception from the following list: female partner with placement of intrauterine device; female partner with established use of oral, injected, or implanted hormonal contraception associated with inhibition of ovulation; male sterilization, with verbal confirmation of surgical success; female partner with bilateral tubal ligation; female partner with established use of progesterone only oral contraception, where inhibition of ovulation is not the primary mode of action; diaphragm, cap, or sponge in conjunction with spermicide

b) Male subjects with female partners who are pregnant or breastfeeding should use a condom with spermicide

c) For male subjects who are exclusively in same sex relationships, contraceptive requirements do not apply

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

e) Male subjects practicing true abstinence, which must be due to the subject's lifestyle choice; ie, the subject should not become abstinent just for the purpose of study participation. Withdrawal or calendar methods are not acceptable.

[1b] female subjects:

Women of childbearing potential must agree to either remain abstinent or use 2 effective methods of contraception for the entirety of the study. Abstinence or contraception must continue for the duration of the study or for 3 months following the dose of investigational product, whichever is longer.

a) Women of child-bearing potential must test negative for pregnancy prior to initiation of treatment as indicated by a negative pregnancy test at the screening visit followed by a negative pregnancy on Day -1.
b) Women of childbearing potential must use a male condom with spermicide in addition to another acceptable method of contraception from the following list: placement of intrauterine device; established use of oral, injected or implanted hormonal contraception associated with inhibition of ovulation; partner with male sterilization, with verbal confirmation of surgical success; bilateral tubal ligation.

Women not of childbearing potential may participate, and include those who are:

a) Infertile due to surgical sterilization (at least 6 weeks after hysterectomy, bilateral salpingectomy, bilateral oophorectomy), congenital anomaly such as mullerian agenesis; or
b) Postmenopausal – defined as a woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone >40 mIU/mL

[2] are between 18 and 65 years of age, inclusive, at the time of screening

[3] have a body mass index (BMI) of 18.0 to 32.0 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 and administration of investigational product for IV administration 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 or Covance employees

[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 3 months prior to screening, 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 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 as clinically significant by the investigator

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

[19] show evidence of human immunodeficiency virus (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 (HBcAb+)

[22] are women who are lactating

[23] have used or intend to use over-the-counter or prescription medication, including herbal medications such as St. John's Wort within 14 days prior to dosing (stable doses of oral contraceptive or hormone replacement therapy may be allowed as per judgment of the investigator)

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

[25] have an average weekly alcohol intake that exceeds 28 units per week (males) and 21 units per week (females), (1 unit alcohol equals 1/2 pint [285 mL] of beer, 1 glass [125 mL] of wine, or 25 mL of distilled spirits) and/or show positive findings on ethanol testing and/or who are unwilling to abide by the alcohol restrictions described in Section 6.3.2

[26] are subjects whose tobacco consumption is more than 10 cigarettes per day or the equivalent or subjects who are not willing to refrain from smoking for approximately 1 hour prior to each ECG and vital sign measurement 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 tuberculosis (TB), as documented by medical history and examination and TB testing: a negative (not indeterminate) QuantiFERON®-TB Gold test, or have had household contact with a person with active TB, unless appropriate and documented prophylaxis for TB has been given.

[29] have received live vaccine(s) (including attenuated live vaccines, and those administered intranasally) within 1 month of screening, or intend to during the study

[30] are immunocompromised

[31] have received treatment with biologic agents (such as monoclonal antibodies, including marketed drugs) within 3 months or 5 half-lives (whichever is longer) prior to dosing.

[32] have significant allergies to humanized monoclonal antibodies

[33] 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)

[34] 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

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

[36] 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 permitted).

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

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

Alcohol consumption is not allowed from 12 hours prior to all study visits and during CRU stays. At all other times, alcohol consumption should be limited to 2 units per day (1 unit alcohol equals 1/2 pint [285 mL] of beer, 1 glass [125 mL] of wine or 25 mL of distilled spirits).

Subjects who smoke should maintain a stable smoking habit throughout the study. Subjects will be asked to refrain from smoking for approximately 1 hour prior to each ECG and vital sign measurements as well as abide by the CRU smoking guidelines.

### *6.3.3. Poppy Seeds*

Foods and beverages containing poppy seeds will not be allowed from 7 days prior to screening until final discharge from the study.

### *6.3.4. Activity*

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

## 6.4. Screen Failures

Subjects who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

# 7. Treatment

## 7.1. Treatment Administered

The proposed LY3074828 test formulation will be prepared extemporaneously as sterile solutions for SC injection and IV infusion, as described in the pharmacy instructions provided by the sponsor to the site. The clinical material for extemporaneous preparation will be supplied as a frozen solution by Lilly.

The LY3074828 reference formulation previously used in Phase 1 and 2 studies will be supplied to the site by Lilly as a sterile lyophilized vial to be reconstituted prior to injection as detailed in the pharmacy instructions.

- 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.

Table AMAL.3 shows the treatment regimens.

Injection sites selected for SC administration should be the abdominal region approximately 5 cm from the umbilicus and the treatment administered with the needle applied at approximately 45 degrees with pinching of 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. Where 2 or more injections are to be administered, the subsequent injection(s) should be given immediately following the previous and administered to another abdominal quadrant. Further information around SC administration will be in pharmacy handling instructions.

The IV formulation of LY3074828 will be administered as a slow IV infusion over at least 30 minutes. The site must have resuscitation equipment, emergency drugs, and appropriately trained staff available during and for at least 6 hours after subjects complete their treatment administration. Further information around IV administration will be in pharmacy handling instructions.

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

**Table AMAL.3. Treatments Administered**

| | LY3074828 | | | |
|---|---|---|---|---|
| **Treatment** | Reference (N = 18) | Test SC 2 × 1-mL (N = 18) | Test SC 1 × 2-mL (N = 18) | Test IV (N = 18) |
| **Regimen** | 250 mg SC [a] | 250 mg SC | 250 mg SC | 250 mg IV |
| **Drug Product formulation** | reference | test | test | test |
| **LY3074828 concentration** | 72 mg/mL | 125 mg/mL | 125 mg/mL | 250 mg/10 mL (25 mg/mL) |
| **Volume per dose** | 2 × 1 mL + 1 × 1.5 mL (3.5 mL total) | 2 × 1 mL (2 mL total) | 1 × 2 mL (2 mL total) | 10 mL infusion |
| **Infusion or injection duration** | NA | NA | Slow versus fast[b] | ≥30 minutes |

Abbreviations: IV = intravenous; NA = not applicable; SC = subcutaneous.

[a] Theoretical total dose 252 mg for Reference.

[b] Odd number subjects will be injected slowly, approximately over 15 seconds and even number subjects will receive the injection over 5 to 10 seconds.

The investigator or designee is responsible for:

- explaining the correct use of the investigational product(s) to the site personnel,
- verifying that instructions are followed properly,
- maintaining accurate records of investigational product dispensing and collection,
- and returning all unused medication to Lilly or its designee at the end of the study.

**Note:** In some cases, sites may destroy the material if, during the 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 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 reference formulation will be supplied for clinical trial use as sterile, lyophilized powder in a glass vial and should be stored under refrigerated conditions (2ºC to 8ºC). Each vial is manufactured to deliver 75 mg of LY3074828 and will be reconstituted with sterile water to a concentration of 72 mg/mL. Contents from multiple vials will be pooled for each injection, as required.

LY3074828 test formulation will be supplied as a frozen solution at a concentration of 125 mg/mL, with approved excipients added. The solution will be thawed at the site, pooled, and undergo terminal sterile filtration into sterile vials before being prepared for clinical trial use, in accordance to the pharmacy instructions provided by the sponsor. The content of the extemporaneously prepared sterile vials will either be dispensed into syringes for SC administration or further diluted for IV administration to the trial subjects.

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 4 treatments using a computer-generated allocation schedule.

### *7.2.1. 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.

### *7.4.1. Special Treatment Considerations*

#### 7.4.1.1. Premedication for Infusions

Premedication for the subjects randomized to receive LY3074828 as an IV infusion is not planned. However, if an infusion reaction occurs, appropriate medication may be used as determined by the study investigator(s) and documented in the eCRF. If one Grade 2 infusion reaction is observed, paracetamol/acetaminophen, 500 to 1000 mg and/or an antihistamine (such as diphenhydramine) will be administered orally 30 to 60 minutes prior to the start of infusion for all subsequent subjects.

The decision to implement premedication for infusions in subsequent subjects will be made by the investigator and recorded in the study eCRF as a concomitant therapy for prophylaxis purpose (see Section 7.7).

#### 7.4.1.2. Management of Infusion Reactions

Due to the risk of an infusion reaction with any biological agent, all subjects should be monitored closely. Symptoms and signs that may occur as part of an infusion reaction include, but are not limited to, fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash, pruritus, myalgia, and dizziness. In the event that a significant infusion reaction occurs, the following guidance should be followed:

- the investigational product infusion should be slowed or stopped, depending on the symptoms/signs present

- if slowed, the infusion should be completed at the slower rate, as tolerated
- if stopped, one attempt to restart at half the original rate will be allowed

- supportive care should be employed in accordance with the symptoms/signs

#### 7.4.1.3. Safety Protocol in the Event of a Retrospective Positive Sterility Finding from extemporaneously prepared study treatment

If a positive sterility finding were to arise in the terminally sterile filtered product, the subjects who were dosed from the impacted batch should be immediately contacted and asked to return to the CRU for a full medical examination. This should include a physical examination, including blood pressure, pulse rate and body temperature. Blood samples should be collected for culture and assayed for inflammatory markers such as C-Reactive Protein and elevations in white blood cell counts.

If the signs and symptoms indicated a subject is suffering from possible infection(s), they will be clinically managed, treated and followed up until resolution. Any adverse events will be recorded as appropriate.

## 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 (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 medications such as St. John's Wort, are not permitted within 14 days prior to dosing and throughout the study. However, stable doses of oral contraceptive or hormone replacement therapy may be allowed as per judgment of the investigator. Paracetamol/acetaminophen (up to 2 g/day) may be allowed at the investigator's discretion. Any other 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

Not applicable for this study.

# 8. Discontinuation Criteria

## 8.1. Discontinuation from Study Treatment

The reason for and date of discontinuation will be collected for all subjects. All randomized subjects who discontinue after receiving study drug will have ED procedures performed as shown in the Schedule of Activities (Section 2).

### *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, the subject will be discontinued from the study and ED assessments will be performed as described in the Schedule of Activities (Section 2).

## 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 4 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.

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, 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.

If a subject's participation is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF.

### *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 patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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.

Although all AEs are recorded in the eCRF after signing informed consent, SAE reporting 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. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

### *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.

- 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.
- The investigational product should be retained under appropriate storage conditions, if available or when obtained, until instructed to return it to Lilly.
- Product complaints for Non-Lilly Products (including concomitant drugs) that do not have a Lilly Product Batch or Control number, are reported directly to the manufacturer per product label.
- The instructions outlined in the Product Complaint Form should be followed for other reporting requirements.

## 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).

### *9.4.2. Vital Signs*

For each subject, vital signs 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. Additional vital signs may be assessed as clinically indicated as well as at the scheduled times, if warranted by the investigator.

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 2 minutes. If the subject feels unable to stand, supine vital signs only will be recorded.

### *9.4.3. Electrocardiograms*

For each subject, ECGs should be collected according to the Schedule of Activities (Section 2) and following 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 first dose of the investigational product, should be reported to Lilly, or its designee, as an AE via eCRF.

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.

### *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, then the subject is excluded from the study.

Subjects who have had household contact with a person with active TB must be excluded unless appropriate and documented prophylaxis 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 research physician 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 incidence of and nature of any infections, infusion reactions, and injection site reactions.

### *9.4.6. Injection / Infusion-Site Assessments*

Local tolerability at the injection or infusion site will be evaluated for erythema, induration, categorical pain, pruritus, and edema as indicated in the Section 2 and reported in the CRF. If one or more symptom(s) of an injection/infusion site reaction is reported during the assessment, a single AE for injection or infusion site reaction will be recorded on the AE page of the CRF.

In addition, pain measurements will be quantified using the the 100-mm validated Visual Analog Scale (VAS) for the subjects receiving Test SC 2 x 1 mL and the Test SC 1 x 2 mL formulation. The VAS is a well-validated tool (Williamson and Hoggart 2005) to assess injection-site pain presented as a 10-cm (100-mm) line, anchored by verbal descriptors, usually “no pain” and “worst imaginable pain.” The patient 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). For the Test SC 2 x 1 mL formulation, the pain assessment will be done only for the first of the 1 mL injections.

Injection site leakage for the Test SC 1 x 2 mL and the first of the Test SC 2 x 1 mL injections 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). For the Test SC 2 x 1 mL formulation, the leakage assessment will be done only for the first of the 1 mL injections. 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.

### *9.4.7. Immunogenicity Assessments*

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

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 (i.e. 1:20) above the minimum required dilution (1:10) if no ADAs were detected at baseline 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, Day 15, Day 29, Day 85, and at follow-up. Subjects that are observed to have significant (i.e. 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.

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 product. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the investigational product.

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and ethics committee (EC) allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to the investigational product. 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 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 (ELISA).

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

Not applicable.

## 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 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 EC 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 it 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

A total of 72 subjects will be enrolled to ensure that approximately 64 subjects complete the study (16 completers per treatment). The estimated total variability (coefficient of variation) in AUC from time zero to infinity (AUC[0-∞]), AUC from time zero to time t, where t is the last sample with a measurable concentration (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 64 subjects will provide a precision of approximately 28% for the geometric means ratio in AUC(0-∞), AUC(0-$t_{last}$), and $C_{max}$ of reference to test 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 28%.

Subjects who are randomized but not administered treatment may be replaced to ensure that approximately 64 subjects 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, or other demographic characteristics will be recorded and summarized by treatment as well as 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 subjects receiving a 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 safety 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-$t_{last}$) of LY3074828. The secondary parameters for analysis will be $C_{max}$ and time to $C_{max}$ ($t_{max}$) of LY3074828. 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 at steady state after extra-vascular administration ($V_Z$/F) may be reported.

The absolute bioavailability of LY3074828 will be calculated using AUC(0-$\infty$) and AUC(0-$t_{last}$) values calculated after SC and IV administration of LY3074828.

### 10.3.2.2. Pharmacokinetic Statistical Inference

Pharmacokinetic parameter estimates will be evaluated to delineate effects of LY3074828 formulation when administered to healthy subjects by SC injection (Reference and Test SC 2 × 1-mL). Log-transformed $C_{max}$, AUC(0-$\infty$), and AUC(0-$t_{last}$) estimates will be evaluated in a linear fixed-effect model with a fixed effect for formulation. The differences between the test (SC 2 × 1-mL) compared to the reference formulation will be back-transformed to present the ratios of geometric least squares means and the corresponding 90% CI.

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.

Similar analyses to those described above will be conducted to delineate the effect of administering the same volume as a single injection (SC 1 × 2-mL) or as 2 injections (SC 2 × 1-mL).

In order to evaluate absolute bioavailability, a fixed-effect model will be used to analyze the log-transformed AUC(0-∞) and AUC(0-$t_{last}$) of LY3074828. The model will contain formulation (SC or IV) as a fixed effect. The absolute bioavailability will be estimated for the ratio of the least-squares geometric means of the formulations (SC/IV). The corresponding 90% CI of the ratios will also be estimated. Data from Test IV will be used for the IV formulation (reference). If the number of injections is not observed to have an effect based on the analyses described above, data from SC 2 × 1-mL and SC 1 × 2-mL will be combined and used for the SC formulation (and will be considered the primary analysis). If the number of injections is observed to have an effect (ie, SC 2 × 1-mL versus SC 1 × 2-mL), analyses to evaluate absolute bioavailability will be done separately (SC 2 × 1-mL versus IV and SC 1 × 2-mL versus IV). The primary analysis will be considered as that including SC 1 × 2-mL.

Where possible, a single linear model with contrasts to test the different objectives will be used.

Additional analyses may be conducted if they are deemed appropriate.

### *10.3.3. Pharmacodynamic Analyses*

Not applicable.

### *10.3.4. Pharmacokinetic/Pharmacodynamic Analyses*

Not applicable.

### *10.3.5. Evaluation of Immunogenicity*

The frequency of antibody formation 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. Interim Analyses*

The Lilly study team and investigator will be unblinded. 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.

Interim analysis is scheduled to occur when safety and PK data through approximately Day 57 (8 weeks postdose) become available from enrolled subjects from each treatment. The purpose of the interim analysis is to: trigger Chemistry, Manufacturing, and Control processes with

respect to LY3074828 formulation; trigger the formal bridging study; and to inform dose selection for Phase 3 first registration.

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# 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. |
| **AUC** | area under the concentration versus time curve |
| **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 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 |
| **CL/F** | apparent total body clearance of drug calculated after extra-vascular administration |
| **$C_{max}$** | 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 (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. |
| **CRU** | clinical research unit |
| **EC** | Ethics Committee |
| **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. |
| **IV** | intravenous(ly) |
| **NA** | not applicable |
| **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. |
| **PK** | pharmacokinetic(s) |
| **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 |

| | |
|---|---|
| **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 |
| **Th17** | T helper 17 |
| **$t_{max}$** | time to maximum observed drug concentration |
| **VAS** | Visual analog scale |
| **$V_Z/F$** | apparent volume of distribution at steady state after extra-vascular administration |

# 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 |
| Monocytes | Alkaline phosphatase (ALP) |
| Eosinophils | Aspartate aminotransferase (AST) |
| Basophils | Alanine aminotransferase (ALT) |
| Platelets | Creatinine |
| Urinalysis[a] | |
| Specific gravity | Ethanol testing[c] |
| pH | Urine drug screen[c] |
| Protein | QuantiFERON-TB Gold test[a,d] |
| Glucose | |
| Ketones | Serology[d] |
| Bilirubin | Hepatitis B surface antigen |
| Urobilinogen | Hepatitis B core antibody |
| Blood | Hepatitis C antibody |
| Nitrite | HIV antibodies |
| Microscopic examination of sediment[b] | |
| | Pregnancy test (serum/urine)[e,f] |
| | Hormone Panel |
| | FSH[d,g] |

Abbreviations: FSH = follicle-stimulating hormone; 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 Urine drug screen and ethanol level will be performed locally at screening and during admission to the clinical research unit. May be repeated at the discretion of the investigator.

d Performed at screening only.

e Women of childbearing potential only. Serum pregnancy test at screening, urine at other times. A positive urine pregnancy test will be confirmed with a serum pregnancy test.

f Refer to Section 2 for specific sampling timing.

g 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 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 ethics committee was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of EC 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 EC(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, 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 ECs 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.

## *Study and Site Closure*

### *Discontinuation of Study Sites*

Study site participation may be discontinued if Lilly or its designee, the investigator, or the EC 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. 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-AMAL 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 | 6 | 45 |
| Pharmacokinetics[b] | 2 | 19 | 38 |
| Immunogenicity[a] | 10 | 5 | 50 |
| Pharmacogenetics | 10 | 1 | 10 |
| Total | | | 157 |
| 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 samples.

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