

Protocol I6T-MC-AMBE

A Safety, Tolerability, and Pharmacokinetic Study of Injections of LY3074828 Solution Using Investigational 1-mL Pre-filled Syringes and Investigational 1-mL Autoinjector in Healthy Subjects

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LY3074828

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1. Protocol Synopsis

Title of Study:

A Safety, Tolerability, and Pharmacokinetic Study of Injections of LY3074828 Solution Using Investigational 1-mL Pre-filled Syringes and Investigational 1-mL Autoinjector in Healthy Subjects

Rationale:

Study I6T-MC-AMBE (AMBE) will assess the pharmacokinetics (PK), safety and tolerability of, and pain associated with, a 125-mg subcutaneous (SC) dose of LY3074828 solution formulation administered using an investigational manual 1-mL pre-filled syringe (PFS) or an investigational 1-mL autoinjector (AI). Both methods of administration will be evaluated at 3 different injection sites (arm, thigh, and abdomen) in order to expand the options for administration in patient use. The study will provide data to bridge PFS administration of LY3074828, with the investigational AI device planned for use in subsequent studies and patient use.

Objectives/Endpoints:

| Objectives | Endpoints |
|---|---|
| Primary <ul style="list-style-type: none">To evaluate the PK after SC administration of 125-mg doses of LY3074828 solution formulation using a 1-mL PFS and a 1-mL AI injector in healthy subjects.To assess pain associated with LY3074828 PFS and AI SC administrations in healthy subjects at 3 different injection sites (arm, thigh, and abdomen). | <ul style="list-style-type: none">The primary PK endpoints will be the C_{max}, $AUC(0-t_{last})$, and $AUC(0-\infty)$ of LY3074828.VAS pain score. |
| Secondary <ul style="list-style-type: none">To assess the safety and tolerability of LY3074828 in healthy subjects. | <ul style="list-style-type: none">Incidence of TEAEs. |

Abbreviations: AI = autoinjector; $AUC(0-\infty)$ = 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; C_{max} = maximum observed drug concentration; PFS = pre-filled syringe; PK = pharmacokinetic; SC = subcutaneous; TEAE = treatment-emergent adverse event; VAS = visual analog scale.

Summary of Study Design:

Study I6T-MC-AMBE (AMBE) is a single-center, randomized, parallel-arm, open-label, Phase 1 single-dose study of LY3074828 solution formulation in healthy subjects. Pharmacokinetics, safety and tolerability of, and pain associated with, 125-mg SC doses administered using a PFS or an investigational AI at 3 different injection sites will be evaluated.

Subjects will be randomized to a 1-mL PFS administration to the arm, thigh, or abdomen or a 1-mL AI administration to the arm, thigh, or abdomen. Subjects will report to the clinical research unit (CRU) on Day -1 and will remain at the CRU until the scheduled procedures have been completed on Day 2. Study drug will be administered by investigative site staff by SC injection per the randomization scheme in the morning of Day 1 after an overnight fast. Subjects will be followed for 12 weeks following dose administration.

Safety and tolerability will be assessed by clinical laboratory tests, vital sign measurements, 12-lead electrocardiograms, recording of adverse events and product complaints, physical examinations/medical assessments, immunogenicity, and injection-site assessments. Pain assessments will be made using an injection-site pain visual analog scale (VAS).

Dosing Regimen Arms and Duration for an Individual Subject:

Subjects will receive a 125-mg SC dose of LY3074828 and will be randomized to 1 of 6 dosing regimen arms:

- Test 1: 1-mL AI injector containing 125 mg LY3074828 solution to be administered in the arm
- Test 2: 1-mL AI injector containing 125 mg LY3074828 solution to be administered in the thigh
- Test 3: 1-mL AI injector containing 125 mg LY3074828 solution to be administered in the abdomen
- Reference 1: 1-mL PFS containing 125 mg LY3074828 solution to be administered in the arm
- Reference 2: 1-mL PFS containing 125 mg LY3074828 solution to be administered in the thigh
- Reference 3: 1-mL PFS containing 125 mg LY3074828 solution to be administered in the abdomen

Total duration of the study for each subject will be approximately 16 weeks (screening period ≤ 28 days, residential period of 2 days, and outpatient follow-up period of 12 weeks).

Number of Subjects:

A total of approximately 66 subjects who fulfill the eligibility criteria will be randomized to 1 of 6 dosing regimen arms, with 11 subjects randomized to each arm to ensure completion of 10 subjects in each (60 subjects completed in total). A subject's study participation is considered as complete if he/she receives the study drug as per the protocol requirements and completes all activities up to and including at least Day 57. A maximum of 2 subjects per arm may be replaced if multiple subjects do not complete the study.

Statistical Analysis:

The area under the concentration versus time curve (AUC) from time zero to infinity ($AUC[0-\infty]$), 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}) will be log-transformed and analyzed using a linear fixed-effects model. The model will include device and injection location as fixed effects. The dosing regimen differences between AI and PFS

administrations will be back-transformed to present the ratios of geometric least squares (LS) means and the corresponding 90% confidence interval (CI).

The time to C_{\max} (t_{\max}) of LY3074828 between AI and PFS administrations will be analyzed using a Wilcoxon rank sum test. Estimates of the median difference, 90% CIs, and p-values from the Wilcoxon rank sum test will be calculated.

Additional PK analyses may be conducted if deemed appropriate.

A linear fixed-effects model will be used to analyze the post-injection pain VAS scores. The model will include device and injection location as fixed effects. The LS means and differences in LS means will be presented along with the corresponding 90% CI.

Safety parameters will be listed and summarized using standard descriptive statistics, as appropriate.

2. Schedule of Activities

Study Schedule Protocol I6T-MC-AMBE

| | Screening | Days | | | | | | | | | | | | | Comments |
|---|-----------|------|------|----|----------|----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|--------------|---|
| Procedure | ≤28 days | -1 | 1 | 2 | 4 ±1d | 8 ±1d | 11 ±1d | 15 ±2d | 22 ±2d | 29 ±2d | 43 ±2d | 57 ±3d | 71 ±3d | 85/ED ±3d | |
| Informed consent | X | | | | | | | | | | | | | | |
| Review/confirm inclusion/exclusion criteria | X | X | | | | | | | | | | | | | Any time prior to dosing. |
| Subject admission to CRU | | X | | | | | | | | | | | | | |
| Subject discharge from CRU | | | | X | | | | | | | | | | | |
| Outpatient visit | X | | | | X | X | X | X | X | X | X | X | X | X | |
| Randomization | | | X | | | | | | | | | | | | Subjects randomized to 1 of 6 dosing regimen arms. |
| LY3074828 injection | | | X | | | | | | | | | | | | Doses administered by investigative site staff. |
| Stopwatch recording | | | X | | | | | | | | | | | | Stopwatch is the source for injection duration capture for PFS and AI. |
| Medical history | X | | | | | | | | | | | | | | |
| Weight, height, and BMI | X | | | | | | | | | | | | | | |
| Vital signs: blood pressure, pulse rate, temperature (hour) | X | X | 0, 6 | 24 | X | X | X | X | X | X | X | | | X | Times with respect to start of dosing. Single ECGs to be collected. Zero-hour collection within 30 minutes before dosing. Time allowance for 6- and 24-hour time points: ±30 and ±90 minutes, respectively. For vital sign assessments, temperature need only be included at predose and when clinically indicated. |
| 12-lead ECG (hour) | X | | 0 | 24 | | | | | | | | | | X | |
| Physical examination/medical assessment | X | X | | X | | | | | | | | X | | X | Full physical examination/medical assessment at screening. Symptom-directed physical examination/medical assessment at all other time points, and as deemed necessary by the investigator. |

| | Screening | Days | | | | | | | | | | | | | Comments |
|--|-----------|------|---------|---|----------|----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|--------------|--|
| Procedure | ≤28 days | -1 | 1 | 2 | 4 ±1d | 8 ±1d | 11 ±1d | 15 ±2d | 22 ±2d | 29 ±2d | 43 ±2d | 57 ±3d | 71 ±3d | 85/ED ±3d | |
| AE review | X | X | X | X | X | X | X | X | X | X | X | X | X | X | AE only after signing ICF. Product complaints and device-related AEs collected as appropriate. |
| QuantiFERON®-TB Gold test | X | | | | | | | | | | | | | | |
| Serology | X | | | | | | | | | | | | | | See Appendix 2 for test details. |
| Ethanol test and urine drug screen | X | X | | | | | | | | | | | | | May be repeated at the discretion of the investigator. Ethanol test may be measured in blood, urine, or expired air. See Appendix 2 for test details. |
| FSH/serum pregnancy test | X | X | | | | | | | | X | | X | | X | Serum pregnancy tests for all female subjects at screening. For all women who are considered to be peri-menopausal, FSH should be drawn at screening to confirm postmenopausal status as defined in inclusion criterion [1b]. Women with confirmed postmenopausal status at screening are exempted from further pregnancy tests during the study. See Appendix 2 for test details. |
| Clinical chemistry, hematology, and urinalysis | X | X | | | | X | | | | X | | X | | X | See Appendix 2 for test details. |
| Creatine phosphokinase | | X | | | | X | | | | X | | | | | |
| Injection-site assessment for erythema, induration, pruritus, and edema (hour) | | | 0, 0.25 | X | | X | | X | | | | | | | Times with respect to start of dosing. Zero-hour assessments within 1 minute following injection. Time allowance for 0.25-hour assessment is ±5 minutes. Additional assessments performed if deemed necessary by the investigator. |
| Injection-site bleeding assessment (hour) | | | 0 | | | | | | | | | | | | Time with respect to start of dosing. Zero-hour assessment within 1 minute following injection. |

| | Screening | Days | | | | | | | | | | | | | Comments |
|---|-----------|------|-----------------------|----|----------|----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|--------------|---|
| Procedure | ≤28 days | -1 | 1 | 2 | 4 ±1d | 8 ±1d | 11 ±1d | 15 ±2d | 22 ±2d | 29 ±2d | 43 ±2d | 57 ±3d | 71 ±3d | 85/ED ±3d | |
| Pain assessment (VAS) (minutes) | | | 1, 5, 15, 30, 60, 120 | | | | | | | | | | | | Time with respect to start of dosing. Time points are minutes post-injection as follows: within 1 minute of the end of injection, 5 (±1.5), 15 (±2), 30 (±2), 60 (±5), 120 (±5) minutes |
| LY3074828 pharmacokinetic sampling (hour) | | | 0, 2, 6 | 24 | X | X | X | X | X | X | X | X | X | X | Times with respect to start of dosing. Zero-hour collection immediately (within 15 minutes) before dosing. Time allowance for 2-, 6-, and 24-hour time points: ±15, ±30, and ±90 minutes, respectively. For the 2-hour postdose timepoint, VAS pain assessment should be conducted prior to PK sample collection. |
| Immunogenicity sample | | | Predose | | | | | X | | X | | X | | X | LY3074828 antibody sample. In the event of an AE that could be immunologically mediated, additional samples may be taken (See Section 9.6.1). Predose sample may be collected within 2 hours prior to planned dosing. |
| Pharmacogenetics sample | | | X | | | | | | | | | | | | |

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

Site should schedule activities as appropriate. For the 2-hour postdose timepoint, VAS pain assessment should be conducted prior to pharmacokinetic sample collection. In other cases where several study procedures are scheduled at the same time, follow this order of priority for procedures: pharmacokinetic samples, clinical laboratory tests, immunogenicity sample, stored sample, ECG, vital signs, pain assessment, injection-site assessment, such that pharmacokinetic sample collection occurs as close to the nominal collection time as possible.

3. Introduction

3.1. Study Rationale

Study I6T-MC-AMBE (AMBE) will assess the pharmacokinetics (PK), safety and tolerability of, and pain associated with, a 125-mg subcutaneous (SC) dose of LY3074828 solution formulation administered using an investigational manual 1-mL pre-filled syringe (PFS) or an investigational 1-mL autoinjector (AI). Both devices will be evaluated at 3 different injection sites (arm, thigh, and abdomen) in order to expand the options for administration in patient use. The study will provide data to bridge PFS administration of LY3074828, with the investigational AI device planned for use in subsequent studies and patient use.

3.2. Background

LY3074828 is a humanized immunoglobulin G4-variant monoclonal antibody that is directed against the p19 subunit of interleukin (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. Neutralization of IL-23 with an anti-mouse IL-23 surrogate antibody (directed against the p19 subunit) significantly reduced the development of arthritis and inhibited ileal inflammation in a mouse model of spondyloarthritis with bowel inflammation (Ruutu et al. 2012). Additionally, neutralization of IL-23 significantly reduced the disease score in the relapsing-remitting experimental autoimmune encephalomyelitis (multiple sclerosis-like) model in mice. Anti-IL-23 antibody also demonstrated some efficacy in preclinical arthritis models, depending on the timing of intervention (Cornelissen et al. 2013).

Psoriasis is one of the most common immune-mediated chronic inflammatory skin diseases, affecting about 2% to 3% of the world's population (Nestle et al. 2009; Perera et al. 2012). A typical organ-specific T-cell-driven inflammatory disease, psoriasis, had been considered a T helper (Th) 1-type skin disease for decades until a new Th population, Th17, was identified (Lew et al. 2004; Steinman 2007; Weaver et al. 2007). However, substantial clinical and basic research observations now suggest that the IL-23/Th17 axis is essential in the pathogenesis of psoriasis (Di Cesare et al. 2009). Treatment of psoriasis with biologic therapy, particularly with those agents targeting the IL-23/Th17 axis, has demonstrated clinical activity in patients with psoriasis (Crow 2012).

As of the Investigator's Brochure (IB) cutoff date (02 February 2018 for Phase 1 studies), there have been approximately 819 participants in studies of LY3074828. These include 245 patients with psoriasis, 248 patients with ulcerative colitis, 85 patients with Crohn's disease, and 241 healthy subjects who were exposed to either placebo or LY3074828 at single doses ranging from 5 to 1200 mg and multiple doses up to a maximum of 1000 mg intravenous (IV) and 300 mg SC.

Data from the clinical pharmacology development program are available for 2 completed Phase 1 studies (Studies I6T-MC-AMAA [AMAA] and I6T-MC-AMAE [AMAE]) and

4 ongoing Phase 1 studies (Studies I6T-JE-AMAD [AMAD], I6T-MC-AMAL [AMAL], I9O-MC-AABA [AABA], and I6T-MC-AMAA [AMAA]).

No deaths, serious adverse events (SAEs), or discontinuations due to an adverse event (AE) have been reported in any of the Phase 1 studies.

In the completed Study AMAA, a total of 82 treatment-emergent AEs (TEAEs) were reported by 37 subjects. The most commonly reported TEAEs in this study were nasopharyngitis and headache. There were no drug-related TEAEs of National Cancer Institute Common Terminology Criteria for Adverse Events Grade 2 or higher reported in Study AMAA.

In the completed Study AMAE, the incidence of TEAEs was similar between the 125 mg LY3074828 lyophilized formulation and the 125 mg LY3074828 PFS solution formulation, with a notably higher number of TEAEs reported by healthy subjects who received 500 mg LY3074828 solution formulation. The most common TEAEs related to study treatment were events occurring at the site of injection, including injection-site reaction (ISR) and injection-site hemorrhage. Across all formulations, the majority of TEAEs reported during the study were mild, with only 1 TEAE that was moderate in severity but not related to study drug.

There were no obvious trends in the pattern of AEs across studies apart from ISRs. Injection-site pain, of short duration (usually hours), has been reported in both the completed and ongoing clinical pharmacology studies. Preliminary data from Studies AMAE and AMAL showed that most ISRs were mild or moderate in severity, with severe injection-site pain reported in 2% of ISRs in the 125-mg SC solution test formulation group.

Immunogenicity evaluations were performed in Study AMAA. Blood samples to evaluate anti-drug antibody (ADA) were collected at baseline and approximately 22, 43, and 85 days postdose. Anti-drug antibody data were available for 45 subjects: 38 who received LY3074828 and 7 who received placebo. All subjects who received placebo were ADA negative at baseline and post-baseline. Only 1 subject who received LY3074828 was positive at baseline. Thirty-one subjects who received LY3074828 (81.6%) were negative at all post-baseline time points evaluated. Seven subjects who received LY3074828 had a post-baseline positive titer; however, only 3 of those subjects (7.9% of LY3074828-treated individuals) developed treatment-emergent ADA (TE-ADA). Treatment-emergent positive ADA was defined as ADA that developed following study drug administration with an increase to $\geq 1:20$ titer (2 dilutions/4-fold increase) after a negative baseline result OR preexisting ADA (ADA positive at baseline) that was increased at least 2 dilutions/4-fold over baseline following study drug administration. None of these cases of TE-ADA were associated with treatment-emergent adverse events (TEAEs) or changes in the clearance of LY3074828 in this study.

Study AMAE evaluated the relative bioavailability of LY3074828 solution formulation in PFSs and a lyophilized formulation. A total of 8 subjects (14.8%) were ADA positive at predose (pre-existing reactivity); none of the pre-existing reactivity confirmed as positive for neutralizing antibodies. The incidence of TEADAs was similar across formulations, with 7 subjects (38.9%) administered 250 mg LY3074828 lyophilized formulation, 6 subjects (33.3%) administered 250 mg LY3074828 PFS solution formulation, and 7 subjects (38.9%) administered 500 mg

LY3074828 PFS formulation testing positive for TEADAs. Most TEADAs were treatment-induced (33.3% of subjects), with only 2 subjects having treatment-boosted TEADAs. Only 1 subject had an ADA titer >1:1000 and there was no obvious trend towards a particular formulation having higher titers.

One subject had a TEADA titer greater than 1:1000 and met the protocol-defined requirement to have follow-up samples tested until titers were trending back to baseline. Multiple attempts were made to contact this subject for follow-up visits, but there was no response and the subject was considered lost to follow-up. The subject's last recorded titer was 1:2560 at the final study visit on Day 85.

3.3. Benefit/Risk Assessment

Based on LY3074828 nonclinical and preliminary clinical data, there are no anticipated risks requiring monitoring beyond those for a typical humanized monoclonal antibody in human studies. As with other immunomodulatory therapies, LY3074828 may increase the risk of developing an infection or may exacerbate an existing serious infection. These may include opportunistic infections and reactivation of latent infections, such as tuberculosis (TB) and hepatitis B. Subjects will therefore be screened for hepatitis B/C, human immunodeficiency virus (HIV), and TB. Immunomodulatory therapies may increase the risk of malignancies; however, due to only single doses of LY3074828 being administered in this study, it is not considered necessary to monitor for such effects.

Based on available data from Studies AMAA and AMAD, TE-ADAs have been observed in 2 of the 11 healthy subjects that received SC doses of LY3074828; however, titers were $\leq 1:160$. In the 33 patients with psoriasis who received single IV doses of LY3074828, TE-ADAs were detected in 3 subjects (Study AMAA).

No clinically significant safety or tolerability concerns have been identified in patients or healthy subjects to date for LY3074828 up to the highest doses given (single 2400-mg IV doses and 2400-mg SC doses).

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

As this study will use PFS and AIs, device-based risks will be evaluated. Possible device-based risks include local effects such as pain at the injection sites from either the needle or the solution entry into the SC tissue, swelling, erythema, bleeding, and bruising. These risks are mitigated by training of investigative site staff on proper injection techniques. Systemic effects may include sweating, feeling faint, or fever, as a sign of infection.

More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of LY3074828 are found in the compound IB, and risks as well as reasonably anticipated adverse device effects of the AI are found in the device IB.

4. Objectives and Endpoints

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

Table AMBE.1. Objectives and Endpoints

| Objectives | Endpoints |
|--|--|
| <p><u>Primary</u></p> <ul style="list-style-type: none"> To evaluate the PK after SC administration of 125-mg doses of LY3074828 solution formulation using a 1-mL PFS and a 1-mL AI injector in healthy subjects. To assess pain associated with LY3074828 PFS and AI SC administrations in healthy subjects at 3 different injection sites (arm, thigh, and abdomen). | <ul style="list-style-type: none"> The primary PK endpoints will be the C_{\max}, $AUC(0-t_{\text{last}})$, and $AUC(0-\infty)$ of LY3074828. VAS pain score. |
| <p><u>Secondary</u></p> <ul style="list-style-type: none"> To assess the safety and tolerability of LY3074828 in healthy subjects. | <ul style="list-style-type: none"> Incidence of TEAEs. |

Abbreviations: AI = autoinjector; $AUC(0-\infty)$ = area under the concentration versus time curve from time zero to infinity; $AUC(0-t_{\text{last}})$ = area under the concentration versus time curve from time zero to time t, where t is the last sample with a measurable concentration; C_{\max} = maximum observed drug concentration; PFS = pre-filled syringe; PK = pharmacokinetic; SC = subcutaneous; TEAE = treatment-emergent adverse event; VAS = visual analog scale.

5. Study Design

5.1. Overall Design

Study I6T-MC-AMBE (AMBE) is a single-center, randomized, parallel-arm, open-label, Phase 1 single-dose study of LY3074828 solution formulation in healthy subjects. Pharmacokinetics, safety and tolerability of, and pain associated with, 125-mg SC doses administered using a PFS or AI at 3 different injection sites will be evaluated.

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

Residential Period (2 days): A total of approximately 66 subjects who fulfill the eligibility criteria will be randomized to 1 of 6 dosing regimen arms, with 11 subjects randomized to each arm to ensure completion of 10 subjects in each:

- Test 1: 1-mL AI injector containing 125 mg LY3074828 solution to be administered in the arm
- Test 2: 1-mL AI injector containing 125 mg LY3074828 solution to be administered in the thigh
- Test 3: 1-mL AI injector containing 125 mg LY3074828 solution to be administered in the abdomen
- Reference 1: 1-mL PFS containing 125 mg LY3074828 solution to be administered in the arm
- Reference 2: 1-mL PFS containing 125 mg LY3074828 solution to be administered in the thigh
- Reference 3: 1-mL PFS containing 125 mg LY3074828 solution to be administered in the abdomen

Subjects will report to the clinical research unit (CRU) on Day -1 and will remain at the CRU until the scheduled procedures have been completed on Day 2. Study drug will be administered by investigative site staff by SC injection per the randomization scheme in the morning of Day 1 after an overnight fast.

Safety and tolerability will be assessed by clinical laboratory tests, vital sign measurements, 12-lead electrocardiograms (ECGs), recording of AEs and product complaints (PCs), physical examinations/medical assessments, immunogenicity, and injection-site assessments. Pain assessments will be made using an injection-site pain visual analog scale (VAS).

Outpatient Follow-up Period (12 weeks): The follow-up period will include outpatient visits for a total of 12 weeks (Days 4, 8, 11, 15, 22, 29, 43, 57, 71, and 85) following dose administration on Day 1 to assess the PK, safety and tolerability of, and pain associated with LY3074828 PFS and AI administrations. Assessment of pain at the Follow-up visits does not include VAS score.

5.2. Number of Participants

A total of approximately 66 subjects who fulfill the eligibility criteria will be randomized to 1 of 6 dosing regimen arms, with 11 subjects randomized to each arm to ensure completion of 10 subjects in each. A subject's study participation is considered as complete if he/she receives the study drug as per the protocol requirements and completes all activities up to and including at least Day 57. A maximum of 2 subjects per arm may be replaced if multiple subjects do not complete the study.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

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

Single doses of LY3074828 and the PK sampling time points have been selected to generate PK profiles sufficient to fulfill the study objectives. This study is not blinded due to the physical difference in devices being evaluated. Subjects and site staff will be aware of the administration route and treatment.

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

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

Methods of administration will be evaluated at 3 different injection sites (arm, thigh, and abdomen) in order to expand the options for administration in patient use.

5.5. Justification for Dose

The doses for this study are based on the volume of solution that can be delivered by the PFS or AI (1 mL) and the solubility of LY3074828 (125 mg/mL), resulting in a dose of 125 mg LY3074828.

Intravenous doses up to 2400 mg and SC doses up to 2400 mg were found to be well tolerated in healthy subjects in the single-dose Studies AMAD and AABA. Subcutaneous bioavailability was approximately 40% in Study AMAA. In addition, 125 mg is one of the doses that are being evaluated in the Phase 3 development program.

6. Study Population

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

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

Screening will 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 male or female subjects, as determined by medical history and physical examination
- [1a] male subjects:
 - no male contraception required except in compliance with specific local government study requirement
- [1b] female subjects:
 - All female subjects must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit. Women of childbearing potential must also have a negative serum pregnancy test within 24 hours prior to initial exposure. Women not of childbearing potential due to postmenopausal status must have follicle-stimulating hormone >40 mIU/mL at the screening visit
 - Women of childbearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception
 - Otherwise, women of childbearing potential participating must agree to use one highly effective method (less than 1% failure rate) of contraception, or a combination of 2 effective methods of contraception (for 12 weeks following dosing with the study drug)

- Either one highly effective method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine device) or a combination of 2 effective methods of contraception (such as male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges) will be used. The subject may choose to use a double-barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not reliable or acceptable methods. Thus, each barrier method must include use of a spermicide. It should be noted that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these methods are combined
 - Women not of childbearing potential may participate and include those who are:
 - infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation) or congenital anomaly such as Müllerian agenesis; or
 - postmenopausal – defined as either:
 - A woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had either:
 - cessation of menses for at least 1 year; or
 - at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone >40 mIU/mL; or
 - A woman 55 years of age or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea; or
 - A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone-replacement therapy
- [2] are between 18 and 65 years of age, inclusive, at time of screening
- [3] have a body mass index (BMI) of 18.0 to 32.0 kg/m², inclusive, at time of screening
- [4] have clinical laboratory test results within normal reference ranges for the investigative site, or results with acceptable deviations that are judged to be not clinically significant by the investigator
- [5] have venous access sufficient to allow for blood sampling as per the protocol
- [6] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures
- [7] are able and willing to give signed informed consent

6.2. Exclusion Criteria

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

- [8] are investigative site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling
- [9] are Lilly employees or employees of Covance
- [10] are currently enrolled in a clinical study involving an investigational product (IP) or any other type of medical research judged not to be scientifically or medically compatible with this study
- [11] have participated in a clinical trial involving an IP within 30 days or 5 half-lives (whichever is longer) prior to screening. If the clinical trial involved treatment with biologic agents (such as monoclonal antibodies, including marketed drugs), at least 3 months or 5 half-lives (whichever is longer) should have elapsed prior to Day 1
- [12] have previously completed or withdrawn from this study or any other study investigating LY3074828, and have previously received the IP
- [13] have ever received anti-IL-12p40 antibodies (for example, ustekinumab [Stelara®]) or anti-IL-23p19 antibodies (for example, risankizumab [BI-655066], brazikumab [MEDI2070], guselkumab [CNTO 1959], or tildrakizumab [MK-3222]) for any indication, including investigational use
- [14] have known allergies to LY3074828, related compounds, or any components of the formulation, or history of significant atopy
- [15] have an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study
- [16] have an abnormal blood pressure as determined by the investigator
- [17] have a history or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the IP; or of interfering with the interpretation of data
- [18] have known or ongoing psychiatric disorders deemed clinically significant by the investigator
- [19] regularly use known drugs of abuse and/or show positive findings on drug screening
- [20] show evidence of HIV infection and/or positive HIV antibodies
- [21] show evidence of hepatitis C and/or positive hepatitis C antibody

- [22] show evidence of hepatitis B and/or positive hepatitis B surface antigen
- [23] are women who are lactating
- [24] have used or intend to use over-the-counter or prescription medications, including herbal medications, within 14 days prior to dosing and for the duration of the study. Stable doses of oral contraceptive or hormone-replacement therapy are permitted, at the discretion of the investigator
- [25] have donated blood of more than 500 mL within 1 month prior to screening
- [26] have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females), have a positive test for ethanol, or are unwilling to abide by the alcohol restrictions described in Section 6.3.2 (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits)
- [27] have a tobacco consumption of more than 10 cigarettes per day (or equivalent), or who are unwilling to abide by the CRU smoking guidelines described in Section 6.3.2
- [28] have had symptomatic herpes zoster within 3 months of screening
- [29] show evidence of active or latent TB, as documented by medical history, examination, and TB testing (negative [not indeterminate] QuantiFERON® -TB Gold test); or have had household contact with a person with active TB, unless appropriate and documented prophylaxis treatment has been given. Subjects with any history of active TB are excluded from the study, regardless of previous or current TB treatments
- [30] have received live vaccine(s), including attenuated live vaccines and those administered intranasally, within 8 weeks of screening, or intend to during the study
- [31] have been treated with oral steroids within 1 month of screening, or intend to during the study (mild topical steroid creams/ointments are permitted)
- [32] are immunocompromised
- [33] have significant allergies to humanized monoclonal antibodies
- [34] have clinically significant multiple or severe drug allergies, or intolerance to topical corticosteroids, or severe posttreatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis)
- [35] have had lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years
- [36] have had breast cancer within the past 10 years

- [37] have excessive tattoos over the arm, thigh, or abdomen that would interfere with injection-site assessments
- [38] in the opinion of the investigator, 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 will fast overnight for at least 8 hours before dosing (water is permitted). Standard meals will be provided at all other times while subjects are resident at the CRU, as per the CRU's policy. Fasting is not required prior to routine safety laboratory tests.

6.3.2. Caffeine, Alcohol, and Tobacco

Subjects will not consume caffeinated beverages (decaffeinated beverages are permitted) while at the CRU, and for 12 hours prior to admission to the CRU. At other times during the outpatient period, subjects will be allowed to maintain their regular caffeine consumption.

Alcohol consumption is not permitted while at the CRU, and for 12 hours prior to each study visit. At other times, alcohol consumption should be limited to 2 units per day (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits).

Subjects who smoke will be advised to not increase their consumption of tobacco products during the study. Subjects will be expected to refrain from smoking while residing in the CRU, and to abide by the CRU smoking guidelines.

6.3.3. Activity

Subjects will be advised to maintain their regular levels of physical activity/exercise during the study, but to refrain from strenuous activity from 24 hours prior to each visit and 48 hours prior to any visit where creatine phosphokinase testing will occur (Day -1, Day 8, and Day 29). While certain study procedures are in progress at the site, subjects may be required to remain recumbent or sitting.

6.3.4. Blood and Plasma Donation

Subjects will not donate blood or plasma for 12 weeks following dosing with the study drug.

6.4. Screen Failures

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

7. Dosing Regimens

7.1. Dosing Regimens Administered

This study will evaluate the PK, safety and tolerability of, and pain associated with 125-mg SC doses administered using 1-mL PFS or an investigational 1-mL AI at 3 different injection sites.

Using the investigational 1-mL AI, the targeted injection duration will be approximately 5 to 10 seconds. Manual injection using the PFS should target an injection duration of about 5 to 10 seconds to approximate the injection time range for the AI. Approximate injection durations for AIs and PFSs will be obtained using a calibrated stopwatch and recorded in the electronic case report form (eCRF).

Drug and device accountability records will be maintained by the site pharmacy.

Table AMBE.2 shows the dosing regimens for the study.

Table AMBE.2. Dosing Regimens Administered

| Dosing Regimen | PFS | | | AI | | |
|------------------------------|-------------------------------|-------------|-------------|-------------------------------|--------|---------|
| Reference/test | Reference 1 | Reference 2 | Reference 3 | Test 1 | Test 2 | Test 3 |
| Injection site | Arm | Thigh | Abdomen | Arm | Thigh | Abdomen |
| Product | LY3074828 | | | LY3074828 | | |
| Dose | 125 mg | | | 125 mg | | |
| Concentration | 125 mg/mL | | | 125 mg/mL | | |
| Injection volumes | 1 mL | | | 1 mL | | |
| Number of injections | 1 | | | 1 | | |
| Injection duration | 5 to 10 seconds per injection | | | 5 to 10 seconds per injection | | |
| Formulation and presentation | Solution in a PFS | | | Solution in an AI | | |

Abbreviations: AI = autoinjector; PFS = pre-filled syringe.

The PFSs and investigational AIs containing LY3074828 will be supplied fully assembled to the clinical site by Lilly.

Injections, whether administered by PFS or AI, will be given into the arm, thigh, or lower quadrant of the abdomen. Investigational product will be administered to subjects on-site by designated trained clinical site personnel.

Prior to the PFS or AI injection, the investigator or his/her designee will prepare the subject's skin per Instructions for Use (IFU). Injections into the arm, thigh, or abdomen will be administered by investigative site staff according to the instructions provided by the sponsor. All study injection sites will be marked using a template for size and with a surgical marker in order to identify study injection sites for later assessments. Further information regarding SC administration will be included in the device IFU for the PFS and in the device IB (which contains IFU) for the AI.

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

7.1.1. Packaging and Labeling

LY3074828 will be supplied by the sponsor or its designee in accordance with current good manufacturing process, and labeled according to the country's regulatory requirements. All IPs will be stored, inventoried, reconciled, and returned or destroyed according to applicable regulations. The following products will be supplied by Lilly:

- pre-assembled LY3074828 PFSs, 1 mL
- pre-assembled investigational LY3074828 AIs, 1 mL

Each investigational device will be individually identified and labeled according to US regulatory requirements for investigational devices.

7.2. Method of Treatment Assignment

Subjects will be randomized to a 1-mL PFS administration to the arm, thigh, or abdomen or a 1-mL AI administration to the arm, thigh, or abdomen ([Table AMBE.2](#)).

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

7.2.1. Selection and Timing of Doses

The actual time of all dose administrations will be recorded in the subject's eCRF.

7.3. Blinding

This is an open-label study.

7.4. Dose Modification

Dose adjustments are not permitted in this study.

7.5. Preparation/Handling/Storage/Accountability

The IPs for this study will be:

- LY3074828 in PFSs
- LY3074828 in investigational AIs

Investigational product will be stored refrigerated at 2°C to 8°C (36°F to 46°F) in its original carton to protect from light. Investigational product should not be frozen or shaken. Sites will be required to monitor temperature of the on-site storage conditions of the IP. The investigator or designee must confirm appropriate temperature conditions have been maintained, as communicated by sponsor, during transit for all IP received and any discrepancies are reported and resolved before use of the study treatment.

The AIs and PFSs containing LY3074828 should be allowed to warm to room temperature before use.

Only participants enrolled in the study may receive IP or study materials, and only authorized site staff may supply or administer IP. All IP should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

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

7.6. Treatment Compliance

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

Paracetamol/acetaminophen (up to 2 g/day) is permitted at the discretion of the investigator, but should be avoided during the 4-hour postdose period when pain assessments are made. Additional drugs are to be avoided during the study, unless required to treat an AE.

If the need for concomitant medication arises per Investigator discretion, continuation of the subject may be at the discretion of the investigator in consultation with a Lilly clinical pharmacologist (CP) or clinical research physician (CRP). Any additional medication used during the course of the study must be documented.

7.8. Treatment after the End of the Study

This section is not applicable for this study.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

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

8.1.1. *Discontinuation of Inadvertently Enrolled Subjects*

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

8.2. Discontinuation from the Study

Subjects will be discontinued in the following circumstances:

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

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

8.3. Subjects Lost to Follow-up

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

9. Study Assessments and Procedures

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

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

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

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 emerging 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.

9.1. Efficacy Assessments

This section is not applicable to this study.

9.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the IP or 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 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, study device, 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 IP, study device, and/or study procedure and the AE.

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

9.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- 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
- when a condition related to the investigational device (PFS or AI) necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of “required intervention” will be assigned.

Study site personnel must alert the Lilly CRP/CP, or its designee, of any SAE as soon as practically possible.

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

Although all AEs are recorded in the eCRF after signing informed consent, SAE reporting to the sponsor begins after the subject has signed informed consent and has received IP. However, if an SAE occurs after signing informed consent, but prior to receiving IP, 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 IP) 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. Adverse Device Effects

Any AE believed to have a reasonable possibility of being related or associated to an issue with the AI or PFS, such as a malfunction or a deficiency, is considered an adverse device event. These events must be clearly indicated as such in the eCRF, and reported to the sponsor. A Product Complaint should also be reported.

For the purpose of this protocol, “unanticipated” serious adverse device effect means any SAE alleged to have a reasonable possibility to be associated or related to the device, which was not previously defined as anticipated in study documents, such as the device IB or IFU. The SAE relatedness must be clearly indicated as such in the eCRF, and reported to the sponsor within 24 hours of site knowledge of the event. A Product Complaint should also be reported.

9.2.1.2. Adverse Events of Special Interest

The following AEs of special interest will be used to determine the safety and tolerability of LY3074828 injections administered by either PFS or investigational AI in this clinical study.

Adverse events of special interest for LY3074828 are:

- infection
- ISRs
- allergic/hypersensitivity reactions

If infections, ISRs, or allergic/hypersensitivity reactions are reported, sites will provide details on these events as instructed on the eCRF. Investigators will also educate subjects about the symptoms of allergic/hypersensitivity reactions and will provide instructions on dealing with these reactions. A blood sample will be collected when possible for any subject who experiences an AE of allergic/hypersensitivity reaction during the study.

9.2.1.3. 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 reports as related to IP or procedure. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Complaint Handling

Lilly collects PCs on IPs 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 IP or drug delivery system so that the situation can be assessed.

A PFS or AI that is associated with a product quality issue or complaint must be returned to Lilly.

The investigator or his/her designee is responsible for reporting and handling the following aspects of the Product Complaints (PC) process in accordance with instructions on the Product Complaints form, and the instructions provided for this study:

- recording a complete description of the PC reported and any associated AEs using the study-specific complaint forms provided for this purpose
- forwarding via email or fax the completed Product Complaint form within 24 hours to Lilly or its designee if associated to an SAE, otherwise within 1 business day.

If the investigator is asked to return the product for investigation, he/she will return a copy of the completed Product Complaint form with the product.

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 study drug IB for further details.

9.4. Safety

9.4.1. Laboratory Tests

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

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

9.4.2. Vital Signs

For each subject, vital sign measurements (blood pressure, pulse rate, and temperature) should be conducted according to the Schedule of Activities (Section [2](#)). Additional vital signs may be measured during the study if warranted.

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

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.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms.

9.4.3. *Electrocardiograms*

For each subject, a single 12-lead digital ECG will be collected according to the Schedule of Activities (Section 2). Electrocardiograms must be recorded before collecting any blood samples. 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. All ECGs recorded should be stored at the investigational site.

Electrocardiograms will be interpreted by 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/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 clinically significant findings from ECGs that result in a diagnosis and that occur after the subject receives the first dose of the IP should be reported to Lilly, or its designee, as an AE via eCRF.

9.4.4. *Other Tests*

9.4.4.1. Tuberculosis Testing

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

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

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

9.4.4.2. Injection Duration Assessments

Injection duration will be measured by a calibrated stopwatch by qualified trained study staff. The duration of injection for the PFS will be defined as the time between when the plunger rod is pressed down and when all of the LY3074828 solution is injected. The duration of injection for the AI will be defined as the time between the first audible click after the injection button is

pressed and the last audible click, which indicates that the needle has retracted and the injection is complete.

9.4.4.3. Injection-Site Assessments

Injection site findings (including erythema, induration, pruritus, and edema) will be captured on a separate ISR form, as indicated in the Schedule of Activities (Section 2).

Data from injection site evaluations (including pain) which are recorded as a result of specific questionnaire/s will not be reported as AEs. If the investigator determines that the ISR is clinically significant or if it is an unsolicited event (volunteered by subject), the event will be captured in the subject's eCRF as an AE.

If an ISR is deemed to be an AE, the ISR form will be used to capture specific information about this reaction (eg, degree and area of erythema).

Injection-site tenderness on contact reported by subjects may be recorded as an AE, but is not required to be captured in ISR form.

9.4.4.4. Bleeding Assessment

All injection sites will be observed at the times indicated in the Schedule of Activities (Section 2) by the investigator or designee, and the presence of visible bleeding will be recorded on the eCRF. A bandage may be placed on the injection site after assessment.

9.4.4.5. Injection-Site Pain

Pain measurements will be quantified using the 100-mm validated VAS pain score for all subjects, whether or not they report injection pain. The VAS is a well-validated tool (Williamson and Hoggart 2005) to assess injection-site pain; it is presented as a 100-mm line anchored by verbal descriptors, usually “no pain” and “worst possible pain.” The subject will be asked to rate any pain at the injection site on a scale of 0 to 100 mm on the line immediately (within 1 minute) following the injection and at the time points listed in the Schedule of Activities (Section 2).

9.4.5. Safety Monitoring

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

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CP or CRP will periodically review the following data:

- trends in safety data
- laboratory analytes
- AEs, including monitoring of incidence of any nature of any infections, and ISRs
- PCs

When appropriate, the Lilly CP or CRP will consult with the functionally independent GPS therapeutic area physician, GPS device physician, or GPS clinical research scientist.

9.4.5.1. Hepatic Safety

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

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

- elevation of serum ALT to $\geq 5 \times$ ULN on 2 or more consecutive blood tests
- elevated serum TBL to $\geq 2 \times$ ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to $\geq 2 \times$ ULN on 2 or more consecutive blood tests
- hepatic event considered to be an SAE

9.4.5.2. Monitoring of Hypersensitivity Reactions

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

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

In the event of drug hypersensitivity reactions (immediate or non-immediate), additional samples will be collected as close to the onset of the event as possible, at the resolution of the event, and approximately 30 days following the event to evaluate ADA, PK, and additional exploratory biomarkers of hypersensitivity which could include tryptase, complement levels and cytokine measurements. 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. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 2 mL each will be collected to determine the serum concentrations of LY3074828. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

9.5.1. Bioanalysis

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor. Concentrations of LY3074828 will be assayed using a validated enzyme-linked immunosorbent assay.

Bioanalytical samples collected to measure IP concentrations will be retained for a maximum of 1 year following last subject visit for the study. During this time, samples remaining after the bioanalysis may be used for exploratory metabolism or exploratory analyses such as bioanalytical assay validation or cross-validation exercises.

9.6. Pharmacodynamics

9.6.1. Immunogenicity Assessments

Blood samples for immunogenicity testing will be collected to determine antibody production against LY3074828, as specified in the Schedule of Activities (Section 2). Additional samples may be collected if there is a possibility that an AE is immunologically mediated. If additional immunogenicity testing samples are taken, matching PK sample collections will also be required. Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of the IP. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the IP.

A risk-based approach will be used to monitor subjects who develop TE-ADAs during and following treatment with LY3074828.

Subjects will have ADA sampling at the visits specified in the Schedule of Activities (Section 2).

Subjects who have clinical sequelae that are considered potentially related to the presence of TE-ADA may be asked to return for additional follow-up testing.

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

9.7. Genetics

A blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities (Section 2), where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable exposure or response to LY3074828 and to investigate genetic variants thought to play a role in autoimmune and inflammatory diseases. Assessment of variable response may include evaluation of AEs or differences in efficacy.

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

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and/or IRB impose shorter time limits, for the study at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3074828 or after LY3074828 is commercially available.

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

9.8. Biomarkers

This section is not applicable for this study.

9.9. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Approximately 66 subjects will be enrolled with a target of 60 subjects completing the study (10 completers per treatment).

Data from AMAL (2 x 1-mL doses of 125 mg LY3074828) and AMAE (2 x 1-mL PFS doses of 125 mg LY3074828) studies showed that the geometric coefficient of variation ranged from 55% to 40% for the PK measurements (ie, area under the concentration versus time curve [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}]). Thus, the geometric coefficient of variation was assumed to be 55% when calculating precision.

A sample size of 60 subjects will provide a precision (ie, half-width of 90% of confidence interval [CI] with a coverage probability of 90%), in log scale, of approximately 0.48 for the geometric means ratio of reference versus test for AUC(0-∞), AUC(0-t_{last}), and C_{max}. Equivalently, there is a 90% probability that the distance between the lower limit of the 90% CI and the point estimate of the geometric means ratio is not larger than 38%.

Subjects who are randomized but not administered treatment, or subjects (maximum of 2 subjects per dose regimen arm) that are administered treatment but do not have PK and ADA samples collected up to and including Day 57, may be replaced to ensure that approximately 10 subjects from each treatment arm may complete the study.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

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

10.2.2. Study Participant Characteristics

The subject's age, sex, weight, BMI, height, race/subrace, and other demographic data will be summarized by dosing regimen and overall.

10.3. Statistical Analyses

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

Pharmacokinetic analyses will be conducted on the full analysis set. This set includes all data from all randomized subjects receiving the dose of LY3074828 with evaluable PK data. 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 IP and protocol procedure AEs and PCs 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 IP 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 IP- and device-related SAEs and any related PCs will be reported.

10.3.1.2. Statistical Evaluation of Safety

10.3.1.2.1. Injection-Site Pain

The intensity of pain at the injection site within 1 minute of the end of injection and 5 minutes after the end of the injection will be evaluated, as reported by the subject and measured according to the 0- to 100-mm VAS. VAS scores will be categorized into mild (0- to 30-mm), moderate (31- to 70-mm), and severe (71- to 100-mm). Assessments will also be performed at 15, 30, 60, and 120 minutes post-injection; however, the primary endpoints will be the 1- and 5-minute assessments.

Descriptive statistics will be used to summarize the intensity of pain at each time point.

A linear fixed-effects model will be used to analyze the 1- and 5-minute post-injection pain VAS scores separately. The model will include device and injection location as fixed effects. The least squares (LS) means and differences in LS means will be presented along with the corresponding 90% CI overall and by location as subgroups. The distribution of the data will be explored prior to analysis to determine whether data transformation is required. It is possible that the pain scores will be 0, so if the distribution of the data implies that a log-transformation is required then the score may be updated to $\log(\text{VAS}+1)$ to allow for the inclusion of the 0 values in the analysis. If the assumptions of this model appear violated, a non-parametric method may be used.

10.3.1.2.2. Duration of Injection

The duration of the injection (measured in seconds) will be summarized for each drug delivery device for each injection site.

10.3.1.2.3. Injection-Site Assessments

The incidence of the following AEs will be listed and summarized for each drug delivery device for each injection site: erythema, induration, pruritus, and edema. Occurrence of bleeding will be listed.

10.3.1.2.4. Statistical Evaluation of Other Safety Parameters

Other safety parameters that will be assessed include clinical laboratory parameters and vital signs. The parameters and changes from baseline (predose), where appropriate, will be listed and summarized using standard descriptive statistics. Additional analyses 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 $AUC(0-\infty)$, $AUC(0-t_{last})$, and C_{max} for LY3074828. The secondary parameter for analysis will be the time to maximum observed drug concentration (t_{max}) of LY3074828. Other noncompartmental parameters, such as half-life associated with the terminal rate constant ($t_{1/2}$), apparent total body clearance of drug calculated after extra-vascular administration (CL/F), and apparent volume of distribution during the terminal phase after extra-vascular administration (V_z/F), may be reported.

10.3.2.2. Pharmacokinetic Statistical Inference

The $AUC(0-\infty)$, $AUC(0-t_{last})$, and C_{max} will be log-transformed and analyzed using a linear fixed-effects model. The model will include device and injection location as fixed effects. The dosing regimen differences between AI and PFS administrations will be back-transformed to present the ratios of geometric LS means and the corresponding 90% CI. Comparisons will be made between the 2 devices and then between the 3 injection locations.

The t_{max} of LY3074828 between AI and PFS administrations will be analyzed using a Wilcoxon rank sum test. Estimates of the median difference, 90% CIs, and p-values from the Wilcoxon rank sum test will be calculated.

Additional PK analyses may be conducted if deemed appropriate.

10.3.3. Pharmacodynamic Analyses

This section is not applicable for this study.

10.3.4. Pharmacokinetic/Pharmacodynamic Analyses

This section is not applicable for this study.

10.3.5. Evaluation of Immunogenicity

The frequency of formation of antibodies to LY3074828 will be determined.

Treatment-emergent ADAs are those that are induced or boosted by exposure to study drug, with a 4-fold or greater 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 or concentrations of LY3074828 may be assessed if deemed appropriate.

10.3.6. Data Review During the Study

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

Available safety data will be reviewed at approximately Day 30 of the last cohort dosed in order to review emerging safety and tolerability data.

10.3.7. Interim Analyses

No formal interim analysis will be conducted. Data may be accessed as described in Section [10.3.6](#).

11. References

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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. |
| AI | autoinjector |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AUC | area under the concentration versus time curve |
| AUC(0-∞) | area under the concentration versus time curve from time zero to infinity |
| AUC(0-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 |
| CI | confidence interval |
| C_{max} | maximum observed drug concentration |
| complaint | A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system. |
| compliance | Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements. |
| confirmation | A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results. |
| CP | clinical pharmacologist |
| CRP | clinical research physician |
| CRU | clinical research unit |
| 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 study are those who have been assigned to a treatment. |
| enter | Subjects entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives. |
| GCP | good clinical practice |
| GPS | Global Patient Safety |
| HIV | human immunodeficiency virus |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| IFU | Instructions for Use |
| IL | interleukin |
| informed consent | A process by which a subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study 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 study data, separated into treatment groups, that is conducted before the final reporting database is created/locked. |
| IP | investigational product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. |
| investigator | A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. |
| IRB | institutional review board |
| ISR | injection-site reaction |
| IV | intravenous(ly) |
| LS | least squares |
| 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. |
| PC | product complaint |

| | |
|------------------------|--|
| PFS | pre-filled syringe |
| PK | pharmacokinetic(s) |
| randomize | The process of assigning subjects/patients to an experimental group on a random basis. |
| SAE | serious adverse event |
| SC | subcutaneous(ly) |
| screen | The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. |
| SUSARs | suspected unexpected serious adverse reactions |
| TB | tuberculosis |
| TBL | total bilirubin |
| TE-ADA | treatment-emergent anti-drug antibody |
| 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. |
| Th | T helper |
| t_{max} | time to maximum observed drug concentration |
| ULN | upper limit of normal |
| VAS | visual analog scale |

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests

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

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

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

b If clinically indicated, per investigator's discretion.

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

d Not collected routinely as part of clinical chemistry panel. Only collected when specified in Schedule of Activities (Section 2).

e Urine drug screen and ethanol level (determined via breath, blood, or urine testing) will be performed locally at screening and on Day -1 during admission to the clinical research unit. May be repeated at the discretion of the investigator.

f Performed at screening only.

g For all females at screening, and only for women of childbearing potential at sampling time points thereafter.

h Refer to Section 2 for specific sampling timing.

i To confirm postmenopausal status (see Section 6.1, inclusion criterion 1b)

Appendix 3. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the subject understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each subject or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (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 study.
- providing a copy of the ICF to the participant or the participant's legal representative and retaining a copy on file.

Recruitment

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

Ethical Review

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

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

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

- the current Investigator's Brochure and updates during the course of the study
- ICF
- relevant curricula vitae.

Regulatory Considerations

This study will be conducted in accordance with the protocol and with:

- 1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences 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 electronic case report forms (eCRFs), and study procedures
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate eCRF data and/or use standard computer edits to detect errors in data collection
- conduct a quality review of the database.

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

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

Data Collection Tools/Source Data

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

Data Protection

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

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

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

| | |
|---------------------------------------|--|
| Hepatic Hematology^a | Haptoglobin^a |
| Hemoglobin | |
| Hematocrit | |
| RBC | Hepatic Coagulation^a |
| WBC | Prothrombin time |
| Neutrophils | Prothrombin time, INR |
| Lymphocytes | |
| Monocytes | Hepatic Serologies^{a,b} |
| Eosinophils | Hepatitis A antibody, total |
| Basophils | Hepatitis A antibody, IgM |
| Platelets | Hepatitis B surface antigen |
| | Hepatitis B surface antibody |
| | Hepatitis C antibody |
| Hepatic Chemistry^a | Hepatitis E antibody, IgG |
| Total bilirubin | Hepatitis E antibody, IgM |
| Conjugated bilirubin | |
| Alkaline phosphatase | |
| ALT | Anti-nuclear antibody^a |
| AST | Alkaline phosphatase isoenzymes^a |
| GGT | Anti-smooth muscle antibody (or anti-actin |
| CPK | antibody)^a |

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

^a Assayed by Lilly-designated or local laboratory.

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

Appendix 5. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study.

Protocol I6T-MC-AMBE Sampling Summary

| Purpose | Blood Volume per Sample (mL) | Number of Blood Samples | Total Volume (mL) |
|---|------------------------------|-------------------------|-------------------|
| Screening tests ^a | 22.5 | 1 | 22.5 |
| Clinical laboratory tests ^a | 12.5 | 5 | 62.5 |
| Pharmacokinetics ^b | 2 | 17 | 34 |
| Immunogenicity ^a | 10 | 5 | 50 |
| Pregnancy tests | 3.5 | 4 | 14 |
| Pharmacogenetics | 10 | 1 | 10 |
| Total | | | 193 |
| Total for clinical purposes [rounded up to nearest 10 mL] | | | 200 |

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

^b Includes a potential 3 additional samples to be matched to additional immunogenicity samples (see Section 9.6.1).

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