Protocol I6T-MC-AMBD (c)

A Single-Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of LY3074828 in Healthy Chinese Subjects

NCT04137380

Approval Date: 28-June-2020

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Confidential Information

LY3074828

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Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly: 10 July 2018
Amendment (a) Electronically Signed and Approved by Lilly: 19-Sep-2018
Amendment (b) Electronically Signed and Approved by Lilly: 05-Sep-2019
Amendment (c) Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 28-Jun-2020 GMT

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1. Protocol Synopsis

Title of Study:

A Single-Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of LY3074828 in Healthy Chinese Subjects

Rationale:

Study I6T-MC-AMBD (AMBD) is a clinical evaluation of LY3074828 in Chinese subjects, and is being conducted to investigate the safety, tolerability, and pharmacokinetics (PK) of single-dose administration of LY3074828 in this population. Data from completed preclinical and clinical studies support the administration to healthy Chinese subjects within the dose range planned for this study. This study will support future Phase 3 clinical studies in Chinese patients.

Objectives/Endpoints:

Objectives	Endpoints
Primary • To assess the safety and tolerability of single LY3074828 IV doses (300, 600, and 1200 mg) and single SC doses (200 and 400 mg) in healthy Chinese subjects.	• Incidence of TEAEs. • VAS pain score.
Secondary • To evaluate the PK of single LY3074828 IV doses (300, 600, and 1200 mg) and single SC doses (200 and 400 mg) in healthy Chinese subjects.	• Including C_{max}, AUC(0-t_{last}), AUC(0-∞), and t_{max} of LY3074828.

Abbreviations: 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; IV = intravenous; PK = pharmacokinetic; SC = subcutaneous; TEAE = treatment-emergent adverse event; t_{max} = time to maximum observed drug concentration; VAS = visual analog scale.

Summary of Study Design:

Study I6T-MC-AMBD (AMBD) is a subject- and investigator-blinded, randomized, parallel-group, placebo-controlled, Phase 1 single-dose study of LY3074828 in healthy Chinese subjects. Native Chinese subjects born in China, with all 4 grandparents and both parents of Chinese origin will be enrolled. The study will consist of 5 planned dose cohorts: 3 intravenous (IV) dose cohorts (300 mg, 600 mg, and 1200 mg) and 2 subcutaneous (SC) dose cohorts (200 mg and 400 mg). Subjects will be randomized within each cohort to receive LY3074828 (10 subjects) or placebo (2 subjects).

Subjects will report to the clinical research unit (CRU) on Day -1. After randomization, study drug will be administered by investigative site staff by either IV administration using a forearm vein or SC injection in the abdomen using pre-filled syringes in the morning of Day 1 after an overnight fast. Subjects will remain at the CRU until the scheduled procedures have been completed on Day 2, and will then be discharged. Subjects will be followed for approximately 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, physical examinations/medical assessments, immunogenicity, and injection-site assessments. Pain assessments will be made using a subject-assessed injection-site pain visual analog scale.

Dosing Regimen Arms and Duration:
Subjects will be randomized within each cohort to receive study drug or placebo:

- Cohort 1: a single dose of LY3074828 300 mg or placebo IV infused over at least 30 minutes (n=12; 10 LY3074828, 2 placebo)
- Cohort 2: a single dose of LY3074828 600 mg or placebo IV infused over at least 60 minutes (n=12; 10 LY3074828, 2 placebo)
- Cohort 3: a single dose of LY3074828 1200 mg or placebo IV infused over at least 2 hours (n=12; 10 LY3074828, 2 placebo)
- Cohort 4: a single dose of LY3074828 200 mg or placebo SC (n=12; 10 LY3074828, 2 placebo)
- Cohort 5: a single dose of LY3074828 400 mg or placebo SC (n=12; 10 LY3074828, 2 placebo)

Dosing of cohorts may be conducted in parallel or sequentially at the discretion of the investigator. Total duration of the study for each subject will be up to approximately 16 weeks (screening period ≤28 days, residential period of 3 days/2 nights, and outpatient follow-up period of approximately 12 weeks).

Number of Subjects:
Sixty subjects who fulfill the eligibility criteria may be enrolled into the study to try to ensure that approximately 50 subjects complete (10 subjects per cohort are required in order to provide the necessary safety and PK data). Furthermore, every effort should be made to enroll subjects so that at least 4 subjects per cohort are female. Each subject will participate in 1 of the 5 cohorts. Subjects who withdraw from the study will not be replaced. For analytical purposes, 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.

Statistical Analysis:
Safety parameters will be listed and summarized using standard descriptive statistics, as applicable.

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

The frequency of formation of antibodies to LY3074828 will be listed. If a neutralization assay is performed, the frequency of neutralizing antibodies will be listed.

Pharmacokinetic parameter estimates for LY3074828 will be calculated by standard noncompartmental methods of analysis. The primary parameters for PK analysis will be 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}). The secondary parameter for analysis will be the time to maximum observed drug concentration (t_{max}) of LY3074828. Other noncompartmental parameters, such as bioavailability following SC administration, half-life, clearance, and volume of distribution (apparent clearance and apparent volume of distribution for SC administration), may be reported.

No formal statistical analysis will be performed for this study. The PK parameters will be summarized by treatment and listed. Additional PK analyses may be conducted if deemed appropriate.

2. Schedule of Activities

Study Schedule Protocol I6T-MC-AMBD

	Screen-ing	**Days**													**Comments**
Procedure	≤28 days	**-1**	**1**	**2**	**4**	**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													
Subject admission to CRU		X													
Subject discharge from CRU				X											
Outpatient visit	X				X	X	X (SC only)	X	X	X	X	X	X	X	
Randomization			X												Subjects randomized to 1 cohort (dose level and administration) and to LY3074828 or placebo within each cohort.
LY3074828 or placebo administration			X												Intravenous or subcutaneous doses administered by investigative site staff. The maximum IV infusion rate is 10 mg per minute; thus, the 300-mg dose must be given over at least 30 minutes, 600 mg over at least 1 hour, and 1200 mg over at least 2 hours.
Medical history	X														
Weight, height, and BMI	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.

	Screen-ing	Days												Comments
Procedure	≤28 days	**-1**	**1**	**2**	**4**	**8** ±1d	**11** ±1d	**15** ±2d	**22** ±2d	**29** ±2d	**43** ±2d	**57** ±3d	**71** ±3d	**85/ED** ±3d	
Vital signs (supine): blood pressure, pulse rate, temperature (hour)	X	X	0, 6	24	X	X	X (SC only)	X	X	X	X	X	X	X	Times with respect to start of dosing. Single ECGs to be collected. ECGs, blood pressure, and pulse rate after 5 minutes supine. Zero-hour collection within 2 hours before dosing. Time allowances (minutes): 6-hour (±30), 24-hour (90). For vital sign assessments, temperature need only be included at predose and when clinically indicated.
12-lead ECG (hour)	X		0, 6	24										X	
AE review	X	X	X	X	X	X	X (SC only)	X	X	X	X	X	X	X	AE only after signing ICF. Device-related AEs collected as appropriate.
Chest X-ray	X														Posterior / anterior and lateral. Not required if chest X-ray was performed within the last 1 year, found to be normal, and report is available.
QuantiFERON®-TB Gold test or TB T-Spot test	X														See Section 9.4.4.1 for further details. regarding retest
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. See Appendix 2 for test details.

	Screen-ing	Days												Comments
Procedure	≤28 days	**-1**	**1**	**2**	**4**	**8** ±1d	**11** ±1d	**15** ±2d	**22** ±2d	**29** ±2d	**43** ±2d	**57** ±3d	**71** ±3d	**85/ED** ±3d	
FSH / serum pregnancy test	X	X								X		X		X	Serum pregnancy tests for all female subjects. 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		X	See Appendix 2 for test details.
Subcutaneous injection-site assessment for erythema, induration, categorical pain, pruritus, edema, visible bleeding, and bruising (hour)			0, 0.25	X		X		X							For Cohorts 4 and 5 only. Times with respect to the time of first injection. Time allowances (minutes): 0-hour (within 5 minutes following first injection), 0.25-hour (±5). Additional assessments performed if deemed necessary by the investigator.
Injection-site pain assessment (VAS) (hour)			0, 0.25, 0.5, 1, 2, 4												For Cohorts 4 and 5 only. Times with respect to the time of first injection. Time allowances (minutes): 0-hour (within approximately 1 minute after start of first injection), 0.25-hour (±5), 0.5-hour (±5), 1-hour (±5), 2-hour (±10) and 4-hour (±10) post first injection.

	Screen-ing	Days													Comments
Procedure	≤28 days	**-1**	**1**	**2**	**4**	**8** ±1d	**11** ±1d	**15** ±2d	**22** ±2d	**29** ±2d	**43** ±2d	**57** ±3d	**71** ±3d	**85/ED** ±3d	
LY3074828 pharmacokinetic sampling (hour)			0, EOI (IV only), 6	24	72	X	X (SC only)	X	X	X	X	X	X	X	Times with respect to start of infusion or time of first injection. Zero-hour collection within 2 hours before dosing. Time allowance (minutes): end of infusion (±2), 6-hour (±30), 24-hour (±90). Postdose samples are taken relative to the start of the infusion or time of first injection. End of infusion collection is relevant to IV administration only. Additional samples may be taken (see Section 9.6.1).
[redacted]			CCI [redacted]					[redacted]		[redacted]				[redacted]	[redacted]

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

Site should schedule activities as appropriate. If multiple procedures take place at the same time point, the following order should be used: ECG, vital signs, and venipuncture. Procedures specified as predose may be performed within 2 hours prior to planned dosing.

3. Introduction

3.1. Study Rationale

Study I6T-MC-AMBD (AMBD) is a clinical evaluation of LY3074828 in Chinese subjects, and is being conducted to investigate the safety, tolerability, and pharmacokinetics (PK) of single-dose administration of LY3074828 in this population. Data from completed preclinical and clinical studies support the administration to healthy Chinese subjects within the dose range planned for this study. This study will support future Phase 3 clinical studies in Chinese patients.

3.2. Background

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

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

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

Data from the clinical pharmacology development program are available for 1 completed Phase 1 study and 4 ongoing Phase 1 studies, as follows.

Completed Phase 1 study:

- Study I6T-MC-AMAA (AMAA): LY3074828 has been evaluated in 5 healthy subjects (single 120-mg SC doses) and in a total of 33 subjects with plaque psoriasis (single ascending IV doses of 5, 20, 60, 120, 200, 350, or 600 mg).

Ongoing Phase 1 studies:

- Study I6T-JE-AMAD (AMAD): A total of 43 healthy Japanese and Caucasian subjects were administered single IV doses of 60, 200, 600, 1200, or 2400 mg LY3074828 (or placebo), or single SC doses of 200 mg LY3074828 (or placebo).
- Study I6T-MC-AMAL (AMAL): A total of 67 healthy subjects were administered single IV or SC doses of 250 mg LY3074828.
- Study I6T-MC-AMAE (AMAE): A total of 54 healthy subjects were administered single SC doses of 250 mg or 500 mg LY3074828; the study is evaluating relative bioavailability of solution compared to lyophilized formulations.
- Study I9O-MC-AABA (AABA): A total of 72 healthy subjects were administered single IV doses of 1200 mg LY3074828, or single SC doses of 250, 1000, or 2400 mg LY3074828 (SC doses coadministered with LY9999QS).

No deaths, serious adverse events (SAEs), or discontinuations due to an adverse event (AE) were reported in any of the Phase 1 studies, as of the IB cutoff date.

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

There were no obvious trends in the pattern of AEs across studies apart from injection-site reactions. Injection-site pain, of short duration (usually hours), has been reported in both the completed and ongoing clinical pharmacology studies. In Study AMAA, injection-site pain (related to study drug) was reported in 3 out of 5 healthy subjects receiving 120 mg LY3074828 via SC administration; however, no infusion reactions were reported. Preliminary data from Studies AMAE and AMAL showed that most injection-site reactions were mild or moderate in severity, with severe injection-site pain reported in 2% of injection-site reactions in the 250-mg SC test formulation group.

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LY3074828 is currently being evaluated in 3 ongoing Phase 2 studies, as follows:

Study I6T-MC-AMAC (AMAC) is being conducted in approximately 250 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. During the open-label extension portion of this study in which IV infusions of 1000 mg of LY3074828 were administered, a patient experienced an acute anaphylactic reaction. As a result of this SAE, LY3074828 was discontinued for this patient.

- Study I6T-MC-AMAF (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 (AMAG) is being conducted in subjects with CD (85 subjects randomized, approximately 180 subjects planned). Three IV doses of 200, 600, or 1000 mg LY3074828 (or placebo) are administered Q4W. LY3074828-treated subjects with an improvement in CD score either continue with this dose regimen (with SC placebo to maintain blind), or are administered 300 mg LY3074828 SC (with IV placebo) Q4W, through Week 48. Subjects who receive placebo or who did not have a clinical improvement in CD score receive 1000 mg LY3074828 IV (with SC placebo) Q4W through Week 48. Subjects with clinical benefit may continue with 300 mg LY3074828 SC Q4W for an additional 52 weeks (open-label). Two events of anaphylaxis were reported in this study, with 1 occurring during an infusion of LY3074828. The other event also occurred during an intravenous infusion, but the study team remained blinded to study treatment. In both cases, the infusions of study medication were stopped and patients were treated with antihistamines, which resulted in resolution of the patients' symptoms. Both patients were discontinued from the study.

To date, evaluation of the unblinded safety data from Studies AMAF and AMAC have not revealed any dose-related safety or tolerability issues.

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%.

A lyophilized SC formulation was used in Studies AMAA and AMAD and is currently being used in the Phase 2 Studies AMAC, AMAF, and AMAG. Data from Study AMAL indicate that the PK of LY3074828 following SC administration is similar in subjects receiving the lyophilized formulation versus the solution formulation that will be used in Phase 3 studies. Preliminary data from Study AMAE also indicate that SC administration of the solution formulation using a pre-filled syringe (PFS) provides comparable LY3074828 exposure as the lyophilized SC formulation used in Phase 1 and 2 studies.

3.3. Benefit/Risk Assessment

Based on LY3074828 nonclinical and preliminary clinical data, there are no anticipated risks requiring monitoring beyond those for a typical humanized monoclonal antibody in human studies. As with other immunomodulatory

therapies, LY3074828 may increase the risk of developing an infection or may exacerbate an existing serious infection. These may include opportunistic infections and reactivation of latent infections, such as tuberculosis (TB) and hepatitis B. Subjects will therefore be screened for hepatitis B/C, human immunodeficiency virus (HIV), and TB. Immunomodulatory therapies may increase the risk of malignancies; however, due to only single doses of LY3074828 being administered in this study, it is not considered necessary to monitor for such effects.

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No clinically significant safety or tolerability concerns have been identified in patients or healthy subjects to date for LY3074828 up to the highest doses given (single 1200-mg IV doses and 2400-mg SC doses).

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

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

More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of LY3074828 are to be found in the IB.

4. Objectives and Endpoints

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

Table AMBD.1. Objectives and Endpoints

Objectives	Endpoints
Primary • To assess the safety and tolerability of single LY3074828 IV doses (300, 600, and 1200 mg) and single SC doses (200 and 400 mg) in healthy Chinese subjects.	• Incidence of TEAEs. • VAS pain score.
Secondary • To evaluate the PK of single LY3074828 IV doses (300, 600, and 1200 mg) and single SC doses (200 and 400 mg) in healthy Chinese subjects.	• Including C_{max}, AUC(0-t_{last}), AUC(0-∞), and t_{max} of LY3074828.
CCI • CCI	[redacted]

Abbreviations: 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; IV = intravenous; PK = pharmacokinetic; SC = subcutaneous; CCI [redacted]; TEAE = treatment-emergent adverse event; t_{max} = time to maximum observed drug concentration; VAS = visual analog scale.

5. Study Design

5.1. Overall Design

Study I6T-MC-AMBD (AMBD) is a subject- and investigator-blinded, randomized, placebo-controlled, parallel-group, Phase 1 single-dose study of LY3074828 in healthy Chinese subjects. Safety, tolerability, and PK of LY3074828 will be evaluated.

Native Chinese subjects born in China will be enrolled; all 4 biological grandparents and both biological parents must be of Chinese origin. Every effort should be made to enroll subjects so that at least 4 subjects in each cohort will be female. However, if the desired number of female subjects is not achieved, this will not constitute a protocol deviation.

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

Residential Period (3 days/2 nights): A total of approximately 60 subjects (12 subjects per cohort) who fulfill the eligibility criteria will be enrolled into the study. Subjects will be randomized within each cohort to receive study drug or placebo:

- Cohort 1: a single dose of LY3074828 300 mg or placebo IV infused over at least 30 minutes (10 LY3074828, 2 placebo)
- Cohort 2: a single dose of LY3074828 600 mg or placebo IV infused over at least 60 minutes (10 LY3074828, 2 placebo)
- Cohort 3: a single dose of LY3074828 1200 mg or placebo IV infused over at least 2 hours (10 LY3074828, 2 placebo)
- Cohort 4: a single dose of LY3074828 200 mg or placebo SC (10 LY3074828, 2 placebo)
- Cohort 5: a single dose of LY3074828 400 mg or placebo SC (10 LY3074828, 2 placebo)

Dosing of cohorts may be conducted in parallel or sequentially at the discretion of the investigator. Subjects will report to the clinical research unit (CRU) on Day -1. After randomization, study drug will be administered by investigative site staff by IV administration using a forearm vein or SC injection in the abdomen using PFSs in the morning of Day 1 after an overnight fast. Subjects will remain at the CRU until the scheduled procedures have been completed on Day 2, and will then be discharged.

Outpatient Follow-up Period (12 weeks): The follow-up period will include outpatient visits for a total of approximately 12 weeks (Days 4, 8, 11 [SC only], 15, 22, 29, 43, 57, 71, and 85) following dose administration on Day 1 to assess the safety, tolerability, and PK of LY3074828 in healthy Chinese subjects.

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

5.2. Number of Participants

Sixty subjects may be enrolled into the study to try to ensure that approximately 50 subjects complete (10 subjects per cohort are required in order to provide the necessary safety and PK data). Furthermore, every effort should be made to enroll subjects so that at least 4 subjects per cohort are female. Each subject will participate in 1 of the 5 cohorts. Subjects who withdraw from the study will not be replaced. For analytical purposes, 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.

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

A subject- and investigator-blinded, randomized, and placebo-controlled design is being used to minimize bias on safety and tolerability assessments.

The parallel group design has been chosen due to the long half-life of LY3074828 and to determine the incidence of ADA formation.

It is not considered necessary to conduct safety data reviews of previous cohorts (lower dose levels) prior to dosing. This is because sufficient safety cover has already been obtained from previous studies to dose the highest IV and SC doses planned in this study (see Section 5.5). Although sequential dosing of cohorts is not considered necessary from a safety perspective, it is anticipated that it may be preferred for logistical reasons. The relative dosing of cohorts (parallel or sequential) will therefore be at the discretion of the investigator.

A single dose on Day 1 will be given in order to evaluate the safety, tolerability, and PK profile of LY3074828 in healthy Chinese 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.

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6. Study Population

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

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

Screening will occur up to 28 days prior to enrollment. Subjects who are not enrolled within 28 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

6.1. Inclusion Criteria

Subjects are eligible for inclusion in the study only if they meet all of the following criteria at screening and/or enrollment:

[1] are overtly healthy male or female subjects, as determined by medical history and physical examination

[1a] male subjects:

- No male contraception required, except in compliance with specific local government study requirements
- Men should refrain from sperm donation for the duration of the study and for 12 weeks following dosing with the study drug

[1b] female subjects:

- 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)
    - Women of childbearing potential participating 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 of study drug

- Either one highly effective method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine device) or a combination of 2 effective methods of contraception (such as male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges) will be used. The subject may choose to use a double-barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide. It should be noted that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these methods are combined

- Women not of childbearing potential may participate and include those who are:
  - infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation) or congenital anomaly such as mullerian agenesis; or
  - postmenopausal – defined as either:
    - A woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had either:
      - cessation of menses for at least 1 year; or
      - at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone >40 mIU/mL; or
    - A woman 55 years 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] native Chinese (all 4 biological grandparents and both biological parents to be of Chinese origin)

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

[4] have a body mass index (BMI) of 18.0 to 32.0 kg/m^2, inclusive, at time of screening

[5] 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

[6] have venous access sufficient to allow for blood sampling and administration of investigational product (IP) or placebo as per the protocol

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

[8] 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:

[9] 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

[10] are Lilly employees or are employees of the third-party organizations involved with the study

[11] are currently enrolled in a clinical study involving an IP or any other type of medical research judged not to be scientifically or medically compatible with this study

[12] 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

[13] have previously completed or withdrawn from this study or any other study investigating LY3074828, and have previously received the IP

[14] have known allergies to LY3074828, humanized monoclonal antibodies, related compounds or any components of the formulation, or history of significant atopy

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

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

[17] have a history or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the IP; or of interfering with the interpretation of data

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

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

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

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

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

[23] are women who are lactating

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

[25] have donated blood of more than 400 mL within 1 month prior to screening

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

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

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

[29] show evidence of active or latent TB, as documented by medical history, examination, chest X-rays (posterior/anterior and lateral), and TB testing (positive or indeterminate for QuantiFERON® -TB Gold test or TB T-Spot test; 1 retest permitted following indeterminate result); 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. See Section 9.4.4.1 for further details.

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

[31] are immunocompromised

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

[33] 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

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

[35] have excessive tattoos over the abdomen that would interfere with injection-site assessments

[36] in the opinion of the investigator or Sponsor, are unsuitable for inclusion in the study

6.3. Lifestyle and/or Dietary Requirements

Throughout the study, subjects may undergo medical assessments and review of compliance with requirements before continuing in the study.

6.3.1. Meals and Dietary Restrictions

Subjects will fast overnight for at least 8 hours before dosing and 2 hours postdose (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 during the outpatient period, 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 measurement, and to abide by the CRU smoking guidelines.

6.3.3. Activity

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

6.3.4. 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. Treatment

7.1. Treatment Administered

The LY3074828 solution formulation (20 mg/mL) for IV infusion will be supplied by Lilly to the investigative site in a sterile vial manufactured to deliver 300 mg of LY3074828. Placebo for IV infusion will be the identical sterile solution without LY3074828, and will be supplied by Lilly to the investigative site in a vial designed to deliver 15 mL.

A 100-mg/mL LY3074828 solution formulation for SC injection will be supplied by Lilly to the investigative site in a PFS designed to deliver 1 mL. Further information regarding SC administration will be included in the device Instructions for Use for the PFS. Placebo for SC injection will be the identical sterile solution without LY3074828, and will be supplied by Lilly to the investigative site in a PFS designed to deliver 1 mL.

Table AMBD.2 shows the treatment regimens.

Table AMBD.2. Treatments Administered

Cohort	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5
Regimen	300 mg IV	600 mg IV	1200 mg IV	200 mg SC	400 mg SC
LY3074828 concentration (or placebo)	20 mg/mL	20 mg/mL	20 mg/mL	100 mg/mL	100 mg/mL
Volume per dose	15 mL	30 mL	60 mL	2 mL	4 mL
Infusion duration (minutes)	≥30	≥60	≥120	NA	NA

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

LY3074828 will be administered using a forearm vein as a slow IV infusion at an infusion rate of no greater than 10 mg per minute. The duration of the placebo infusions will match those of the LY3074828 infusions to maintain subject and investigator blinding to study treatment. Subcutaneous administration of the 200-mg dose of LY3074828 or placebo will be given by investigative site staff as 2 x 1-mL injections, with 1 injection into the skinfold of the left lower abdominal wall and the other into the skinfold of the right lower abdominal wall. The SC administration of the 400-mg dose of LY3074828 will be given by investigative site staff as 4 x 1-mL injections, with the first 2 injections given into separate lower abdominal quadrants, and the final 2 injections given into separate upper abdominal quadrants.

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

The investigator or designee is responsible for returning all unused medication to Lilly or its designee at the end of the study.

The site may destroy used syringes 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 materials.

7.1.1. Packaging and Labeling

LY3074828 and placebo will be supplied to the investigator by Lilly or its designee. Clinical trial materials will be labeled according to the country's regulatory requirements. All IPs will be stored, inventoried, reconciled, and destroyed according to applicable regulations. Clinical trial materials are manufactured in accordance with current good manufacturing practices.

Study drug will be supplied as a single-use solution vial or a single-use PFS containing LY3074828 or placebo with study-specific labels. The 15-mL vial of LY3074828 is manufactured to deliver 300 mg (20 mg/mL). The 1-mL PFS is manufactured to deliver 100 mg (100 mg/mL). LY3074828 cannot be distinguished visually from placebo. Vials and PFSs will be supplied in cartons, with the appropriate quantity specific to the planned dispensing schedule of the IP.

7.2. Method of Treatment Assignment

Subjects will be randomized to LY3074828 or placebo within each cohort.

Randomization will be performed using a randomization table.

7.2.1. Selection and Timing of Doses

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

7.3. Blinding

This is a subject- and investigator-blinded study. The Sponsor and site pharmacists will be unblinded. Blinding will be maintained throughout the conduct of the study.

Emergency codes will be available to the investigator. A code, which reveals the treatment for a specific study subject, may be opened during the study only if the subject's well-being requires knowledge of the subject's treatment assignment.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted for medical management of the event. The subject's safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

Upon completion of the study, all codes must be returned to Lilly or its designee.

7.4. Dose Modification

Dose adjustments are not permitted in this study.

7.5. Preparation/Handling/Storage/Accountability

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

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

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

7.6. Treatment Compliance

The 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, until the subject's last visit. However, stable doses of oral contraceptive or hormone-replacement therapy (estrogen and thyroid) 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 procedures as shown in the Schedule of Activities (Section 2). The reason for, and the date of discontinuation, will be collected for all subjects.

8.1.1. Discontinuation of Inadvertently Enrolled Subjects

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

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
- Investigator Decision
    - the investigator decides that the subject should be discontinued from the study
- Subject Decision
    - the subject, or legal representative, requests to be withdrawn from the study.

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.

Unless otherwise stated in subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

This section is not applicable 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, concomitant treatment, or pathologies.

A "reasonable possibility" means that there is a potential 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 (for example, drug delivery system) 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 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 product complaint (PC) should also be reported.

For the purpose of this protocol, "unanticipated" adverse device effect means any SAE alleged to be associated with 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 PFS 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.

Although an increased risk of malignancy may be associated with immunomodulatory therapies, such effects will not be monitored in this study as subjects will only receive a single dose of LY3074828 or placebo.

Depression and suicidality may be increased with certain autoimmune disorders. For this program of work, and where consistent with the study protocols, patients should be monitored for signs and symptoms of such behavior. Specific monitoring (e.g. Columbia Suicide Severity Rating Scale, Hamilton Depression Rating Scale) is not considered necessary for this study as the study population is healthy subjects (i.e. do not have autoimmune disorders such as ulcerative colitis or CD) and only single doses will be administered.

9.2.1.3. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator reports as related to IP or procedure. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.1.4. Adverse Event Monitoring with a Systematic Questionnaire

Before the self-assessed pain VAS is conducted (see Section 9.4.4.2.3), study site personnel will question the subject about any change in the preexisting condition(s) (first assessment time point only) and the occurrence and nature of any AEs.

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 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).

With the exception of safety laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a local laboratory used for the study.

9.4.2. Vital Signs

For each subject, vital sign measurements 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 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 which includes a QuantiFERON-TB Gold test or TB T-Spot 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. Subcutaneous Injection-site Assessments

9.4.4.2.1. Subcutaneous Injection-Site Reactions

Injection-site reactions will be evaluated through the collection of pain assessments and specific site assessments for local tolerability which will evaluate erythema, induration, categorical pain, pruritus, edema, and bruising as indicated in the Schedule of Activities (Section 2). Data from injection site evaluations (including pain VAS [9.4.4.2.3]) which are recorded as a result of specific questionnaires will not be reported as AEs. Any spontaneous reports by the subject will be reported as AEs. Additionally, if during the assessment of the injection sites, a clinically significant reaction (including pain) is observed by site staff, an AE will be reported at the discretion of the Investigator. For injection site reactions reported as an AE, additional characterization of the event will be documented using the injection site eCRF form.

9.4.4.2.2. Subcutaneous 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. Injection site bleeding may be recorded as AE at the discretion of the investigator.

9.4.4.2.3. Subcutaneous Injection-site Pain Visual Analog Scale

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 first injection and at the time points listed in the Schedule of Activities (Section 2).

9.4.5. Safety Monitoring

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

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

- trends in safety data
- laboratory analytes
- AEs, including monitoring of incidence of any nature of any infections, injection-site reactions, and allergic/hypersensitivity 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 creatinine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator based on consultation with the Lilly 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 immunogenic response with any biological agent, including hypersensitivity reactions (including non-immediate hypersensitivities), anaphylactic reactions, and infusion-related reactions. Symptoms and signs that may occur as part of such a response include, but are not limited to, fever, chills, weakness of limbs, rash, itching, urticaria, dizziness, headache, tightening of throat, and wheezing. 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. Any potential hypersensitivity events will be evaluated, during the trial level safety review and/or the preparation of the study report, by a Lilly CRP based on accepted criteria (Sampson et al. 2006).

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 2 mL each will be collected to determine the serum concentrations of LY3074828. A maximum of 3 samples may

be collected at additional time points during the study if warranted and agreed upon between 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.

Drug concentration information that may unblind the study will not be reported to investigative site or blinded personnel until the study has been unblinded.

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. Analyses of samples collected from placebo-treated subjects are not planned.

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

CCI

CCI [redacted]

9.7. Biomarkers

This section is not applicable for this study.

9.8. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Sixty subjects who fulfill the eligibility criteria may be enrolled into the study to try to ensure that approximately 50 subjects (10 subjects per cohort) complete. The number of subjects in Study AMBD is not sufficient for any formal ethnic comparison, but the safety, tolerability, and PK data will be assessed in Chinese subjects and will be used to support the inclusion of Chinese subjects in future studies involving LY3074828.

The sample size is customary for Phase 1 studies evaluating safety and PK, and is not powered on the basis of statistical hypothesis testing.

Subjects who withdraw from the study will not be replaced. For analytical purposes, 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.

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, 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 data from all subjects who receive IP and have evaluable PK. Safety analyses will be conducted for all enrolled subjects, whether or not they completed all protocol requirements. Analysis will be according to the treatment the subjects actually received.

Additional exploratory analyses of the data will be conducted as deemed appropriate. CCI [redacted]

No adjustments for multiple comparisons will be made.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

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

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

new or increased in severity during the study. Each symptom will be classified by the most suitable term from the medical regulatory dictionary.

The number of IP- and device-related SAEs and any related PCs will be reported.

10.3.1.2. Statistical Evaluation of Safety

10.3.1.2.1. Injection-site Pain

The intensity of pain at the injection sites immediately (approximately within 1 minute after start of first injection, designated as "0-hour assessment") following the start of the first injection will be evaluated, as reported by the subject and measured according to the 0 to 100 mm VAS. Assessments will also be performed at 0.25, 0.5, 1, 2, and 4 hours post first injection; however, the 0-hour assessment will be considered the primary endpoint for injection-site pain assessment.

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

10.3.1.2.2. Injection-site Assessments

Incidence of erythema, induration, categorical pain, pruritus, edema, bleeding, and bruising will be listed.

10.3.1.2.3. Statistical Evaluation of Other Safety Parameters

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

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for LY3074828 will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be AUC 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}) for LY3074828. The secondary parameter for analysis will be the time to maximum observed drug concentration (t_{max}) of LY3074828. Other PK parameters, such as bioavailability following SC administration, $t_{1/2}$, clearance, and volume of distribution (apparent clearance and apparent volume of distribution for SC administration), may be reported.

10.3.2.2. Pharmacokinetic Statistical Inference

No formal statistical analysis will be performed for this study. The PK parameters will be summarized by treatment and listed. Additional analyses may be conducted as 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.

CCI [redacted]

[redacted]

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.

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.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	anti-drug antibody
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AUC	area under the concentration versus time curve
AUC(0-∞)	area under the concentration versus time curve from time zero to infinity
AUC(0-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
CL/F	apparent total body clearance of drug calculated after extra-vascular administration
C_{max}	maximum observed drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CP	clinical pharmacologist
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRU	clinical research unit
ECG	electrocardiogram
eCRF	electronic case report form

enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the study are those who have been assigned to a treatment.
enter	Subjects entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
GCP	good clinical practice
GPS	Global Patient Safety
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IL-23	interleukin-23
informed consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
investigational product (IP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IV	intravenous(ly)
PC	product complaint
PFS	pre-filled syringe
PK	pharmacokinetic(s)
Q4W	every 4 weeks
Q8W	every 8 weeks
randomize	The process of assigning subjects to an experimental group on a random basis.
SAE	serious adverse event
SC	subcutaneous(ly)

screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life associated with the terminal rate constant
TB	tuberculosis
TBL	total bilirubin
CCI	[redacted]
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
Th	T helper
t_{max}	time to maximum observed drug concentration
ULN	upper limit of normal
VAS	visual analog scale
V_z/F	apparent volume of distribution during the terminal phase after extra-vascular administration

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests

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

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

a Performed by local laboratory. 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, conjugated (direct) bilirubin and unconjugated (indirect) bilirubin may be measured.

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

e Performed at screening only.

f Performed by local laboratory at screening.

g Serum pregnancy tests for all female subjects; women with confirmed postmenopausal status at Screening can be exempted from further pregnancy tests during the study.

h Refer to Section 2 for specific sampling timing.

i 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. 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 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 ethical review board (ERB) was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

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

The study site's ERB 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.

If the study is conducted at more than 1 site, the investigator with the most enrolled subjects will serve as the final report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the final report coordinating investigator.

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 ERB 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 ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Conjugated (direct) 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 = creatinine 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 table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study. Fewer venipunctures and blood draws may actually occur, but this will not require a protocol amendment.

Protocol I6T-MC-AMBD Sampling Summary

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	6	75
Pharmacokinetics[b]	2	16	32
Immunogenicity[a]	10	4	40
Pregnancy tests	3.5	4	14
Total			180.5
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).

Appendix 6. Protocol Amendment I6T-MC-AMBD(c) Summary
A Single-Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of LY3074828 in Healthy Chinese Subjects

Overview

Protocol I6T-MC-AMBD, "A Single-Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of LY3074828 in Healthy Chinese Subjects", has been amended. The new protocol is indicated by Amendment (c) and will be used to conduct the study in place of any preceding version of the protocol.

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

- The statement that this is a single-site study has been removed throughout in order to allow flexibility in the number of sites at which the study may be conducted.
- A description of how the final report coordinating investigator will be identified if the study is conducted at more than 1 site has been added.

Revised Protocol Sections

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

1. Protocol Synopsis

Summary of Study Design:

Study I6T-MC-AMBD (AMBD) is a ~~single center,~~ subject- and investigator-blinded, randomized, parallel-group, placebo-controlled, Phase 1 single-dose study of LY3074828 in healthy Chinese subjects. Native Chinese subjects born in China, with all 4 grandparents and both parents of Chinese origin will be enrolled. The study will consist of 5 planned dose cohorts: 3 intravenous (IV) dose cohorts (300 mg, 600 mg, and 1200 mg) and 2 subcutaneous (SC) dose cohorts (200 mg and 400 mg). Subjects will be randomized within each cohort to receive LY3074828 (10 subjects) or placebo (2 subjects).

5.1 Overall Design

Study I6T-MC-AMBD (AMBD) is a ~~single center,~~ subject- and investigator-blinded, randomized, placebo-controlled, parallel-group, Phase 1 single-dose study of LY3074828 in healthy Chinese subjects. Safety, tolerability, and PK of LY3074828 will be evaluated.

12. Appendices

Appendix 3. Study Governance, Regulatory and Ethical Considerations

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~~with the analyses, results, and conclusions of the report~~.

If the study is conducted at more than 1 site, the investigator with the most enrolled subjects will serve as the final report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the final report coordinating investigator.

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.

Leo Document ID = 89e992c5-8742-49f1-ba82-64c2be7103e9

Approver: PPD

Approval Date & Time: 28-Jun-2020 00:50:29 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 28-Jun-2020 23:43:51 GMT

Signature meaning: Approved