Protocol I6T-MC-AMAQ (b)

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

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LY3074828

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Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly:
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1. Protocol Synopsis

Title of Study:

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

Rationale:

Study I6T-MC-AMAQ (AMAQ) will assess the pharmacokinetics (PK), safety and tolerability of, and pain associated with, a 250-mg subcutaneous (SC) dose of LY3074828 solution formulation administered as 1 x 2-mL 125-mg/mL injection using an investigational manual pre-filled syringe (PFS; Test 1) and administered as 2 x 1-mL 125-mg/mL injections using an investigational manual PFS (Reference). The study will also compare safety and tolerability of, and pain associated with, a 250-mg SC dose of LY3074828 solution formulation administered as 1 x 2-mL 125-mg/mL injection using an investigational 2-mL autoinjector (AI) with slow (Test 2) and fast (Test 3) injection speeds, and a 125-mg dose administered as 1 x 1-mL 125-mg/mL injection using an investigational 1-mL AI with slow (Test 4) and fast (Test 5) injection speeds. The study will bridge 2 different PFSs administering the same total volume, from 2 injections with the 1-mL PFS used to administer LY3074828 solution in Study I6T-MC-AMAE (AMAE) to 1 injection with a 2-mL investigational PFS. Investigational 1- and 2-mL AI administrations are to be evaluated primarily for pain and injection site reactions.

Objectives/Endpoints:

Objectives	Endpoints
Primary Part A • To evaluate the PK of LY3074828 solution formulation after administration of 250-mg doses using 2 x 1-mL and 1 x 2-mL PFS injections in healthy subjects. • To assess the safety and tolerability of, and pain associated with, LY3074828 PFS administrations in healthy subjects.	Part A • The primary PK endpoints will be the C_{max}, AUC(0-t_{last}), and AUC(0-∞) of LY3074828. • Incidence of TEAEs. • SF-MPQ, including VAS pain score.
Primary Part B • To compare the safety and tolerability of, and pain associated with, LY3074828 solution formulation after administration of 125- and 250-mg doses using 1-mL AI and 2-mL AI SC injections with different injection speeds (slow and fast) in healthy subjects.	Part B • Incidence of TEAEs. • SF-MPQ, including 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; SF-MPQ = Short Form McGill Pain Questionnaire; TEAE = treatment-emergent adverse event; VAS = visual analog scale.

Summary of Study Design:

Study I6T-MC-AMAQ (AMAQ) is a single-center, randomized, parallel-treatment, open-label, Phase 1 single-dose study of LY3074828 solution formulation in healthy subjects. In Part A, PK, safety and tolerability of, and pain associated with, SC doses administered using 1- and 2-mL PFS injections will be evaluated. In Part B, safety and tolerability of, and pain associated with, 1- and 2-mL AI injections administered with 2 different injection speeds will be evaluated.

For Part A, subjects will report to the clinical research unit (CRU) on Day -1 and will remain at the CRU until the scheduled procedures have been completed on Day 2. After randomization to either a 2 x 1-mL or a 1 x 2-mL 125-mg/mL PFS dose regimen, study drug will be administered by investigative site staff by SC injection in the abdomen in the morning of Day 1 after an overnight fast. Subjects will be followed for 12 weeks following dose administration.

For Part B, subjects will report to the CRU on Day -1 and will remain at the CRU until the scheduled procedures have been completed on Day 3. Subjects will be randomized to receive, on Days 1 and 2, either a 1 x 1-mL or a 1 x 2-mL 125-mg/mL AI dose regimen. The allocated AI dose regimen will be self-administered by slow and fast SC injection(s) on consecutive days (sequence randomized) in the abdomen after an overnight fast. Subjects will be followed for 12 weeks following dose administration.

Safety and tolerability will be explored 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 the Short Form McGill Pain Questionnaire (SF-MPQ), which includes a subject-assessed injection-site pain visual analog scale (VAS).

Dosing Regimen Arms and Duration:
Subjects will receive a 125- or 250-mg SC dose of LY3074828 and will be randomized to 1 of 2 dosing regimen arms within 1 study part:

Part A

- Reference: 250 mg LY3074828 solution formulation, 2 x 1-mL 125-mg/mL PFS injections using an investigational PFS targeting 5- to 10-second injection time for each injection
- Test 1: 250 mg LY3074828 solution formulation, 1 x 2-mL 125-mg/mL PFS injection using an investigational PFS targeting 5- to 15-second injection time

Part B

- Tests 2 and 3: 250 mg LY3074828 solution formulation, 1 x 2-mL 125-mg/mL AI slow injection (Test 2; targeting approximately 13-second injection time) and fast injection (Test 3; targeting approximately 5-second injection time) using an investigational 2-mL AI
- Tests 4 and 5: 125 mg LY3074828 solution formulation, 1 x 1-mL 125-mg/mL AI slow injection (Test 4; targeting approximately 7-second injection time) and fast injection (Test 5; targeting approximately 4.5-second injection time) using an investigational 1-mL AI

Total duration of the study for each subject will be approximately 16 weeks (screening period ≤28 days, residential period of 2 or 3 days [depending on study part], and outpatient follow-up period of 12 weeks).

Number of Subjects:
A total of approximately 72 subjects (approximately 36 subjects per study Parts A and B) who fulfill the eligibility criteria will be randomized to 1 of 2 dosing regimen arms within their assigned study part, with 18 subjects randomized to each arm in order to ensure completion of 16 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 for Part A or up to and including at least Day 15 for Part B. A maximum of 4 subjects per arm per study part may be replaced if multiple subjects do not complete the study.

Statistical Analysis:

For Part A, 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 dosing regimen arm as a fixed effect. The dosing regimen differences between the Test 1 arm and the Reference arm 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 the 2 x 1-mL PFS (Reference) and the 1 x 2-mL PFS (Test 1) will be analyzed using a Wilcoxon rank sum test for Part A. 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 for Part A if deemed appropriate.

In Part A, a linear fixed-effects model will be used to analyze the 0-hour (post-injection) pain VAS score and SF-MPQ total score. The model will include treatment (Reference or Test 1) as a fixed effect. The LS means and differences in LS means (between Test 1 and Reference) will be presented along with the corresponding 90% CI.

A similar model will be used to analyze the 0-hour (post-injection) pain VAS score and SF-MPQ total score in Part B.

The following comparisons will be performed in Part B:

- Test 2 versus Test 3 (slow versus fast injection for 2-mL AI)
- Test 4 versus Test 5 (slow versus fast injection for 1-mL AI)

For Parts A and B, 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-AMAQ – Part A

	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 x 2-mL or 2 x 1-mL PFS arm.
LY3074828 injection			X												Doses administered by investigative site staff.
Stopwatch recording			X												Stopwatch is the source for injection duration capture.
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.
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														

	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	
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 either breath or urine testing. See Appendix 2 for test details.
FSH / serum pregnancy test	X	X								X		X		X	Serum pregnancy tests for all female subjects at screening and on Day -1, and only for women of childbearing potential on Days 29, 57, and 85/ED. 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 can be 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, categorical pain, pruritus, edema, and visible bleeding (hour)			0, 0.25	X		X		X							Times with respect to start of dosing. Zero-hour assessments within 5 minutes following injection. Time allowance for 0.25-hour assessment is ±5 minutes. Additional assessments performed if deemed necessary by the investigator.
Pain assessment (SF-MPQ, including pain VAS)			X												Immediately after the start of injection (t = 0) (within approximately 5 minutes) and at 15 (±5), 30 (±5), 60 (±5), 120 (±10), and 240 (±10) minutes post injection. For 1-mL PFS, assessments to be completed on the first of the 2 injections only.
LY3074828 pharmacokinetic sampling (hour)			0, 2, 6	24	72	168	240	336	504	672	1008	1344	1680	2016	Times with respect to start of dosing. Zero-hour collection immediately (within 15 minutes) before dosing. Time allowance for 2-, 6-, and 24-hour time points: ±15, ±30,

	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	
															and ±90 minutes, respectively.
Immunogenicity sample			Predose					X		X		X		X	LY3074828 antibody sample.
Pharmacogenetics sample		X													

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

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

Study Schedule Protocol I6T-MC-AMAQ – Part B

	Screening	**Days**							**Comments**
Procedure	≤28 days	**-1**	**1**	**2**	**3**	**15** ±2d	**43** ±2d	**86/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	
Randomization			X						Subjects randomized to 1-mL or 2-mL AI arm, and then further randomized within the arm in respect to sequence of injection speed on Days 1 and 2 (slow/fast or fast/slow).
Injection training		X							
LY3074828 injection			X	X					Doses self-administered.
Stopwatch and video recording			X	X					Stopwatch is the source for injection duration capture. Video recording for device functionality.
AI Use Assessment Questionnaire			X	X					Clinical staff who observe the subject's self-injection with the AI will fill out the AI Use Assessment Questionnaire
Medical history	X								
Weight, height, and BMI	X								
Vital signs: blood pressure, pulse rate, temperature (hour)	X	X	0, 6	0, 6	24	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	0	24			X	
Physical examination / medical assessment	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**	**3**	**15** ±2d	**43** ±2d	**86/ED** ±3d	
AE review	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 either breath or urine testing. See Appendix 2 for test details.
FSH / serum pregnancy test	X	X				X	X	X	Serum pregnancy tests for all female subjects at screening and on Day -1, and only for women of childbearing potential on Days 15, 43, and 86/ED. 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 can be exempted from further pregnancy tests during the study. See Appendix 2 for test details.
Clinical chemistry, hematology, and urinalysis	X	X				X	X	X	See Appendix 2 for test details.
Creatine phosphokinase		X				X	X		
Injection-site assessment (Day 1 injection) for erythema, induration, categorical pain, pruritus, edema, and visible bleeding (hour)			0, 0.25	24		X			Times with respect to start of dosing. Zero-hour assessments within 5 minutes following injection. Time allowance for 0.25-hour assessment is ±5 minutes. Additional assessments performed if deemed necessary by the investigator.
Injection-site assessment (Day 2 injection) for erythema, induration, categorical pain, pruritus, edema, and visible bleeding (hour)				0, 0.25	24	X			Times with respect to start of dosing. Zero-hour assessments within 5 minutes following injection. Time allowance for 0.25-hour assessment is ±5 minutes. Additional assessments performed if deemed necessary by the investigator.
Pain assessment (SF-MPQ, including pain VAS)			X	X					Immediately after the start of each injection (t = 0) (within approximately 5 minutes) and at 15 (±5), 30 (±5), 60 (±5), 120 (±10), and 240 (±10) minutes post injection.
LY3074828 pharmacokinetic						X	X	X	Samples collected to match immunogenicity collections.

	Screening	**Days**							**Comments**
Procedure	≤28 days	**-1**	**1**	**2**	**3**	**15** ±2d	**43** ±2d	**86/ED** ±3d	
sampling			Predose						Samples will be stored and will only be sent for bioanalysis at a later date based on immunogenicity or safety results from Part B of the study.
Immunogenicity sample			Predose			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; SF-MPQ = Short Form McGill Pain Questionnaire; 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: ECG, vital signs, clinical laboratory tests, pain assessment, injection-site assessment, immunogenicity and pharmacokinetic samples, stored sample. Procedures specified as predose may be performed within 2 hours from planned dosing.

3. Introduction

3.1. Study Rationale

Study I6T-MC-AMAQ (AMAQ) will assess the pharmacokinetics (PK), safety and tolerability of, and pain associated with, a 250-mg subcutaneous (SC) dose of LY3074828 solution formulation administered as 1 x 2-mL 125-mg/mL injection using an investigational manual pre-filled syringe (PFS; Test 1) and administered as 2 x 1-mL 125-mg/mL injections using an investigational manual PFS (Reference). The study will also compare safety and tolerability of, and pain associated with, a 250-mg SC dose of LY3074828 solution formulation administered as 1 x 2-mL 125-mg/mL injection using an investigational 2-mL autoinjector (AI) with slow (Test 2) and fast (Test 3) injection speeds and a 125-mg dose administered as a 1 x 1-mL 125-mg/mL injection using an investigational 1-mL AI with slow (Test 4) and fast (Test 5) injection speeds. The study will bridge 2 different PFSs administering the same total volume, from 2 injections with the 1-mL PFS used to administer LY3074828 solution in Study I6T-MC-AMAE (AMAE) to 1 injection with a 2-mL investigational PFS. Investigational 1- and 2-mL AI administrations are to be evaluated primarily for pain and injection-site reactions.

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).

LY3074828 has been evaluated in 5 healthy subjects (single 120-mg SC doses) and in 33 subjects with plaque psoriasis (single ascending intravenous [IV] doses of 5, 20, 60, 120, 200, 350, or 600 mg) in Study I6T-MC-AMAA (AMAA). Furthermore, 43 healthy Japanese and Caucasian subjects were administered single IV doses of 60, 200, 600, or 1200 mg LY3074828, or placebo, or single SC doses of 200 mg LY3074828, or placebo, in Study I6T-MC-AMAD (AMAD).

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

from Study AMAA indicated that serum exposure of LY3074828 increases in a dose-proportional manner, and that the mean half-life associated with the terminal rate constant ($t_{1/2}$) was 10.5 days, which did not appear to be dependent on dose. Maximum concentrations were observed 3 days postdose following SC administration and, based on the area under the concentration versus time curve (AUC), the SC bioavailability was 40%.

Treatment-emergent anti-drug antibodies (TE-ADAs) developed in 3 of 33 subjects after administration of single IV doses of LY3074828 in Study AMAA; however, there was no correlation between TE-ADA titers and the doses of LY3074828. The earliest time point at which TE-ADAs were detected was Day 22, which was the first postdose time point at which immunogenicity was assessed. 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 ADA.

Treatment-emergent ADAs developed in 2 of 6 subjects following single SC doses of 200 mg LY3074828 in Study AMAD; however, titers were ≤1:160.

LY3074828 is currently being evaluated in three Phase 2 studies:

- Study I6T-MC-AMAC is being conducted in approximately 240 subjects with ulcerative colitis. Three IV doses of 50, 200, or 600 mg LY3074828 (or placebo) are administered every 4 weeks (Q4W) during the induction period. Subjects with a clinical response are subsequently administered SC doses of 200 mg LY3074828 (or placebo) Q4W or 200 mg LY3074828 every 12 weeks during the 92-week maintenance period. Subjects with no clinical response in the induction period may be administered 3 further 1000 mg LY3074828 IV doses Q4W, followed by 200 mg LY3074828 SC Q4W for 80 weeks.
- Study I6T-MC-AMAF is being conducted in approximately 200 subjects with plaque psoriasis. Two SC doses of 30, 100, or 300 mg LY3074828 (or placebo) are administered every 8 weeks (Q8W) during the induction period, followed by 30, 100, or 300 mg Q8W or as required during the 88-week maintenance period.
- Study I6T-MC-AMAG is to be conducted in approximately 180 subjects with Crohn's disease (CD). Three IV doses of 200, 600, or 1000 mg LY3074828 (or placebo) will be administered Q4W. LY3074828-treated subjects with an improvement in CD score will either continue with this dose regimen, or will be administered 300 mg LY3074828 SC Q4W, over a period of 40 weeks. Subjects who receive placebo or who did not have a clinical improvement in CD score will receive 1000 mg LY3074828 IV Q4W. Subjects with clinical benefit may continue with 300 mg LY3074828 SC Q4W for an additional 52 weeks.

LY3074828 is currently being evaluated in 2 bioavailability studies:

- Study I6T-MC-AMAL is being conducted in approximately 72 healthy subjects. The relative bioavailability, absolute bioavailability, and tolerability of LY3074828 lyophilized and solution formulations will be assessed. Dosing using the IV route will allow the absolute bioavailability of LY3074828 to be determined.

- Study I6T-MC-AMAE is being conducted in approximately 54 healthy subjects. The study will assess relative bioavailability of LY3074828 solution formulation in pre-filled 1-mL syringes compared to lyophilized formulation (250 mg). Doses of 250 (2 x 1-mL syringes) and 500 mg (4 x 1-mL syringes) of LY3074828 are included in the assessment.

3.3. Benefit/Risk Assessment

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

Treatment-emergent ADAs have been observed in 2 of the 11 healthy subjects that have been administered SC doses of LY3074828; however, titers were ≤1:160. No clinically significant safety or tolerability concerns have been identified in patients or subjects to date for LY3074828 up to the highest dose given (single 1200-mg IV doses).

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

Possible device-based risks include local effects such as pain at the injection site from either the needle or the solution entry into the SC tissue, swelling, erythema, bleeding, and bruising. Systemic effects may include sweating, feeling faint, or fever, as a sign of infection. These risks are mitigated by sterile filling of the semi-finished syringes (SFSs), assembly of devices that meet regulatory standards, training of investigative site staff and subjects on proper injection techniques, and monitoring of the subjects to ensure injections are performed properly.

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

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

Table AMAQ.1. Objectives and Endpoints

Objectives	Endpoints
Primary Part A • To evaluate the PK of LY3074828 solution formulation after administration of 250-mg doses using 2 x 1-mL and 1 x 2-mL PFS injections in healthy subjects. • To assess the safety and tolerability of, and pain associated with, LY3074828 PFS administrations in healthy subjects.	Part A • The primary PK endpoints will be the C_{max}, AUC(0-t_{last}), and AUC(0-∞) of LY3074828. • Incidence of TEAEs. • SF-MPQ, including VAS pain score.
Part B • To compare the safety and tolerability of, and pain associated with, LY3074828 solution formulation after administration of 125- and 250-mg doses using 1-mL AI and 2-mL AI SC injections with different injection speeds (slow and fast) in healthy subjects.	Part B • Incidence of TEAEs. • SF-MPQ, including 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; SF-MPQ = Short Form McGill Pain Questionnaire; TEAE = treatment-emergent adverse event; VAS = visual analog scale.

5. Study Design

5.1. Overall Design

Study I6T-MC-AMAQ (AMAQ) is a single-center, randomized, parallel-treatment, open-label, Phase 1 single-dose study of LY3074828 solution formulation in healthy subjects. In Part A, PK, safety and tolerability of, and pain associated with, SC doses administered using 1- and 2-mL PFS injections will be evaluated. In Part B, safety and tolerability of, and pain associated with, single AI injections of 1- and 2-mL that will be administered with 2 different injection speeds will be evaluated.

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

Residential Period (2 days [Part A] or 3 days [Part B]): A total of approximately 72 subjects (approximately 36 subjects per study Parts A and B) who fulfill the eligibility criteria will be randomized to 1 of 2 dosing regimen arms within their assigned study part, with 18 subjects randomized to each arm in order to ensure completion of 16 subjects in each:

Part A

- Reference: 250 mg LY3074828 solution formulation, 2 x 1-mL 125-mg/mL PFS injections using an investigational PFS targeting 5- to 10-second injection time for each injection
- Test 1: 250 mg LY3074828 solution formulation, 1 x 2-mL 125-mg/mL PFS injection using an investigational PFS targeting 5- to 15-second injection time

Part B

- Tests 2 and 3: 250 mg LY3074828 solution formulation, 1 x 2-mL 125-mg/mL AI slow injection (Test 2; targeting approximately 13-second injection time) and fast injection (Test 3; targeting approximately 5-second injection time) using an investigational 2-mL AI
- Tests 4 and 5: 125 mg LY3074828 solution formulation, 1 x 1-mL 125 mg/mL AI slow injection (Test 4; targeting approximately 7-second injection time) and fast injection (Test 5; targeting approximately 4.5-second injection time) using an investigational 1-mL AI

For Part A, subjects will report to the clinical research unit (CRU) on Day -1 and will remain at the CRU until the scheduled procedures have been completed on Day 2. After randomization to either a 2 x 1-mL or a 1 x 2-mL 125-mg/mL PFS dose regimen, study drug will be administered by investigative site staff by SC injection in the abdomen in the morning of Day 1 after an overnight fast.

For Part B, subjects will report to the CRU on Day -1 and will remain at the CRU until the scheduled procedures have been completed on Day 3. Subjects will be randomized to receive, on Days 1 and 2, either a 1 x 1-mL or a 1 x 2-mL 125-mg/mL AI dose regimen. The allocated

AI dose regimen will be self-administered by slow and fast SC injection(s) on consecutive days (sequence randomized) in the abdomen 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 for Part A; Days 15, 43, and 86 for Part B) following dose administration on Day 1 to assess the PK, safety, and tolerability of, and pain associated with, LY3074828 PFS administrations for Part A, and to assess the safety and tolerability of, and pain associated with, LY3074828 investigational AI administrations for Part B.

Safety and tolerability will be explored by clinical laboratory tests, vital sign measurements, 12-lead ECGs, recording of AEs and product complaints, physical examinations/medical assessments, immunogenicity, and injection-site assessments. Pain assessments will be made using the Short Form McGill Pain Questionnaire (SF-MPQ), which includes a subject-assessed injection-site pain visual analog scale (VAS).

5.2. Number of Participants

A total of approximately 72 subjects (approximately 36 subjects per study Parts A and B) who fulfill the eligibility criteria will be randomized to 1 of 2 dosing regimen arms within their assigned study part, with 18 subjects randomized to each arm in order to ensure completion of 16 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 for Part A or up to and including at least Day 15 for Part B. A maximum of 4 subjects per arm per study part 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. Healthy subjects are frequently used in the assessment of bioavailability of both small and large molecules.

For Part A, 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 for Part A 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.

For Part B, only an evaluation of safety and tolerability of, and pain associated with, the investigational AI administrations is intended. Pharmacokinetic samples are collected only in conjunction with immunogenicity samples to provide concentrations of LY3074828 to aid in the interpretation of ADA data if needed.

For Part A, 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.

For Part B, a crossover design was chosen as PK analysis is not an endpoint and a relatively short time between injections will allow a more accurate comparison of injection-site pain by subjects

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

5.5. Justification for Dose

CCI [redacted]

Doses up to 1200 mg were found to be well tolerated when administered by IV infusion in healthy subjects in the single-dose Study AMAD. 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 (e.g., 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 followed by a negative serum pregnancy test within 24 hours prior to exposure
- 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 (e.g., 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 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, and/or hepatitis B core antibody

[22] are women who are lactating

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

[24] have donated blood of more than 500 mL within 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 steroids within 1 month of screening, or intend to during the study

[31] are immunocompromised

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

[33] have significant allergies to humanized monoclonal antibodies

[34] have clinically significant multiple or severe drug allergies, or intolerance to topical corticosteroids, or severe 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 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 in Part A, and Day -1, Day 15, and Day 43 in Part B). 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 evaluates the PK, safety, and tolerability of, and pain associated with, LY3074828 solution formulation SC dose administered by investigational site staff using 2 x 1-mL and 1 x 2-mL PFS injections (Part A); and compares the safety and tolerability of, and pain associated with, 1 x 1-mL and 1 x 2-mL AI injections self-administered with 2 different injection speeds (Part B).

Using the investigational 2-mL AI, the targeted injection duration will be approximately 13 seconds for slow injection rate and approximately 5 seconds for fast injection rate. Using the investigational 1-mL AI, the targeted injection duration will be approximately 7 seconds for slow injection rate and approximately 4.5 seconds for fast injection rate. Manual injections using the investigational PFS should target an injection duration of about 5 to 10 seconds for 1-mL PFS for each injection and about 5 to 15 seconds for 2-mL PFS, to approximate the injection time range for AIs. 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 AMAQ.2 and Table AMAQ.3 show the dosing regimens for Part A and Part B, respectively.

Table AMAQ.2. Dosing Regimens Administered – Part A

Dosing Regimen	PFS (250 mg)	PFS (250 mg)
Reference/test	**Reference**	**Test 1**
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 rate	5 to 10 seconds	5 to 15 seconds
Formulation and presentation	Solution in a PFS	Solution in a PFS

Abbreviations: PFS = pre-filled syringe.

Table AMAQ.3. Dosing Regimens Administered – Part B

Dosing Regimen	2-mL AI (250 mg)	1-mL AI (125 mg)
Reference/test	**Test 2 and Test 3**	**Test 4 and Test 5**
Product	LY3074828	LY3074828
Dose	250 mg	125 mg
Concentration	125 mg/mL	125 mg/mL
Injection volumes	1 × 2 mL (2 mL total)	1 × 1 mL (1 mL total)
Number of injections	1	1
Injection rate	Approximately 13 seconds (Test 2) Approximately 5 seconds (Test 3)	Approximately 7 seconds (Test 4) Approximately 4.5 seconds (Test 5)
Formulation and presentation	Solution in an AI	Solution in an AI

Abbreviations: AI = autoinjector.

Investigational AIs will be assembled at the site by Lilly Delivery and Device Research and Development engineers. Device Development Quality Assurance will inspect the assembled investigational devices on site to ensure basic good manufacturing practice (GMP) guidelines are met, and that assembly is performed as per GMP procedures, prior to use in the clinical trial. The investigational PFSs containing LY3074828 will be supplied by Lilly fully assembled.

Adjustments to the device (such as changing the spring) will be based on injection duration and tolerability/AEs (pain, bleeding, bruising, leakage, induration, swelling, pruritus, and erythema/redness), and will be performed on site. Device issues that result in AEs will be reported as product quality complaints (PCs).

All injections, whether administered by PFS or AI, will be given into the lower quadrant of the abdomen, with site staff or subject selecting left or right quadrant when a single injection is being given. For administrations requiring 2 injections, injections will be given into separate lower quadrants (right and left). Investigational product administered using PFS will be administered to subjects on-site by designated trained clinical site personnel. Investigational product administered using AI will be self-administered by subjects on-site after receiving instruction from trained clinical site personnel.

Further information regarding SC administration will be included in the device Instructions for Use (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 GMP, and labeled according to the country's regulatory requirements. The following products will be supplied by Lilly:

- pre-assembled investigational LY3074828 PFSs, 1-mL and 2-mL
- LY3074828 (solution for injection) SFS

Each SFS will be supplied as a 1- or 2-mL single-use syringe designed to deliver LY3074828 125 mg/mL. Members of Lilly Delivery and Device Research and Development will attend the study site and assemble the SFS and appropriate device components, to form the investigational AIs.

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 within 1 study part (Part A or Part B) to 1 of 2 dosing regimen arms (Table AMAQ.2 and Table AMAQ.3). In addition, the sequence of injections on Days 1 and 2 (fast/slow versus slow/fast) for subjects participating in Part B will be randomized.

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

7.2.1. Selection and Timing of Doses

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

7.3. Blinding

This is an open-label study; however, subjects in Part B will not be informed as to whether the AI is fast or slow injection speed.

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 an investigational PFS
- LY3074828 in an SFS incorporated into an investigational AI

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 the sponsor, during transit for all IP received and ensure any discrepancies are reported and resolved before use of the study treatment.

The SFSs assembled into AIs containing LY3074828 and the PFSs containing LY3074828 should be allowed to warm to room temperature for at least 30 minutes before use.

Parts to be used for the assembly of AIs may be stored at room temperature.

Only participants enrolled in the study may receive IP or study materials, and only authorized site staff may supply 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. 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 performed as shown in the Schedule of Activities (Section 2). The reason for, and the date of discontinuation, will be collected for all subjects.

8.1.1. Discontinuation of Inadvertently Enrolled Subjects

If the sponsor or investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly CP or CRP and the investigator to determine if the subject may continue in the study. If a subject is inadvertently enrolled into Part B and this is discovered prior to the scheduled administration of the second dose, the second dose would not be administered. Any subjects that are inadvertently enrolled subjects 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.

Investigators must document their review of each laboratory safety report.

9.1. Efficacy Assessments

This section is not applicable for this study.

9.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

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

After the informed consent form 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 subject 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, 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 investigational device (AI) or to the use of the study device (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 serious adverse event 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 investigational PFS or investigational AI in this clinical study.

Adverse events of special interest for LY3074828 are:

- infection
- injection-site reactions
- allergic/hypersensitivity reactions

If infections, injection-site reactions, 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 identifies 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.

9.2.1.4. Adverse Event Monitoring with a Systematic Questionnaire

Before administering the SF-MPQ, study site personnel will question the subject about any change in the preexisting condition(s) and the occurrence and nature of any AEs.

Injection-site assessment at the scheduled protocol time points will not be double reported in the AE form, but will be captured in the eCRF.

Only *serious* AEs elicited through the SF-MPQ are to be recorded as AEs via electronic data entry and reported to Lilly or its designee within 24 hours as SAEs.

Unsolicited AEs (e.g., headache, redness reported by subjects during the follow-up period) will be reported in the AE form.

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 Product Complaint 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 Product Complaint Form with the product.

9.3. Treatment of Overdose

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

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

Refer to the study drug IB for further details.

9.4. Safety

9.4.1. Laboratory Tests

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

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

9.4.2. Vital Signs

For each subject, vital 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.

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

9.4.3. Electrocardiograms

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

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

If a clinically significant finding is identified (including, but not limited to, changes in QT/corrected QT 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 Instructions

Prior to the PFS or AI injection, the investigator or his/her designee will prepare the subject's skin. The injections will be given according to the instructions provided by the sponsor. Pre-filled syringe injections into the abdomen will be administered by investigative site staff. All subjects will receive training on how to use the AI to self-administer into the abdomen. The investigator or his/her designee will answer any questions the subject may have and will demonstrate the steps required for injection according to the IFU. Subjects will be monitored while using the AI to ensure successful self-injections. Investigative site staff who observe the subject's self-injection with the AI will fill out the AI Use Assessment Questionnaire. 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.

9.4.4.3. Injection Speed Assessments and Video Recording

Injection duration will be measured by a calibrated stopwatch by qualified trained study staff. For Part A, the duration of injection for the PFSs will be defined as the time between when the plunger rod is pressed down and when all of the LY3074828 solution is injected. For Part B, the duration of injection for the AIs 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.

For Part B, a video recorder will be used to record the AI injection site and the device as it is being used. The video recordings may be examined to explore device functionality. The subject's face, voice, or identifiable markings will not be video recorded. The video recording will be identified by the subject number. The video data will be managed by the sponsor and securely stored electronically in the sponsor's network. Further analysis of the video recordings may be performed by qualified sponsor personnel after completion of the study.

9.4.4.4. Injection-site Assessments

While the SF-MPQ will be administered to capture data for pain on injection, other injection-site reactions will be captured in the subjects' eCRF as AEs (including erythema, induration, categorical pain, pruritus, and edema).

9.4.4.5. 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.

9.4.4.6. Injection-site Pain

9.4.4.6.1. Short Form McGill Pain Questionnaire

Acute pain from SC injection will be assessed using the 15-item short form of the SF-MPQ (Melzack 1987) modified to meet the purpose of the study at times specified in the Schedule of Activities (Section 2).

As part of the SF-MPQ, pain measurements will be quantified using the 100-mm validated VAS 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 on a scale of 0 to 100 mm on the line immediately (approximately within 5 minutes) following the start of the injection and at the time points listed in the Schedule of Activities (Section 2).

For 1-mL PFS, assessments are to be completed on the first of the 2 injections only.

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 injection-site reactions
- PCs

When appropriate, the Lilly CP or CRP will consult with the functionally independent Global Patient Safety (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 for Parts A and B. 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.

Pharmacokinetic samples will be collected in both Part A and Part B; however, PK statistical analyses will only be performed for Part A. Samples from Part B will be stored and will only be sent for bioanalysis at a later date based on immunogenicity or safety results from Part B of the study.

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.

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) for Parts A and B. 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. Treatment-emergent ADAs are defined as either a 2-fold

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

Given that the subjects have only a single exposure to LY3074828 in Part A, and only 2 doses over an approximately 24-hour period in Part B, any ADA response is anticipated to peak and then diminish due to lack of additional exposures. Subjects will have ADA sampling at baseline (predose) and Days 15, 29, 57, and 85 in Part A, and at baseline (predose) and Days 15, 43, and 86 in Part B. Subjects that are observed to have a titer greater than 1:1000, or non-decreasing titers that meet the definition of TE-ADA, will be requested to return every 3 months after the last sample to have follow-up ADA samples tested until the titer has returned to within 1 titer of their baseline or is clearly trending back to the baseline titer. The rationale for the definitions of both TE-ADA and return to baseline is based on the premise that a 1-titer change may result from expected assay variability.

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

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

A total of approximately 72 subjects (approximately 36 subjects per study Parts A and B) who fulfill the eligibility criteria will be randomized to 1 of 2 dosing regimen arms within their assigned study part, with 18 subjects randomized to each arm in order to ensure completion of 16 subjects in each. The estimated total variability (coefficient of variation) in AUC from time zero to infinity AUC(0-∞), AUC from time zero to time t, where t is the last sample with a measurable concentration (AUC[0-t_{last}]), and maximum observed drug concentration (C_{max}) was 49%, 49%, and 23%, respectively, in Study AMAA following a single SC dose of 120 mg LY3074828. The coefficient of variation of 49% was used for precision estimates and is assumed for all dosing regimen arms. A sample size of 64 subjects will provide a precision, in log scale, of approximately 0.28 for the geometric means ratio in AUC(0-∞), AUC(0-t_{last}), and C_{max} of 1- to 2-mL solution formulation injection. That is, there is a 90% probability that the half-length of the 90% confidence interval (CI) of the geometric means ratio in log scale is not larger than 0.28. Subjects who are randomized but not administered treatment, or subjects that are administered treatment but do not have PK and ADA samples collected up to and including Day 57, may be replaced (maximum of 4 per arm per study part) to ensure that approximately 16 subjects from each dosing regimen arm 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 in Part A. 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

For Parts A and B, the intensity of pain at each injection site immediately (approximately within 5 minutes) following the start of the injection will be evaluated, as reported by the subject and measured according to the 0 to 100 mm VAS that forms part of the SF-MPQ. Assessments will also be performed at 15, 30, 60, 120, and 240 minutes post injection; however, the primary endpoint will be the 0-hour assessment.

Descriptive statistics will be used to summarize the intensity and type of pain at each time point as captured by the SF-MPQ.

In Part A, a linear fixed-effects model will be used to analyze the 0-hour (post-injection) pain VAS score and SF-MPQ total score. The model will include treatment (Reference or Test 1) as a fixed effect. The least squares (LS) means and differences in LS means (between Test 1 and Reference) 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.

A similar model will be used to analyze the 0-hour (post-injection) pain VAS score and SF-MPQ total score in Part B.

The following comparisons will be performed in Part B:

- Test 2 versus Test 3 (slow versus fast injection for 2-mL AI)
- Test 4 versus Test 5 (slow versus fast injection for 1-mL AI)

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 dosing regimen.

10.3.1.2.3. Injection-site Assessments

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

10.3.1.2.4. Statistical Evaluation of Other Safety Parameters

Other safety parameters that will be assessed include clinical laboratory parameters, vital signs, and ECG parameters. The parameters, and changes from baseline (predose) where appropriate, will be listed and summarized using standard descriptive statistics. Additional analyses will be performed if warranted upon review of the data.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

For Part A, PK 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 $t_{1/2}$, 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.

For Part B, no PK parameters will be evaluated. Pharmacokinetic samples are collected only in conjunction with immunogenicity samples to provide serum concentrations of LY3074828 to aid in the interpretation of ADA data if needed. Samples will be stored and will only be sent for bioanalysis at a later date based on immunogenicity or safety results from Part B of the study.

10.3.2.2. Pharmacokinetic Statistical Inference

For Part A, the AUC(0-∞), AUC(0-t_{last}), and C_{max} will be log-transformed and analyzed using linear fixed-effects model. The model will include dosing regimen arm as a fixed effect. The dosing regimen differences between the Test 1 arm and the Reference arm will be back-transformed to present the ratios of geometric LS means and the corresponding 90% CI.

The t_{max} of LY3074828 between the 2 x 1-mL PFS (Reference) and the 1 x 2-mL PFS (Test 1) will be analyzed using a Wilcoxon rank sum test for Part A. 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 for Part A 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.

For Parts A and B of the study, available safety data will be reviewed at approximately Day 30 in order to review emerging safety and tolerability data.

For Part A of the study, data review is scheduled to occur when safety and PK data through approximately Day 57 (8 weeks postdose) become available for at least 12 subjects from each dosing regimen arm. The purpose of the data review is to trigger Chemistry, Manufacturing, and Control processes with respect to LY3074828 formulation, and to inform dose selection for Phase 3 first registration.

10.3.7. Interim Analyses

An exploratory interim analysis is planned for this study. This will be for internal purposes only.

11. References

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Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	anti-drug antibody
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AI	autoinjector
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AUC	area under the concentration versus time curve
AUC(0-∞)	area under the concentration versus time curve from time zero to infinity
AUC(0-t_{last})	area under the concentration versus time curve from time zero to time t, where t is the last sample with a measurable concentration
BMI	body mass index
CD	Crohn's disease
CI	confidence interval
CL/F	apparent total body clearance of drug calculated after extra-vascular administration
C_{max}	maximum observed drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the trial-related requirements, good clinical practice 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
CPK	creatine phosphokinase
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 trial are those who have been assigned to a treatment.
enter	Subjects entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
GCP	good clinical practice
GMP	good manufacturing 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 trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical trial data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
IP	investigational product
IRB	institutional review board
IV	intravenous(ly)
LS	least squares
open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participant are aware of the drug therapy received during the study.

PC	product quality complaint
PFS	pre-filled syringe
PK	pharmacokinetic(s)
Q4W	every 4 weeks
Q8W	every 8 weeks
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 trial.
SF-MPQ	Short Form McGill Pain Questionnaire
SFS	semi-finished syringe
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	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.
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)

Urinalysis[a]
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Bilirubin
- Urobilinogen
- Blood
- Nitrite
- Microscopic examination of sediment[b]

- Ethanol testing[d]
- Urine drug screen[d]
- QuantiFERON-TB Gold test[a,e]

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

- Serum Pregnancy test[f,g]
- Hormone Panel
  - Follicle-stimulating hormone [e,h]

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 Urine drug screen and ethanol level (determined via breath 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 Performed at screening only.

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

g Refer to Section 2 for specific sampling timing.

h To be done for women 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 subjects. Individual investigators may have additional local requirements or processes. Study-specific recruitment material should be approved by Lilly.

Ethical Review

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

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

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

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

Regulatory Considerations

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

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

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

Protocol Signatures

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

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

Final Report Signature

The final report coordinating investigator or designee will sign the clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The 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/scientist.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin time
WBC	Prothrombin time, INR
Neutrophils	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Conjugated bilirubin	Hepatitis E antibody, IgM
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

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

Protocol I6T-MC-AMAQ Sampling Summary – Part A

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	19.5	1	19.5
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			190
Total for clinical purposes [rounded up to nearest 10 mL]			190

[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).

Protocol I6T-MC-AMAQ Sampling Summary – Part B

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	19.5	1	19.5
Clinical laboratory tests[a]	12.5	4	50
Pharmacokinetics[b]	2	7	14
Immunogenicity[a]	10	4	40
Pregnancy tests	3.5	4	14
Pharmacogenetics	10	1	10
Total			147.5
Total for clinical purposes [rounded up to nearest 10 mL]			150

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

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

Overview

Protocol I6T-MC-AMAQ, A Safety, Tolerability, and Pharmacokinetic Study of 1- and 2-mL Injections of LY3074828 Solution Using Investigational Pre-filled Syringes and Investigational Autoinjectors in Healthy Subjects, has been amended. The new protocol is indicated by Amendment (b) 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 described in the following table:

Table AMAQ.4. Amendment Summary for Protocol I6T-MC-AMAQ Amendment(b)

Section # and Name	Description of Change	Brief Rationale
Section 10.3.7. Interim Analysis	An update has been made to introduce an exploratory interim analysis to this study.	An exploratory interim analysis is planned for this study.

Revised Protocol Sections

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

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.~~ An exploratory interim analysis is planned for this study. This will be for internal purposes only.

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