Protocol I6T-MC-AMAR (a)

A Safety, Tolerability, and Pharmacokinetic Study of Injections of LY3074828 Solution Using Investigational 1-mL Pre-filled Syringes and Investigational 2-mL Autoinjector in Healthy Subjects

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LY3074828

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Protocol Electronically Signed and Approved by Lilly: 11 June 2018
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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 2-mL Autoinjector in Healthy Subjects

Rationale:

Study I6T-MC-AMAR (AMAR) will assess the pharmacokinetics (PK), safety and tolerability of, and pain associated with, a 250-mg subcutaneous (SC) dose of LY3074828 solution formulation administered using an investigational manual pre-filled syringe (PFS) or an investigational autoinjector (AI). The administration by AI will be a 1 x 2-mL 125-mg/mL fast-speed injection and the administration by PFS will be 2 x 1-mL 125-mg/mL injections. 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 (as used in Study I6T-MC-AMAE [AMAE]) of LY3074828, a monoclonal antibody, with the investigational AI device planned for use in subsequent studies and patient use.

Objectives/Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the PK after administration of 250-mg doses of LY3074828 solution formulation using 2 x 1-mL PFS and 1 x 2-mL AI injections in healthy subjects.	• The primary PK endpoints will be the C_{max}, AUC(0-t_{last}), and AUC(0-∞) of LY3074828.
• To assess the safety and tolerability of LY3074828 in healthy subjects.	• Incidence of TEAEs.
• To assess pain associated with LY3074828 PFS and AI SC administrations in healthy subjects at 3 different injection sites (arm, thigh, and abdomen).	• VAS pain score.

Abbreviations: AI = autoinjector; 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; 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-AMAR (AMAR) 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, 250-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 2 x 1-mL PFS arm, thigh, or abdomen administration or a 1 x 2-mL AI arm, thigh, or abdomen administration. 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 250-mg SC dose of LY3074828 and will be randomized to 1 of 6 dosing regimen arms:

- Test 1: 250 mg LY3074828 solution formulation, 1 x 2-mL 125-mg/mL AI injection administered in the arm
- Test 2: 250 mg LY3074828 solution formulation, 1 x 2-mL 125-mg/mL AI injection administered in the thigh
- Test 3: 250 mg LY3074828 solution formulation, 1 x 2-mL 125-mg/mL AI injection administered in the abdomen
- Reference 1: 250 mg LY3074828 solution formulation, 2 x 1-mL 125-mg/mL PFS injections administered in the arm
- Reference 2: 250 mg LY3074828 solution formulation, 2 x 1-mL 125-mg/mL PFS injections administered in the thigh
- Reference 3: 250 mg LY3074828 solution formulation, 2 x 1-mL 125-mg/mL PFS injections 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. 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-∞]), 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 Test and Reference arms 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 Test and Reference arms 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.

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

2. Schedule of Activities

Study Schedule Protocol I6T-MC-AMAR

	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 postmenopausal, 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												Time points are minutes post-injection as follows: within 1 minute of the end of injection, 5 (±1.5), and 15 (±2) minutes. For 1-mL PFS, the second injection will be administered 20 minutes (±2) after first injection.
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.
Immunogenicity sample			Predose					X		X		X		X	LY3074828 antibody sample.
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. In 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. Procedures specified as predose may be performed within 2 hours from planned dosing.

3. Introduction

3.1. Study Rationale

Study I6T-MC-AMAR (AMAR) will assess the pharmacokinetics (PK), safety and tolerability of, and pain associated with a 250-mg subcutaneous (SC) dose of LY3074828 solution formulation administered using an investigational manual pre-filled syringe (PFS) or an investigational autoinjector (AI). The administration by AI will be a 1 x 2-mL 125-mg/mL injection and the administration by PFS will be 2 x 1-mL 125-mg/mL injections. 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 (as used in Study I6T-MC-AMAE [AMAE]) of LY3074828, a monoclonal antibody, 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-23 (IL-23) and does not bind interleukin-12. LY3074828 is being developed for the treatment of autoimmune diseases in which the IL-23 pathway is thought to have a significant pathogenic role. Neutralization of IL-23 with an anti-mouse IL-23 surrogate antibody (directed against the p19 subunit) significantly reduced the development of arthritis and inhibited ileal inflammation in a mouse model of spondyloarthropathy with bowel inflammation (Ruutu et al. 2012). 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, 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-AMAQ [AMAQ]).

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 250 mg LY3074828 lyophilized formulation and the 250 mg LY3074828 PFS solution formulation, with a notably higher number of TEAEs reported by 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. In Study AMAA, injection-site pain (related to study drug) was reported in 3 out of 5 healthy subjects receiving 120 mg LY3074828 via SC administration; however, no infusion reactions were reported. 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 250-mg SC test formulation group.

Treatment-emergent anti-drug antibodies (TE-ADAs) developed in 3 of 33 patients with psoriasis receiving single IV doses of LY3074828 in Study AMAA. The TE-ADAs were observed in the 120- and 350-mg dose groups. The earliest time point at which TE-ADAs were detected was Day 22, which was the first postdose time point at which immunogenicity was assessed and, where present, TE-ADAs were generally still detectable at Day 85. The highest anti-drug antibody (ADA) titer observed was 1:320. None of the healthy subjects (n=5) who received 120 mg SC LY3074828 developed TE-ADAs.

Treatment-emergent ADAs developed (by Days 29 and 85, respectively) in 2 of 6 subjects following single SC doses of 200 mg LY3074828 in Study AMAD; however, titers were $\leq$1:160. Based on preliminary data for this study, a similar proportion of subjects developed TE-ADAs following IV doses of LY3074828 (9 of 26) compared to SC doses, mostly occurring at Day 85. However, the highest titer of 1:5120 (declining to 1:320 after eight months) occurred in a Japanese subject who received 200 mg IV LY3074828.

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 ≤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 1200-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 IB.

More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of the AI is found in the device IB.

4. Objectives and Endpoints

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

Table AMAR.1. Objectives and Endpoints

Objectives	Endpoints
Primary • To evaluate the PK after administration of 250-mg doses of LY3074828 solution formulation using 2 x 1-mL PFS and 1 x 2-mL AI injections in healthy subjects. • To assess the safety and tolerability of LY3074828 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).	• The primary PK endpoints will be the C_{max}, AUC(0-t_{last}), and AUC(0-∞) of LY3074828. • Incidence of TEAEs. • VAS pain score.

Abbreviations: AI = autoinjector; 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; 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-AMAR (AMAR) 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, 250-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: 250 mg LY3074828 solution formulation, 1 x 2-mL 125-mg/mL AI injection, administered in the arm
- Test 2: 250 mg LY3074828 solution formulation, 1 x 2-mL 125-mg/mL AI injection, administered in the thigh
- Test 3: 250 mg LY3074828 solution formulation, 1 x 2-mL 125-mg/mL AI injection, administered in the abdomen
- Reference 1: 250 mg LY3074828 solution formulation, 2 x 1-mL 125-mg/mL PFS injections targeting a 5- to 10-second injection time for each injection, administered in the arm
- Reference 2: 250 mg LY3074828 solution formulation, 2 x 1-mL 125-mg/mL PFS injections targeting a 5- to 10-second injection time for each injection, administered in the thigh
- Reference 3: 250 mg LY3074828 solution formulation, 2 x 1-mL 125-mg/mL PFS injections targeting a 5- to 10-second injection time for each injection, 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.

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 visual analog scale (VAS) score.

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 VAS.

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. As the primary endpoints of this study are PK-related and are not subject to bias, it is not considered necessary for this study to be blinded. Subjects and site staff will be aware of the administration route 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 and AI (1 or 2 mL) and the solubility of LY3074828 (125 mg/mL), resulting in a dose of 250 mg LY3074828. CCI [redacted]

Intravenous doses up to 1200 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.

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:

- Men, regardless of their fertility status, with non-pregnant women of childbearing potential partners must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms as well as one additional highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine devices) or effective method of contraception (such as diaphragms with spermicide or cervical sponges) for the duration of the study and for 24 weeks following dosing with the study drug
    - Men and their partners may choose to use a double-barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception. Thus, each barrier method must include use of a spermicide. It should be noted, however, 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 barrier methods are combined
    - 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
- Men with pregnant partners should use condoms during intercourse for the duration of the study and for 24 weeks following dosing with the study drug

- Men should refrain from sperm donation for the duration of the study and for 24 weeks following dosing with the study drug
- Men who are in exclusively same-sex relationships (as their preferred and usual lifestyle) are not required to use contraception

[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 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 a reliable or acceptable method. Thus, each barrier method must include use of a spermicide. It should be noted that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these methods are combined
- 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 mullerian 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/m^2, inclusive, at time of screening

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

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

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

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

6.2. Exclusion Criteria

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

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

[9] are Lilly employees or employees of Covance

[10] are currently enrolled in a clinical study involving an investigational product (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 known allergies to LY3074828, related compounds, or any components of the formulation, or history of significant atopy

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

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

[16] have a history or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, 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

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

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

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

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

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

[22] are women who are lactating

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

[24] have donated blood of more than 500 mL within 1 month prior to screening

[25] have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females), have a positive test for ethanol, or are unwilling to abide by the alcohol restrictions described in Section 6.3.2 (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits)

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

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

[28] show evidence of active or latent TB, as documented by medical history, examination, and TB testing (negative [not indeterminate] QuantiFERON® -TB Gold test); or have had household contact with a person with active TB, unless appropriate and documented prophylaxis treatment has been given. Subjects with any history of active TB are excluded from the study, regardless of previous or current TB treatments

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

[30] have been treated with oral steroids within 1 month of screening, or intend to during the study (mild topical steroid creams/ointments are permitted)

[31] are immunocompromised

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

[33] have significant allergies to humanized monoclonal antibodies

[34] have clinically significant multiple or severe drug allergies, or intolerance to topical corticosteroids, or severe 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.

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 asked to refrain from smoking for approximately 1 hour prior to each ECG and vital sign measurements, and to abide by the CRU smoking guidelines.

6.3.3. Activity

Subjects will be advised to maintain their regular levels of physical activity/exercise during the study, but to refrain from 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 250-mg SC doses administered using 2 x 1-mL PFSs or an investigational 1 x 2-mL AI at 3 different injection sites.

Using the investigational 2-mL AI, the targeted injection duration will be approximately 5 seconds. Manual injections using the PFS should target an injection duration of about 5 to 10 seconds for each 1-mL injection to approximate the injection time range for the AI. The second of the 2 PFS injections should be administered 20 (±2) minutes after the first injection to allow for collection of 3 VAS pain score time points prior to administration of the second injection. 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 AMAR.2 shows the dosing regimens for the study.

Table AMAR.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	250 mg			250 mg		
Concentration	125 mg/mL			125 mg/mL		
Injection volumes	2 × 1 mL (2 mL total)			1 × 2 mL (2 mL total)		
Number of injections	2			1		
Injection duration	5 to 10 seconds per injection			Approximately 5 seconds		
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. For PFS administrations requiring 2 injections, subjects randomized to a group with the arm or thigh as the injection site will have both injections administered to the same limb (same arm or same thigh). Subjects randomized to the group with the abdomen as the injection site will have the 2 PFS injections administered to separate lower quadrants (right and left) 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, 2 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 2 x 1-mL PFS arm, thigh, or abdomen administration or a 1 x 2-mL AI arm, thigh, or abdomen administration (Table AMAR.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 (including both the first and second of the 2 PFS injections) 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, inclusion or continuation of the subject may be at the discretion of the investigator after consultation with a Lilly clinical pharmacologist (CP) or clinical research physician (CRP). 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 be related to an issue with the AI or PFS is considered an adverse device event. These events must be clearly indicated as such in the eCRF, and reported to the sponsor. A PC should also be reported.

For the purpose of this protocol, "unanticipated" adverse device effect means any SAE alleged to be associated or related to the device, and which has been confirmed as such by the sponsor. 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 PC 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 handling the following aspects of the PC process in accordance with 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
- faxing the completed PC form within 24 hours to Lilly or its designee.

If the investigator is asked to return the product for investigation, he/she will return a copy of the PC 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).

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) ≥3× upper limit of normal (ULN), alkaline phosphatase (ALP) ≥2× ULN, or elevated total bilirubin (TBL)

≥2× ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, aspartate aminotransferase, 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 ≥5× ULN on 2 or more consecutive blood tests
- elevated serum TBL to ≥2× ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2× ULN on 2 or more consecutive blood tests
- hepatic event considered to be 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).

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 baseline (predose) and on Days 15, 29, 57, and 85 (see 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 250 mg LY3074828) and AMAE (2 x 1-mL PFS doses of 250 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. Assessments will also be performed at 15 minutes post-injection; however, the primary endpoints will be the 1- and 5-minute assessments. For 1-mL PFS, the second injection will be administered 20 (±2) minutes after the first injection.

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 post-injection pain VAS scores. 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. 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(VAS+1) to allow for the inclusion of the 0 values in the analysis.

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-∞), 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-∞), 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 Test and Reference arms will be back-transformed to present the ratios of geometric LS means and the corresponding 90% CI.

The t_{max} of LY3074828 between Test and Reference arms 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

Exploratory interim analysis is scheduled to occur upon completion of all VAS assessments for all subjects. The analysis will include determination of the mean/median VAS scores and standard deviation, and categorical grouping of VAS data. The VAS data from all 3 cohorts will be included in this interim analysis. The purpose of the interim analysis is to examine the data prior to distribution to other teams within Eli Lilly & Company. The analysis will be for internal purposes only and there is no intention for the analysis to change the conduct of the trial.

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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
CL/F	apparent total body clearance of drug calculated after extra-vascular administration
C_{max}	maximum observed drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the 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-23	interleukin-23
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.
investigational product (IP)	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.

randomize	The process of assigning subjects/patients to an experimental group on a random basis.
PC	product complaint
PFS	pre-filled syringe
PK	pharmacokinetic(s)
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
$t_{1/2}$	half-life associated with the terminal rate constant
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
V_z/F	apparent volume of distribution during the terminal phase after extra-vascular administration

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests

Hematology[a]
- Hematocrit
- Hemoglobin
- Erythrocyte count (RBC)
- Mean cell volume
- Mean cell hemoglobin
- Mean cell hemoglobin concentration
- Leukocytes (WBC)
- Cell morphology
  - Absolute counts of:
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils
  - Platelets

Clinical Chemistry[a]
- Sodium
- Potassium
- Calcium
- Phosphorus
- Glucose (random)
- Blood urea nitrogen (BUN)
- Uric acid
- Total cholesterol
- Total protein
- Albumin
- Total bilirubin[c]
- Alkaline phosphatase (ALP)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Creatinine
- Creatine phosphokinase (CPK)[d]

Urinalysis[a]
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Bilirubin
- Urobilinogen
- Blood
- Nitrite

Microscopic examination of sediment[b]

Ethanol testing[e]

Urine drug screen[e]

QuantiFERON-TB Gold test[a,f]

Serology[f]
- Hepatitis B surface antigen
- Hepatitis C antibody
- HIV antibodies

Serum Pregnancy test[g,h]

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 on Day -1, 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.

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 patients. 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	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis 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 antibody)[a]**
CPK	

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

a Assayed by Lilly-designated or local laboratory.

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

Appendix 5. Blood Sampling Summary

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

Protocol I6T-MC-AMAR 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).

Appendix 6. Protocol Amendment I6T-MC-AMAR(a) Summary: A Safety, Tolerability, and Pharmacokinetic Study of Injections of LY3074828 Solution Using Investigational 1-mL Pre-filled Syringes and Investigational 2-mL Autoinjector in Healthy Subjects

Overview

Protocol I6T-MC-AMAR [A Safety, Tolerability, and Pharmacokinetic Study of Injections of LY3074828 Solution Using Investigational 1-mL Pre-filled Syringes and Investigational 2-mL Autoinjector in Healthy Subjects] has been amended. The new protocol is indicated by Amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- addition of a footnote for creatine phosphokinase in the clinical laboratory tests in order to clarify that it will only be assessed at the time points specified in the Schedule of Activities (ie, Day -1, 8, and 29) rather than at each time point clinical laboratory tests are performed.
- addition of exploratory interim analyses, for internal use only, to inform program decisions of investigational product development.
- update to the order of priority in cases where several study procedures are scheduled at the same time, to minimize the number of blood draws.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

2. Schedule of Activities (footnote)

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

10.3.7. Interim Analyses

~~No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the Lilly CP, CRP/investigator, or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.~~ Exploratory interim analysis is scheduled to occur upon completion of all VAS assessments for all subjects. The analysis will include determination of the mean/median VAS scores and standard deviation, and categorical grouping of VAS data. The VAS data from all 3 cohorts will be included in this interim analysis. The purpose of the interim analysis is to examine the data prior to distribution to other teams within Eli Lilly & Company. The analysis will be for internal purposes only and there is no intention for the analysis to change the conduct of the trial.

Appendix 2. Clinical Laboratory Tests

Clinical Chemistry[a]
…
…
Creatine phosphokinase (CPK)[d]
Ethanol testing[~~d~~ e]
Urine drug screen[~~d~~ e]
QuantiFERON-TB Gold test[a,~~e~~ f]
Serology[~~e~~ f]
Hepatitis B surface antigen
Hepatitis C antibody
HIV antibodies
Serum Pregnancy test[~~f~~ g, h]
Hormone Panel
Follicle-stimulating hormone [~~e~~ f, ~~h~~ i]

…

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

~~d~~ 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.

~~e~~ f Performed at screening only.

~~f~~ g For all females at screening and on Day -1, and only for women of childbearing potential at sampling time points thereafter.

~~g~~ h Refer to Section 2 for specific sampling timing.

~~h~~ i To confirm postmenopausal status.

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