I6T-JE-AMAD (a) Protocol

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

NCT02568423

Date: 23-Jan-2018

1. Protocol I6T-JE-AMAD(a)
A Single-Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of LY3074828 in Japanese and Caucasian Healthy Subjects

Confidential Information

LY3074828

Study I6T-JE-AMAD is a single-site, subject- and investigator-blind, randomized, placebo-controlled, single-dose study to assess the safety, tolerability, and pharmacokinetics of LY3074828 in Japanese and Caucasian healthy subjects. The study will consist of 6 planned dose cohorts: 5 intravenous cohorts (60 mg, 200 mg, 600 mg, 1200 mg, and 2400 mg) and 1 subcutaneous cohort (200 mg). Subjects in each cohort will be randomized to receive LY3074828 or placebo.

Eli Lilly Japan K.K.
Kobe Hyogo Japan

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

Approval Date: 23-Jan-2018 GMT

2. Synopsis

Clinical Pharmacology Protocol Synopsis: Study I6T-JE-AMAD

Name of Investigational Product: LY3074828
Title of Study: A Single-Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of LY3074828 in Japanese and Caucasian Healthy Subjects
Number of Planned Subjects: approximately 50 subjects | **Phase of Development:** 1
Length of Study: approximately 16 weeks
Objectives: The primary objective is to explore the safety and tolerability of LY3074828 in healthy Japanese and Caucasian subjects to define an appropriate dose for further clinical research in Japan. The secondary objectives of this study are to estimate the pharmacokinetic (PK) parameters of LY3074828 following intravenous (IV) and subcutaneous (SC) administration in healthy Japanese and Caucasian subjects and to explore the safety, tolerability, and PK of LY3074828 in Japanese subjects in relation to Caucasian subjects.
Study Design: Study I6T-JE-AMAD is a single-site, subject- and investigator-blind, randomized, placebo-controlled, single-dose study to assess the safety, tolerability, and PK of LY3074828 in Japanese and Caucasian healthy subjects. The study will consist of 6 planned dose cohorts: 5 IV cohorts (60 mg, 200 mg, 600 mg, 1200 mg, and 2400 mg) and 1 SC cohort (200 mg). Subjects in each cohort will be randomized to receive LY3074828 or placebo. Subjects will be inpatient in the clinical research unit (CRU) for treatment administration and will then be discharged and followed as outpatients for 12 weeks after treatment administration.
Diagnosis and Main Criteria for Inclusion and Exclusion: This study will enroll healthy male and female subjects who are 20 years to 64 years, inclusive, with a body mass index of 18.0 kg/m^2 to 32.0 kg/m^2, inclusive, at screening. Japanese subjects must be first-generation Japanese, defined as the subject, the subject's biological parents, and the subject's biological grandparents are all of exclusive Japanese descent and were born in Japan.
Investigational Product, Dosage, and Mode of Administration: A single dose of LY3074828 will be administered IV at the planned dose levels of 60 mg, 200 mg, 600 mg, 1200 mg, and 2400 mg. A single dose of LY3074828 will be administered SC at a planned dose of 200 mg.
Comparator, Dose, and Mode of Administration: A single dose of placebo (sterile normal saline [0.9% sodium chloride]) will be given IV or SC, as per cohort.
Planned Duration of Treatment: LY3074828 or placebo will be given as a single dose.
Criteria for Evaluation: Safety: Adverse events (AEs), serious adverse events, physical examinations, vital signs, electrocardiograms (ECGs), and clinical laboratory evaluations including immunogenicity. Bioanalytical: Serum for the measurement of LY3074828 concentrations will be collected at select visits. Pharmacokinetic: The primary parameters for analysis will be maximum drug concentration (C_{max}) and area under the concentration versus time curve (AUC) of LY3074828. Other noncompartmental parameters, such as half-life, clearance, and volume of distribution (apparent clearance and apparent volume of distribution for SC administration) may be reported.

Evaluation Methods:

Statistical: Up to 60 subjects may be enrolled in order that approximately 50 subjects complete the study. It is intended that 10 subjects (6 Japanese and 4 Caucasian) will be randomized in Cohort 1, and 8 subjects (4 Japanese and 4 Caucasian) will be randomized in Cohorts 2, 3, 4, 5, and 6. The sample size is customary for Phase 1 studies evaluating safety, tolerability, and PK parameters. The first interim analysis is scheduled to occur when safety and PK data through Day 15 become available from at least 8 subjects in Cohort 1, including at least 3 Japanese subjects on LY3074828. An additional interim analysis may occur when safety and PK data through Day 15 becomes available from at least 6 subjects in Cohort 6, including at least 3 Japanese subjects on LY3074828. All safety and PK data available by this time will be included in the interim analysis.

Safety: Safety parameters that will be assessed include vital signs, ECG parameters, and safety lab parameters. The parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

Bioanalytical: Serum concentrations of LY3074828 will be assayed using a validated enzyme-linked immunosorbent assay.

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

3. Table of Contents

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

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4. Abbreviations and Definitions

Term	Definition
ADA	antidrug antibody
AE	adverse event: any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AUC	area under the concentration versus time curve
audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
blinding	a procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the subject is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and his staff and the subject are not. A double-blind study is one in which neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
CD	Crohn's disease
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum drug concentration
complaint	a complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	a process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CRF	case report form/electronic case report form: sometimes referred to as clinical report form; a printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.

CRU	clinical research unit
CSE	clinically significant event: a moderate to severe adverse event (AE), abnormal clinical sign, or clinical laboratory finding that may pose a risk to the well-being of the subject
CTCAE	Common Terminology Criteria for Adverse Events
end of study	End of study is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last patient/subject.
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.
ERB	ethical review board/institutional review board: a board or committee (institutional, regional, or national) composed of medical professionals and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the subjects participating in a clinical trial are protected
GCP	good clinical practice: a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate and that the rights, integrity, and confidentiality of trial subjects are protected
IB	Investigator's Brochure: a compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IL-12	interleukin-12
IL-23	interleukin-23
informed consent	a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical trial data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product (IP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, 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 trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
IV	intravenous
NOAEL	no-observed-adverse-effect level
PASI	Psoriasis Area and Severity Index
PK	pharmacokinetic
randomize	the process of assigning subjects to an experimental group according to the randomization schedule for the trial
rescreen	to screen a subject who was previously declared a screen failure for the same study
SAE	serious adverse event: any untoward medical occurrence that at any dose results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect
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. In this study, screening involves invasive procedures and/or tests (for example, x-rays and blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
SC	subcutaneous
subject	an individual who is or becomes a participant in clinical research, either as a recipient of the investigational product(s) or as a control. A subject may be either a healthy human or a patient.
SUSARs	suspected unexpected serious adverse reactions
TB	tuberculosis
Th17	T helper 17
TST	tuberculin skin test
TEAE	treatment-emergent adverse event: any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and which does not necessarily have to have a causal relationship with this treatment
TPO	third-party organization

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

5. Introduction

5.1. General Introduction

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

Treatment of autoimmune or inflammatory diseases with IL-23–targeted therapy is being pursued by many companies. The first such biologic to demonstrate clinical benefit in autoimmune disease was ustekinumab, which is now an approved medicine for the treatment of patients with psoriasis and psoriatic arthritis (Stelara package insert, 2013) and CD (Toussirot et al. 2013). Ustekinumab is a monoclonal antibody that recognizes the common p40 subunit of IL-12 and IL-23; therefore, it does not target IL-23 specifically. Blockade of the IL-12 pathway may prevent Th1 cell–induced interferon blockade of Th17 cell development, thus potentially limiting the clinical activity of p40 targeting antibodies. Experimental studies suggest that blocking the IL-23/Th17/interleukin-17 immune axis (and not IL-12) is sufficient to treat autoimmune inflammation (Monteleone et al. 2009). IL-23–specific medicines targeted to the IL-23 p19 subunit have demonstrated clinical activity in psoriasis and CD (Kopp et al. 2015; Sofen et al. 2014; Krueger et al. 2015; Sands et al. 2015). Although clinical evaluation of an IL-23–targeted therapy in ulcerative colitis has yet to occur, the IL-23/Th17 pathway is suggested to have a significant role in patients with ulcerative colitis (Gheita et al. 2014; Globig et al. 2014; El-Bassat et al. 2014); therefore, evaluation of an IL-23 antibody in this disease would be the next logical step. Therefore, the planned Phase 2 study, I6T-MC-AMAC (AMAC), will evaluate the hypothesis that LY3074828 can induce significantly higher rates of clinical remission compared to placebo in subjects with moderate to severe ulcerative colitis.

LY3074828 is a humanized immunoglobulin G4–variant monoclonal antibody that is directed against the p19 subunit of IL-23 and does not bind IL-12. LY3074828 is being developed for the treatment of autoimmune diseases in which the IL-23 pathway is thought to have a significant pathogenic role. LY3074828 does not bind rodent IL-23, so a surrogate molecule was developed to neutralize mouse IL-23 for use in preclinical studies. Neutralization of IL-23 with this surrogate antibody significantly reduced the development of arthritis and inhibited ileal inflammation in a mouse model of spondyloarthropathy with bowel inflammation (Ruutu et al. 2012). In addition, neutralization of IL-23 significantly reduced the disease score in the

relapsing-remitting experimental autoimmune encephalomyelitis (multiple sclerosis–like) model in mice. Anti–IL-23 antibody also demonstrated some efficacy in preclinical arthritis models, depending on the timing of intervention (Cornelissen et al. 2013).

One study, Study I6T-MC-AMAA (AMAA): A Phase 1, Randomized, Placebo-Controlled Study of LY3074828, an Anti-IL-23 Humanized Antibody in Subjects With and Without Psoriasis, has been completed. This study evaluated LY3074828 in healthy volunteers and in subjects with plaque psoriasis. Seven cohorts of subjects with active psoriasis received single doses of intravenous (IV) LY3074828 (up to 600 mg) or placebo. A single cohort of 5 healthy subjects received single subcutaneous (SC) doses of LY3074828 (120 mg). A total of 33 subjects with psoriasis and 5 healthy subjects were administered LY3074828. Seven subjects with psoriasis received placebo.

- No deaths, serious adverse events (SAEs), or discontinuations due to an adverse event (AE) were reported. Treatment-emergent adverse events (TEAEs) reported as related to investigational product (IP) included one Grade 1 event of headache experienced by a single subject in the 200-mg IV cohort and five Grade 1 events of injection site pain experienced by 3 subjects in the 120-mg SC cohort. No LY3074828 TEAEs of Grade 2 or higher were reported. No dose-dependent trends in adverse events (AEs) were seen. No clinically important changes in vital signs, electrocardiograms (ECGs), or clinical laboratory results were observed.
- Following single IV doses of LY3074828 in Study AMAA, the area under the curve (AUC) and maximum drug concentration ($_{Cmax}$) increased in approximately a dose-proportional manner. The mean terminal phase half-life across all IV doses was 10.5 days and did not appear to be dependent on dose, and the mean clearance is within the range expected for human monoclonal antibodies. The overall mean clearance across all doses following IV administration was approximately 0.526 L/day and is within the range expected for human monoclonal antibodies. Maximum concentrations were observed 3 days postdose following SC administration. Based on the AUC, the SC bioavailability was 40% relative to IV administration.
- Immunogenicity evaluations were performed in Study AMAA. Blood samples to evaluate anti-drug antibodies (ADA) were collected at baseline and approximately 22, 43, and 85 days postdose. ADA data were available for 45 subjects, 38 who received LY3074828 and 7 who received placebo. All subjects who received placebo were ADA negative at baseline and postbaseline. Only one subject who received LY3074828 was positive at baseline. Thirty-one subjects who received LY3074828 (81.6%) were negative at all postbaseline time points evaluated. Seven subjects who received LY3074828 had a postbaseline positive titer; however, only 3 of those subjects (7.9% of LY3074828-treated individuals) developed treatment-emergent ADA, defined as a 4-fold or greater change in titer from baseline. None of these cases of treatment-emergent anti-drug antibodies (TE-ADA) were associated with treatment-emergent adverse events (TEAEs).

- In Study AMAA, clinical activity was explored in subjects with psoriasis, with a follow-up period of approximately 12 weeks. Figure AMAD.1 presents mean data by cohort for the percentage change in the Psoriasis Area and Severity Index (PASI) score. The PASI measures the severity of disease on a scale from 0 to 72 (in which a score of 72 indicates extreme disease severity) by combining assessments of the extent of body surface involvement in the head, trunk, arms, and legs with the severities of desquamation, erythema, and plaque induration. Preliminary PASI data show improvement of psoriasis after a single dose of LY3074828 in the higher-dose cohorts.

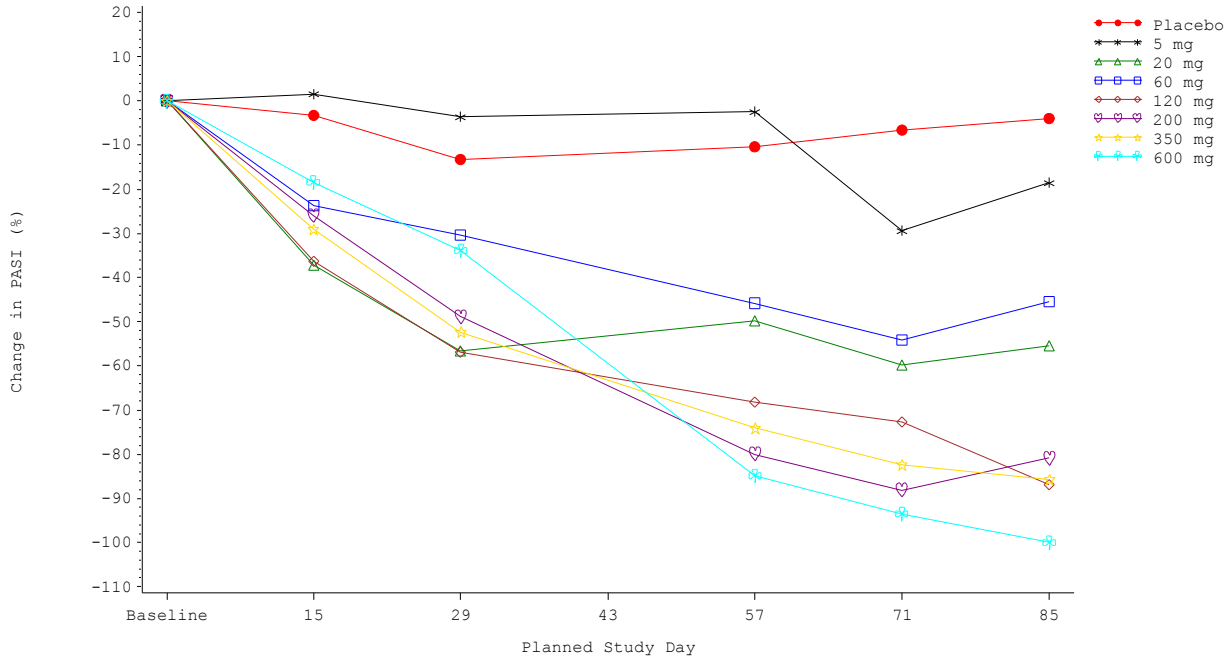


Figure AMAD.1. Mean percentage change from baseline in the Psoriasis Area and Severity Index score by dose group.

Phase 2 studies investigating the efficacy of LY3074828 as a potential treatment for psoriasis (AMAF), ulcerative colitis (AMAC), and Crohn's disease (AMAG) are currently ongoing.

Phase 1 Study I6T-JE-AMAD (AMAD) will provide safety, tolerability, and pharmacokinetic (PK) data after IV and SC administration of LY3074828 in Japanese and Caucasian healthy subjects.

More information about the known and expected benefits, risks, and reasonably anticipated AEs may be found in the Investigator's Brochure (IB). Information on AEs expected to be related to the IP may be found in Section 6 (Development Core Safety Information) of the IB.

5.2. Rationale and Justification for the Study

This study intends to characterize the safety, tolerability, and PK of LY3074828 after single-dose administration in healthy Japanese and Caucasian subjects. Characterization of safety and PK in Japanese subjects is essential for further clinical development in Japan.

6. Objectives

6.1. Primary Objective

The primary objective is to explore the safety and tolerability of LY3074828 in healthy Japanese and Caucasian subjects to define an appropriate dose for further clinical research in Japan.

6.2. Secondary Objectives

The secondary objectives of this study are

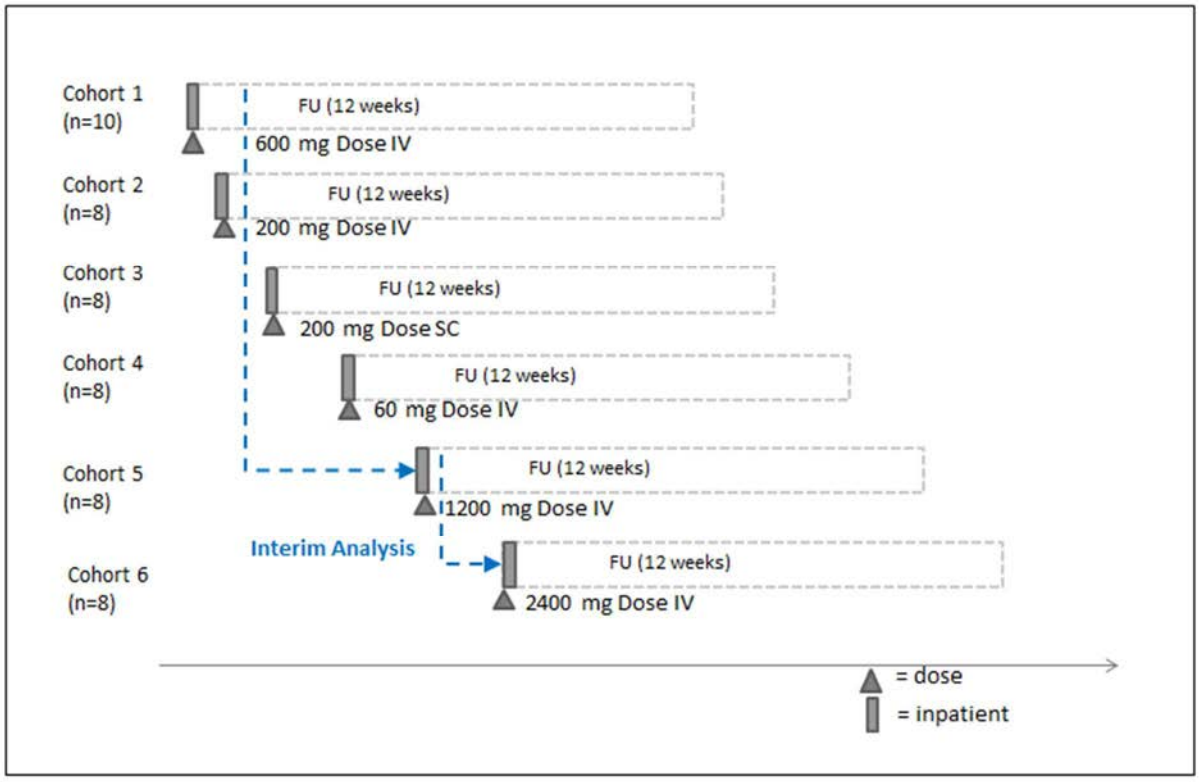
- to estimate the PK parameters of LY3074828 following IV and SC administration in healthy Japanese and Caucasian subjects
- to explore the safety, tolerability, and PK of LY3074828 in Japanese subjects in relation to Caucasian subjects

7. Investigational Plan

7.1. Summary of Study Design

This is a single-site, subject- and investigator-blind, randomized, placebo-controlled, single-dose study to assess the safety, tolerability, and PK of LY3074828 in Japanese and Caucasian healthy subjects. Subjects will be randomized to LY3074828 or placebo within 1 of 6 cohorts, as shown in Figure AMAD.2. Cohort 1 will consist of 10 subjects (6 Japanese and 4 Caucasian) who will be randomized so that 5 Japanese subjects and 3 Caucasian subjects will receive LY3074828 while 1 Japanese subject and 1 Caucasian subject will receive placebo. Cohorts 2 through 6 will consist of 8 subjects (4 Japanese and 4 Caucasian) who are randomized in a 3:1 ratio of LY3074828 to placebo. For each cohort, 3 Japanese subjects and 3 Caucasian subjects will receive LY3074828 while 1 Japanese subject and 1 Caucasian subject will receive placebo.

Single doses up to 600 mg IV have been studied and shown to be well tolerated, therefore all cohorts, with the exception of Cohort 5 and Cohort 6, may be dosed in parallel if the site is able to accommodate more than 1 cohort at a time. Cohort 5 will be dosed after confirming the safety and PK data from Cohort 1. Cohort 6 will be dosed last after confirming the safety and PK data from Cohort 5. Two additional Japanese subjects will be included in Cohort 1 to ensure that a sufficient number of Japanese subjects will have received LY3074828 at the time of the interim analysis. An interim analysis is planned based on Cohort 1 data through Day 15 (see Section 11.3) to support Japanese patients being included in the planned global Phase 2 study, Study I6T-MC-AMAC (AMAC).



Abbreviations: FU = follow up; IV = intravenous; SC = subcutaneous.

Figure AMAD.2. Study design for Protocol I6T-JE-AMAD.

Treatment:
Four IV dose levels and 1 SC dose level of LY3074828 will be assessed in Cohorts 1 through 6. The following treatments are planned:

Cohort 1: a single dose of LY3074828 600 mg or placebo IV

Cohort 2: a single dose of LY3074828 200 mg or placebo IV

Cohort 3: a single dose of LY3074828 200 mg or placebo SC

Cohort 4: a single dose of LY3074828 60 mg or placebo IV

Cohort 5: a single dose of LY3074828 1200 mg or placebo IV

Cohort 6: a single dose of LY3074828 2400 mg or placebo IV

Study Procedures:
Each subject will have a screening visit within 28 days prior to dosing, as shown in the Study Schedule (Attachment 1). AEs, including injection-site reactions, will be assessed on all clinical research unit (CRU) visit days and when spontaneously reported. Physical examination, vital

signs, ECGs, laboratory tests, PK and other sample collections will be performed at times specified in the Study Schedule (Attachment 1).

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

Extension of admission to the CRU and additional outpatient visits may be required for safety reasons at the discretion of the investigator. If any safety findings warrant follow-up and/or preclude discharge from the study, further visits may be arranged as appropriate.

Sequential PK sampling and safety monitoring will occur through the end of study. There will be outpatient visits over approximately 12 weeks after study drug administration, including an End of Study visit (Day 85) that will occur approximately 12 weeks after the dose.

7.2. Discussion of Design and Control

This is a single-site, subject- and investigator-blind, randomized, placebo-controlled, single-dose study in healthy Japanese and Caucasian subjects. Healthy Caucasian subjects are included in this study to enable comparison between healthy Japanese and Caucasian subjects, as most of the subjects in Study AMAA were Caucasian patients with psoriasis. The number of subjects in Study AMAD is not sufficient for any formal ethnic comparison, but the safety, tolerability, and PK data will be assessed in both Japanese and Caucasian subjects and will be used to support the inclusion of Japanese subjects in future studies involving LY3074828. The study will be subject- and investigator-blind, with the subjects, investigators, and site staff (except for site pharmacy staff) unaware of actual treatment (LY3074828 or placebo), but aware of dose level assigned to the cohort. This design is being used to minimize bias in safety and tolerability assessments.

Dosing will begin with the 600 mg IV cohort because the timing of this cohort will determine the timing of the interim analysis and subsequent inclusion of Japanese subjects in the LY3074828 global studies. Single doses up to 600 mg have already been shown to be well tolerated in Study AMAA. The dose levels included in this single-dose study are within the range of doses studied previously, with the exception of the planned 1200 mg and 2400 mg IV dose cohort. Preliminary population PK analyses of interim data from Study AMAA indicate that body weight has no clinically significant impact on clearance or volume of distribution of LY3074828. Therefore, the AUC and maximum drug concentration (C_{max}) in Japanese subjects who may have lower body weight are expected to be similar to those of subjects in Study AMAA.

The follow-up period will be 12 weeks for all cohorts after dosing. This duration will allow ample time for assessment of the PK of LY3074828 (>5 half-lives) and for an initial assessment of ADAs.

8. Study Population

8.1. Criteria for Enrollment

Eligibility of subjects for study enrollment will be based on the results of a screening medical history, physical examination, vital signs, electrocardiogram (ECG), and clinical laboratory tests (Attachment 1).

A chest x-ray will be completed at screening unless one has been obtained within the past 12 months, and the x-ray and/or report are available for the investigator's review.

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

Screening may occur up to 28 days prior to dosing. 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.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened. However, if individuals have met the criteria for participation in this study but their screening assessments were collected outside of the 28-day screening window, those assessments may be repeated.

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

8.1.1. Inclusion Criteria

Subjects are eligible for enrollment in the study only if they meet all of the following criteria:

[1] are overtly healthy males or females, as determined by medical history and physical examination

[1a] male subjects:

will be sterile (including vasectomy) or agree to use a reliable method of birth control and will not donate sperm during the study and for 3 months following administration of the study drug

[1b] female subjects:

are women of childbearing potential who test negative for pregnancy before receiving study treatment based on serum pregnancy test and agree to use a reliable method of birth control (for example: barrier methods such as condom, sponge, or diaphragm combined with spermicide in foam, gel, or cream; hormonal contraception [oral, intramuscular, implant, or transdermal], which includes Depo-Provera, Evra, and NuvaRing; intrauterine device; or complete abstinence from sexual intercourse with men) during the study and for 3 months following administration of the study drug

or

are women not of childbearing potential due to surgical sterilization (at least 6 weeks after bilateral oophorectomy and/or hysterectomy or at least 6 weeks after tubal ligation) confirmed by medical history, or postmenopausal, defined as either:

1) spontaneous amenorrhea for at least 12 months, not induced by a medical condition or medications

or

2) spontaneous amenorrhea for 6 to 12 months with a follicle-stimulating hormone level greater than 40 mIU/mL at screening

[2] are first-generation Japanese or are Caucasian. CCI [redacted]

[3] are 20 years to 64 years, inclusive, at the time of initial screening

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

[5] have a body weight of 40.0 kg or higher for Cohorts 1 to 4 and 48.0 kg or higher for Cohort 5 and Cohort 6

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

[7] have venous access sufficient to allow for blood sampling and administration of IP as per the protocol

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

[9] have given written informed consent approved by Lilly and the ethical review board (ERB) governing the site

8.1.2. Exclusion Criteria

Subjects will be excluded from study enrollment if they meet any of the following criteria:

[10] are investigator site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[11] are Lilly employees or employees of the third-party organizations (TPOs) involved with the study

[12] are currently enrolled in a clinical trial involving an IP or off-label use of a drug or device or are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study

[13] have participated, within the last 30 days, in a clinical trial involving an IP. If the previous IP has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed.

[14] are persons who have previously completed or withdrawn from this study or any other study investigating LY3074828 or any other anti-IL-23 antibody and have previously received the IP

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

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

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

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

[19] have a significant history of or current 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 study medication; or of interfering with the interpretation of data

[20] have known or ongoing psychiatric disorders

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

[22] show evidence of human immunodeficiency virus (HIV) infection and/or positive human HIV antibodies at screening

[23] show evidence of hepatitis C and/or positive hepatitis C antibody at screening

[24] show evidence of hepatitis B and/or positive hepatitis B surface antigen or positive hepatitis B core antibody (HBcAb+) at screening

[25] are women who are lactating

[26] have used or intend to use over-the-counter or prescription medication, including herbal medications, within 14 days prior to dosing (stable doses of oral contraceptive, hormone replacement therapy, or vitamins at usual doses may be allowed as per judgment of the investigator)

[27] have donated blood of more than 500 mL within the last month

[28] are subjects who have an average weekly alcohol intake that exceeds 21 units per week for males and 14 units per week for females or who are unwilling to abide by the alcohol restrictions described in Section 9.5

[29] are subjects whose tobacco consumption is more than 10 cigarettes per day or the equivalent or subjects who are not willing to refrain from smoking for approximately 2 hours prior to each ECG and vital-sign measurement during the study or who are unwilling to abide by the CRU smoking guidelines (Section 9.5)

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

[31] show evidence of active or latent tuberculosis (TB), as documented by medical history and examination, chest x-rays (posterior anterior and lateral), and TB testing: to qualify for the study, subject must have either a negative tuberculin skin test (TST; defined as a skin induration <5 mm at 48 hours to 72 hours, regardless of BCG [Bacillus Calmette-Guerin] or other vaccination history), or a negative (not indeterminate) QuantiFERON®-TB Gold test. The choice to perform a TST or a QuantiFERON-TB Gold test will be made by the investigator according to local licensing and standard of care.

[32] have received live vaccine(s) within 1 month of screening or intend to during the study

[33] are immunocompromised

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

[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] in the opinion of the investigator or sponsor are unsuitable for inclusion in the study for any reason

8.1.3. Rationale for Exclusion of Certain Study Candidates

Criteria [10] and [11] prevent conflict of interest in study participants. Criteria [12] through [37] exclude medical conditions, medication intolerance, and concomitant medication use that may constitute a risk for the subject and/or may confound the assessment of study endpoints.

8.2. Discontinuation

The reason for and date of discontinuation will be collected for all subjects. All randomized subjects who discontinue after receiving study drug will have procedures performed as shown in the Study Schedule (Attachment 1).

8.2.1. Discontinuation of Subjects

8.2.1.1. Subjects Inadvertently Enrolled

The criteria for enrollment must be followed explicitly. If the investigator site identifies a subject who did not meet enrollment criteria and who was inadvertently enrolled, the sponsor must be notified. If the sponsor identifies a subject who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the Lilly clinical pharmacologist or clinical research physician and the investigator to determine whether the subject may continue in the study without IP. The subject may not continue in the study if the Lilly clinical pharmacologist or clinical research physician does not agree with the investigator's determination it is medically appropriate for the subject to continue. The investigator must obtain documented approval from Lilly clinical pharmacologist or clinical research physician to allow the inadvertently enrolled subject to continue in the study.

8.2.1.2. Discontinuations from Investigational Product or from the Study

Subjects will be discontinued from the IP and/or from the study in the following circumstances:

- enrollment in any other clinical trial involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- investigator decision
    - the investigator decides that the subject should be discontinued from the study
- subject decision
    - the subject requests to be discontinued from the study
- sponsor decision
    - Lilly stops the study or stops the subject's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- adverse event
    - if a clinically significant event (CSE) occurs during the IV infusion or SC injection, the IP is to be discontinued and appropriate measures taken. Lilly or its designee should be alerted immediately. A CSE will be defined as a moderate to severe AE, abnormal clinical sign, or clinical laboratory finding that may pose a risk to the well-being of the subject. Refer to Safety Evaluations (Section 10.5).
    - a clinically significant systemic hypersensitivity reaction occurs following administration of the IP (for example, drug-related symptomatic bronchospasm, allergy-related edema/angioedema, or hypotension) that requires parenteral medication, does not respond to symptomatic medication, or results in clinical sequelae or an anaphylactic reaction

A dose group may be discontinued from the IP if the following are met:

2 or more subjects/cohort develop AEs that are severe, unless there is an obvious explanation other than IP or study procedures for the event(s)

OR

if greater than 40% of subjects in a cohort experience moderate treatment-related AEs that impair normal activities

OR

after the introduction of premedication in accordance with the protocol, 2 or more subjects develop (according to Common Terminology Criteria for Adverse Events [CTCAE], version 4.0) ≥Grade 2 acute AEs related to the infusion, during or within 2 hours of completing the infusion, that do not resolve with a reduced infusion rate and/or supportive care

Following the investigator's determination that CSE criteria have been met and the investigator's judgment of relatedness to the IP is documented, a decision will be made between the investigator and Lilly or its designee regarding subject discontinuation.

The nature of any conditions, clinical signs or symptoms, or abnormal laboratory values present at the time of discontinuation and any applicable follow-up procedures will be documented.

Refer to the Study Schedule (Attachment 1) for data collected at the time of discontinuation.

8.2.1.3. 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.

8.2.2. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ERB of the study site judges it necessary for any reason consistent with applicable laws, regulations, and GCP.

8.2.3. Discontinuation of the Study

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

9. Treatment

9.1. Treatment Materials and Supplies

LY3074828 will be supplied to the investigator by Lilly. Clinical trial materials are manufactured in accordance with good manufacturing practices. All IPs will be stored, inventoried, reconciled, and destroyed according to applicable regulations.

LY3074828 is supplied for clinical trial use as lyophilized powder in a glass vial and should be stored in refrigerated conditions (2ºC to 8ºC). The vial is manufactured to deliver 75 mg of LY3074828 and will be reconstituted before administration. Detailed instructions for the preparation and handling of LY3074828 will be provided by the sponsor.

When reconstituted and in a syringe, LY3074828 cannot be distinguished visually from placebo. Subjects and blinded site staff will not be able to see the difference because the label on the syringe will cover the solution. See Table AMAD.1 for additional details regarding the IP regimens.

Placebo will be sterile normal saline (0.9% sodium chloride), which should be supplied by investigative site(s).

Clinical trial materials will be labeled according to the country's regulatory requirements.

9.2. Treatment Administration

The investigator or designee is responsible for:

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

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

Subjects will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the IP so that the situation can be assessed.

All clinical trial material provided to the investigator will be stored in a secure place, and allocated and dispensed by appropriately trained persons. The allocation and dispensing of the IPs will be fully documented and verified by a second person. Detailed records of the amounts of the IP received, dispensed, and remaining at the end of the study will be maintained.

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

The IP will be administered as a slow IV infusion of at least 30 minutes. SC administration of LY3074828 will be given as 2 injections of 1.4 mL into the skinfold of the left or right abdominal wall. Sites must have resuscitation equipment, emergency drugs, and appropriately trained staff available for at least 6 hours after the start of the infusion or postdose for SC administration.

Table AMAD.1. Investigational Product Regimens

	LY3074828 or Placebo					
Cohort	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6
Regimen	600 mg IV	200 mg IV	200 mg SC	60 mg IV	1200 mg IV	2400 mg IV
LY3074828 concentration	25 mg/mL	20 mg/mL	72 mg/mL	6 mg/mL	25 mg/mL	25 mg/mL
Volume per dose	24 mL	10 mL	2.8 mL (1.4 mL × 2 injections)	10 mL	48 mL	96 mL

Abbreviations: IV = intravenous; SC = subcutaneous.

9.3. Rationale for Selection of Dose

The 5 IV doses for this study are 60, 200, 600, 1200, and 2400 mg and the SC dose for this study is 200 mg.

The low dose of 60 mg IV for this study is chosen as one of the doses that was administered in the global single-dose study (Study AMAA) and is close to the low dose in the Phase 2 ulcerative colitis study (Study AMAC).

The 200-mg IV dose is one of the starting doses in Study AMAC and is one of the doses that was administered in Study AMAA. A dose of 200 mg SC is being administered in the maintenance period of Study AMAC.

The 600-mg IV dose is the highest dose being tested in Study AMAC and is the highest dose that was administered in Study AMAA.

The original highest dose of 1200 mg IV was tested for safety and tolerability based on the safety results at each escalation cohort of this study. Findings from these results supported the highest dose of 1000 mg IV in the Phase 2 Crohn's disease study (Study AMAG).

The amended maximum dose of 2400 mg IV is selected to support potential future studies in patients with ulcerative colitis and Crohn's disease, where high IV doses (potentially beyond 1200 mg) during induction treatment may be required to maximize efficacy (Sandborn et al. 2012; Adedokun et al. 2016; Feagan et al. 2016).

The margin of safety at 2400 mg IV is 1.9-fold. This value is based on the predicted exposure at 2400 mg compared to the observed exposure at 100 mg/kg IV, administered once weekly, in the 4-week, repeat-dose monkey study. In this study, 100 mg/kg was the no observed adverse-effect level (NOAEL) and also the highest dose tested. (see Table AMAD.2).

LY3074828 does not recognize rodent IL-23, which precludes its use in preclinical toxicity assessment and in efficacy disease models. The monkey is a pharmacologically relevant species

for assessing nonclinical toxicity because LY3074828 binds with similar affinity to human and cynomolgus IL-23 (21 pM and 55 pM, respectively). To assess the toxicity of LY3074828 and establish a margin of safety for clinical trials (Table AMAD.2), 4-week and 6-month toxicity studies in normal cynomolgus monkeys were performed with evaluation of safety pharmacology as part of the 4-week study. The weekly administration of LY3074828 to cynomolgus monkeys resulted in no adverse drug-related findings at doses of 0 mg/kg (vehicle), 1 mg/kg and 30 mg/kg (SC), or 100 mg/kg (IV) for 4 weeks, with an 8-week recovery period, or at doses of 0 mg/kg, 10 mg/kg, and 100 mg/kg (SC) for 6 months. Therefore, the NOAEL was 100 mg/kg/week for both studies; this was the highest dose tested. A safety pharmacology assessment performed during the 4-week monkey study included evaluation of body temperature, cardiovascular safety (including quantitative evaluation of ECG measurements and qualitative evaluation for abnormal waveform morphology and arrhythmias), observations for central nervous system signs with neurologic examinations, and qualitative assessments of respiratory depth with quantitative estimates of respiratory rate. No drug-related changes occurred in any of these parameters.

Due to a lack of a preclinical disease model, the anticipated minimally effective dose for LY3074828 is unknown. The clinical dose range for LY3074828 is not yet known, and the maximum planned LY3074828 dose level to be evaluated in Study AMAC is 600 mg. However, it is possible that dose levels higher than 600 mg could be required in certain patients (for example, those with more severe disease activity) to achieve higher exposures in patients with inflammatory bowel disease (IBD), in part due to greater clearance observed in these patients (Ordás et al. 2012). Higher drug exposures, particularly during an induction dosing period (Yarur et al. 2014), may be required to support the best clinical outcomes in many auto-inflammatory disease indications, including IBD.

Therefore, this study planned to evaluate the safety, tolerability, and PK of a 1200-mg IV dose of LY3074828. The 1200-mg IV dose cohort (Cohort 5) was dosed after safety, tolerability, and PK data were confirmed from the 600-mg dose cohort (Cohort 1). Other dose levels were dosed concurrently in this study because these doses have already been shown to be well tolerated in Study AMAA. Evaluation of 1200-mg IV dose cohort (Cohort 5) provided safety and PK data to support the use of a higher dose level in Study AMAC and Study AMAG.

In addition to the above evaluation, this study is amended to add the evaluation of safety, tolerability, and PK of a 2400-mg IV dose of LY3074828, since there is a possibility to evaluate a higher dose level up to 2400 mg IV in later clinical development. The proposed dose of 2400-mg IV infusion has a sufficient margin of safety in terms of dose. Moreover, the clinical safety profile of LY3074828 available to date supports 2400-mg IV administration in this study. Single doses of up to 1200 mg IV were evaluated in healthy subjects from Study AMAD and no dose-related safety or tolerability issues were observed. Evaluation of the safety data available to date in the ongoing Study AMAC and Study AMAG that are evaluating higher and more frequent dose regimens of up to 1000 mg IV Q4W for up to 52 weeks has not revealed any differences in the safety profile. The PK profile of this drug was found to be approximately linear up to 1200-mg IV administration. Since the 2400-mg IV dose is only 2-fold of 1200 mg, it

is unlikely that an unexpected PK profile will be observed after administration of a 2400-mg IV dose. Therefore, evaluation of this additional higher dose cohort (2400 mg) will provide safety and PK data to support the use of a higher dose level beyond 1200 mg during the clinical development of this compound.

Table AMAD.2. Margin of Safety for Intravenous Administration of 2400 mg LY3074828 Based on Administered Dose and Predicted Exposure

	Dose (mg/kg)	Dose Multiple[a]	$AUC_{0\text{-}672h,ss}$ (µg•h/mL)	Margin of Safety[b]
Human highest dose (2400 mg)[c]	36.9 (IV)		110000	
Monkey NOAEL[d] 6-month study	100 (SC)	2.7	85800[e]	0.78
Monkey NOAEL[f] 4-week study	100 (IV)	2.7	204200[g]	1.9

Abbreviations: AUC = area under the concentration vs time curve; $AUC_{0\text{-}672h,ss}$ = AUC over 672 hours at steady state; $AUC_{0\text{-}168h}$ = AUC over 168 hours; $AUC_{0\text{-}\infty}$ = AUC from time zero to infinity; C_{max} = maximum drug concentration; IV = intravenous; NOAEL = no observed-adverse-effect level; SC = subcutaneous.

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

b Margin of safety is the calculated mean AUC in animals divided by predicted mean AUC in humans after adjusting for differences in dosing frequency.

c Highest proposed dose in this study; a body weight of 65 kg is assumed. Human $AUC_{0\text{-}672h,ss}$ is equivalent to the expected $AUC_{0\text{-}\infty}$ following a single dose. Human $AUC_{0\text{-}672h,ss}$ at 2400 mg IV is predicted on the basis of the average IV clearance (0.526 L/day) from Study I6T-MC-AMAA. AUC and C_{max} were observed to increase in proportion to dose in Study I6T-MC-AMAA.

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

e Monkey AUC value was based on average of male and female Day 176 means of $AUC_{0\text{-}168h}$ and has been multiplied by 4 to align with the 4-week AUC interval projected for humans and planned for Phase 2 Study I6T-MC-AMAC.

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

g Monkey AUC value was based on average of male and female Day 29 means of $AUC_{0\text{-}168h}$ and has been multiplied by 4 to align with the 4-week AUC interval projected for humans and planned for Phase 2 Study I6T-MC-AMAC.

9.4. Dose Escalation

All doses in this study, with the exception of the 1200-mg and 2400-mg doses, have been previously tested and shown to be well tolerated in Study AMAA. The only dose escalation decisions in this study will be made to proceed from the 600-mg cohort (Cohort 1) to the 1200-mg cohort (Cohort 5) and the 1200-mg cohort (Cohort 5) to the 2400-mg dose cohort (Cohort 6). Safety and PK data reviewed at the time of the first interim analysis will be used for the escalation decision to the 1200-mg dose. Safety and PK data up to the 1200-mg dose cohort will be reviewed before dose escalation to 2400 mg. The dose escalation cannot occur without prior discussion and agreement between the investigator and the Lilly clinical pharmacologist.

9.4.1. Dose Escalation Method

Safety data, in particular AEs, SAEs, and adverse laboratory abnormalities, will be independently assessed by the investigator, and will be considered related to the IP unless there is clear evidence that the event is not related. The assessment of AE relatedness is detailed in Section 10.5.1. PK data included in the interim analysis will also be assessed.

After review of the data, an agreement on the appropriate dose escalation will be made by the investigator and sponsor for Cohort 6. None of the following scenarios occurred at 1200-mg LY3074828:

2 or more subjects develop AEs that are severe, unless there is an obvious explanation other than IP or study procedures for the event(s)

OR

if greater than 40% of subjects experience moderate treatment-related AEs that impair normal activities

OR

after the introduction of premedication in accordance with the protocol, 2 or more subjects develop (according to Common Terminology Criteria for Adverse Events [CTCAE]) ≥Grade 2 acute AEs related to the infusion, during or within 2 hours of completing the infusion, that do not resolve with a reduced infusion rate and/or supportive care.

9.5. Specific Restrictions/Requirements

Prior to beginning the study, the subjects will complete informed consent. Throughout the study, subjects may undergo medical assessments and review of compliance with restrictions before continuing in the study.

Meals/Diet—Subjects should fast overnight for at least 8 hours before dosing (water permitted) and before each laboratory test.

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

Alcohol—Alcohol consumption is not allowed from 12 hours prior to all study visits and during CRU stays. At all other times, alcohol consumption should be limited to 21 units per week for males and 14 units per week for females (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).

Smoking—Subjects who smoke should maintain a stable smoking habit throughout the study. Subjects will be asked to refrain from smoking for approximately 2 hours prior to each ECG and vital sign measurements as well as abide by the CRU smoking guidelines.

Exercise—Strenuous activity should be avoided from 24 hours prior to admission until discharge from the CRU.

Contraception—Subjects with partners of childbearing potential must agree to use a reliable method of birth control during the study and until 3 months after the subject's dose.

9.5.1. Special Treatment Considerations

9.5.1.1. Premedication for Infusions

Premedication for the infusions is not planned. However, if an infusion reaction occurs, appropriate medication may be used as determined by the study investigator(s) (see Section 9.7). If infusion reactions are observed but review of the data suggests that dose escalation may continue, administration of acetaminophen 500 mg to 1000 mg, and/or an antihistamine, such as diphenhydramine (Benadryl®), may be administered orally 30 minutes to 60 minutes prior to the start of infusion for subsequent subjects.

The decision to implement premedication for infusions in subsequent cohorts will be made by the investigator and sponsor and recorded in the study documentation, along with the dose-escalation decision.

Any premedications given will be documented as a concomitant therapy (see Section 9.7).

9.5.1.2. Management of Infusion Reactions

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

- the IP infusion should be slowed or stopped, depending on the symptoms/signs present
    - if slowed, the infusion should be completed at the slower rate, as tolerated
    - if stopped, no further attempts to administer the IP will be made
- supportive care should be employed in accordance with the symptoms/signs

9.6. Blinding

This is a subject- and investigator-blind study. The sponsor and site pharmacists will be unblinded.

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete. The Lilly clinical pharmacologist will have open access to this table. Subject randomization codes and drug accountability records will be held in a secure location at the CRU, accessible only by individuals involved with study drug preparation. Individuals involved with study drug preparation will not be involved in any clinical aspects of the study including study drug

administration and AE assessments. Refer to Attachment 4 for details on the blinding/unblinding plan.

Emergency codes will be available to the investigator. A code, which reveals the treatment group 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. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly clinical pharmacologist or clinical research physician prior to unblinding a study subject's treatment assignment. If a study subject's treatment assignment is unblinded, Lilly must be notified immediately. Upon completion of the study, all codes must be returned to Lilly or its designee.

9.7. Concomitant Therapy

Over-the-counter or prescription medication, including herbal medications, are not permitted within 14 days prior to dosing and throughout the study. However, stable doses of oral contraceptive, hormone replacement therapy, or vitamins at usual doses may be allowed as per judgment of the investigator. Any other drugs are to be avoided during the study unless required to treat an AE. If the need for concomitant medication arises, inclusion or continuation of the subject may be at the discretion of the investigator after consultation with a Lilly clinical pharmacologist or clinical research physician. Any additional medication used during the course of the study must be documented.

10. Sample Collection and Safety Data Collection

Attachment 1 lists the schedule for sample collections in this study.

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

Attachment 3 summarizes the blood volumes for all blood sampling during the study.

10.1. Laboratory Samples

Blood and urine samples will be collected to determine whether subjects meet inclusion/exclusion criteria and to monitor subject health at the visits and times specified in the Study Schedule (Attachment 1). Routine clinical laboratory tests will be analyzed by a local laboratory.

Investigators must document their review of each laboratory safety report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

10.2. Samples for Pharmacokinetic and Pharmacodynamic Evaluations

10.2.1. Pharmacokinetic Samples

At the visits and times specified in the Study Schedule (Attachment 1), blood samples of approximately 2 mL each will be collected to determine the serum concentrations of LY3074828. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

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

10.2.2. 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.

10.3. Samples for Biomarker Research

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics, mechanism of action, variability of patient response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including DNA, RNA, proteins, lipids, and other cellular elements.

10.3.1. Samples for Genetic Biomarker Research

A blood sample will be collected for pharmacogenetic analysis as specified in the Study Schedule (Attachment 1) where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to LY3074828. Assessment of variable response may include evaluation of AEs or differences in efficacy.

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

Samples will be retained for a maximum of 15 years after the last subject visit for the study, or for a shorter period if local regulations and/or ERBs impose shorter time limits, at a facility selected by the sponsor. 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 becomes 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, and candidate gene studies. Regardless of technology utilized genotyping data generated will be used only for the specific research scope described in this section.

10.3.2. Samples for Exploratory Evaluation

Samples will be collected for potential nonpharmacogenetic biomarker research where local regulations allow. Samples may be used for research on IL-23, pathways associated with IL-23 biology, mechanism of action of LY3074828, and/or research method or in validating diagnostic tools or assay(s) related to ulcerative colitis.

Whole blood mRNA, serum, and plasma will be collected at the times specified in the study schedule (Attachment 1). Proteomic, gene-expression, genomic, epigenetic, or metabolomic analysis may be performed on these samples.

Samples will be identified by the subject number (coded) and stored for up to a maximum of 15 years after the last subject visit for the study at a facility selected by the sponsor.

10.4. Samples for Immunogenicity Research

Blood samples for immunogenicity testing will be collected as specified in the Study Schedule (Attachment 1) to determine antibody production against the IP. Additional samples may be collected if there is a possibility that an AE is immunologically mediated. Immunogenicity will be assessed by a validated assay designed to detect antidrug antibodies in the presence of the IP. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the IP. Immunogenicity samples may also be analyzed for LY3074828 concentrations to facilitate in the interpretation of immunogenicity data.

Samples may be stored for a maximum of 15 years following last subject visit for the trial at a facility selected by the sponsor to enable further analysis of immune responses to the IP. The duration allows the sponsor to respond to regulatory requests related to the IP.

10.5. Safety Evaluations

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. Planned safety assessments and measures are detailed in Section 10.5.3, but additional assessments and safety tests may be performed at the investigator's discretion.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to study treatment or the study, or that caused the subject to discontinue before completing the study. The subject should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

In addition to records of observations made at specific times, unexpected signs and symptoms and concomitant medications will be recorded in the clinical trial records throughout the study.

10.5.1. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent.

Cases of pregnancy that occur during maternal or paternal exposures to the IP should be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

After the informed consent form (ICF) is signed, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs. All AEs related to protocol procedures are reported to Lilly or designee.

Any clinically significant findings from ECGs, laboratory values, vital sign measurements, and other procedures should be reported as an AE to Lilly or its designee.

In addition, all AEs occurring after the subject receives the first dose of the IP must be reported to Lilly or its designee via CRF.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure, IP, and/or drug delivery system via the CRF.

The investigator decides whether he or she interprets the observed AEs as either related to disease, study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to the IP, the following terminologies are defined:

- **Related**: A direct cause and effect relationship between the study treatment and the AE is likely.
- **Possibly related**: A cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable but is also not impossible.
- **Unrelated**: Without question, the AE is definitely not associated with the study treatment.

As per Lilly's standard operating procedures all "related" and "possibly related" AEs and SAEs will be defined as related to the IP.

If a subject's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to Lilly or its designee via CRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

10.5.2. Serious Adverse Events

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

- 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
- considered significant by the investigator for any other reason

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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

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

SAE collection begins after the subject has signed informed consent and has received IP. If a subject experiences an SAE after signing informed consent but prior to receiving IP, the event will NOT be reported as serious unless the investigator feels the event may have been caused by a protocol procedure.

SAEs occurring up to and including the subject's last study visit will be collected, regardless of the investigator's opinion of causation, in the clinical data collection database and the pharmacovigilance system at the sponsor.

The investigator does not need to actively monitor subjects for AEs once the trial has ended unless specified in the protocol. However, if an investigator becomes aware of SAEs occurring to a subject after the subject's participation in the trial has ended, the investigator should report them to the sponsor, regardless of the investigator's opinion of causation, and the SAEs will be entered in the pharmacovigilance system at the sponsor.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the trial may be found in the IB.

10.5.2.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to IP or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

10.5.3. Other Safety Measures

10.5.3.1. Physical Examination

Physical examinations and routine medical assessments will be conducted as specified in the Study Schedule and as clinically indicated (Attachment 1).

10.5.3.2. Vital Signs

Blood pressure and pulse rate will be measured as specified in the Study Schedule and as clinically indicated (Attachment 1).

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

If orthostatic measurements are required, subjects should be supine for at least 5 minutes and stand for at least 3 minutes.

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

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured during each study period as per judgment of the investigator.

Body temperature (oral) will be measured as specified in the Study Schedule and as clinically indicated (Attachment 1).

10.5.3.3. Body Weight and Height

Body weight will be recorded as specified in the Study Schedule and as clinically indicated (Attachment 1). Height will be measured only at screening; subject is to remove shoes.

10.5.3.4. Electrocardiograms

For each subject, a 12-lead digital electrocardiogram (ECG) will be collected as replicates (triplicates) except for screening visit according to the Study Schedule (Attachment 1). 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. Consecutive replicate ECGs will be obtained at approximately 1-minute intervals. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of additional ECGs at a particular time point is allowed to ensure high-quality records.

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

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the subject for symptoms (for example, palpitations, near syncope, syncope) to determine whether 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 evaluation from at least 1 of the replicate ECGs from each time point.

Digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly. The central ECG laboratory will perform a basic quality control check (for example, demographics and study details) then store the ECGs in a database. At a future time, the stored ECG data may be overread at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements.

The machine-read ECG intervals and heart rate may be used for data analysis and report writing purposes unless a cardiologist overread of the ECGs is conducted prior to completion of the final study report (in which case the overread data would be used).

10.5.4. Safety Monitoring

The Lilly clinical pharmacologist or clinical research physician/scientist will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly clinical pharmacologist or research physician will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist when appropriate and periodically review:

- trends in safety data
- laboratory analytes
- AEs including monitoring of incidence of and nature of any infections, infusion reactions, and injection-site reactions

10.5.5. Complaint Handling

Lilly collects product complaints 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.

Complaints related to unblinded comparator drugs or concomitant drugs/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

For blinded studies, all product complaints associated with material packaged, labeled, and released by Lilly or its designee will be reported.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint 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.

10.6. Appropriateness and Consistency of Measurements

For this study, the safety and PK assessments are appropriate and follow standard practice during Phase 1 drug development.

10.7. Compliance

Every attempt will be made to select subjects who have the ability to understand and comply with instructions. Noncompliant subjects may be discontinued from the study. The time and day of drug administration will be recorded. Drug accountability records will be maintained by the study site.

The specifications in this protocol for the timings of safety and PK sampling are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based upon the safety and PK information obtained. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the CRF.

Any major modifications that might affect the conduct of the study, subject safety, and/or data integrity will be detailed in a protocol amendment.

11. Sample Size and Data Analyses

11.1. Determination of Sample Size

Up to 60 subjects may be enrolled in order that approximately 50 subjects complete the study. It is intended that 10 subjects (6 Japanese and 4 Caucasian) will be randomized in Cohort 1, and 8 subjects (4 Japanese and 4 Caucasian) will be randomized in Cohorts 2, 3, 4, 5, and 6. The sample size is customary for Phase 1 studies evaluating safety, tolerability, and PK parameters.

Subjects who are randomized but not administered treatment or do not provide sufficient safety and/or PK data may be replaced if judged necessary by the Lilly clinical pharmacologist. The replacement subject should be assigned to the same treatment as the discontinued subject and should be Japanese or Caucasian to match the discontinued subject.

11.2. Data Analysis Plans

11.2.1. General Considerations

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

PK analyses will be conducted on the full analysis set. This set includes all data from all randomized subjects receiving at least one dose of the IP according to the treatment the subjects actually received. Safety analyses will be conducted for all enrolled subjects, whether or not they completed all protocol requirements.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Analyses will be fully detailed in the statistical analysis plan. 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.

Data from subjects receiving placebo in the IV cohorts will be pooled to form 1 placebo group.

Data will be also summarized by race (Japanese and Caucasian) where appropriate.

11.2.2. Study Participant Disposition

All subjects who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

11.2.3. Study Participant Characteristics

The subject's age, sex, weight, BMI, height, race/subrace, or other demographic characteristics will be recorded and summarized by treatment group as well as overall.

11.2.4. Pharmacokinetic Analyses

11.2.4.1. Pharmacokinetic Parameter Estimation

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

The primary parameters for analysis will be C_{max} and AUC of LY3074828. Other noncompartmental parameters, such as half-life, clearance, and volume of distribution (apparent clearance and apparent volume of distribution for SC administration) may be reported.

11.2.4.2. Pharmacokinetic Statistical Inference

PK parameter estimates following IV administration will be evaluated to delineate effects of dose proportionality. Log-transformed C_{max} and AUC estimates will be evaluated in a power model with log-transformed dose as the explanatory variable. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% confidence interval (CI). Exploratory power model analysis based on the model including race and race-by-dose interaction terms will be also performed to examine the effect of the race on dose proportionality.

For the SC dose, the bioavailability relative to IV infusion at the same dose will be evaluated via a log-transformed model. The log-transformed C_{max} and AUC will be the response variable, and route of administration (IV or SC) is the explanatory variable and ratio (SC/IV), and its 90% CI will be calculated based on the model to assess the absolute bioavailability.

11.2.5. Pharmacodynamic Analyses

Not applicable.

11.2.6. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable.

11.2.7. Safety Analyses

11.2.7.1. Clinical Evaluation of Safety

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

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

11.2.7.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include vital signs, ECG parameters, and safety lab parameters. The parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

11.2.7.3. Evaluation of Immunogenicity

The frequency of antibody formation to LY3074828 and ADA titer will be determined. 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, etc.) will be assessed. Likewise, the relationship between the presence of antibodies and PK parameters will be assessed.

11.3. Interim Analyses

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

The first interim analysis is scheduled to occur when safety and PK data through Day 15 become available from at least 8 subjects in Cohort 1 including at least 3 Japanese subjects on LY3074828. All safety and PK data available from other cohorts by this time will be included in the interim analysis. The purpose of the interim analysis is to support the future inclusion of Japanese subjects in Study AMAC and to determine if dose escalation to 1200 mg should occur. The investigator and the Lilly study team will review the safety and tolerability data. The investigator will remain blinded and the Lilly study team will be unblinded during this interim review.

The data review for dose escalation to 2400 mg will not be included in the interim review.

An additional interim analysis may occur when safety and PK data through Day 15 becomes available from at least 6 subjects in Cohort 6, including at least 3 Japanese subjects. The purpose of this interim analysis is to support a future potential higher dosage in Study AMAG. The investigator and the Lilly study team will review the safety and tolerability data. The investigator will remain blinded and the Lilly study team will be unblinded during this interim review.

If ADA follow-up described in the Protocol Addendum 1 is needed for subjects in Cohort 6, another interim analysis may occur when all procedures of the main protocol for Cohort 6 are completed, even if the ADA follow-up is in process. The investigator and the Lilly study team will review all available data. The investigator will remain blinded and the Lilly study team will be unblinded during this interim review.

12. Data Management Methods

12.1. 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
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, 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 CRF 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 ERBs with direct access to the original source documents.

12.2. Data Capture Systems

12.2.1. Source Data and Case Report Form

A source document is the first record of data. These can be paper (for example, ECG tracing or patient diary), a paper CRF on which the data is initially recorded, or data captured directly on an investigator site electronic system (for example, Holter monitor record data files or electronic health record). The site must retain all source records and must maintain a record of any data where source data are directly entered into the paper CRF.

Data may then be entered into either an electronic or paper CRF, and the process will be documented and communicated by the sponsor to the investigator site before first patient visit.

Some investigator site data may be collected directly in the paper CRF whereas other data that is collected by the site on paper or electronic records may be transferred to the paper CRF.

Lilly does not allow direct source data entry into Lilly computer systems, with the exception of the investigator site systems at the Lilly clinical research unit.

For data handled by a data management TPO, CRF data and some or all data that are related will be managed and stored electronically in the TPO system. Subsequent to the final database lock, validated data will be transferred to the sponsor.

For data handled internally, CRF data and some or all data that are related will be managed by the sponsor and stored electronically in the sponsor's system.

12.2.2. Ancillary Data

Data managed by a central vendor will be stored electronically in the central laboratory's database system. Data will subsequently be transferred from the central vendor to the Lilly generic labs system and the TPO's system.

Bioanalytical data will be stored electronically in the bioanalytical laboratory's database. Data will subsequently be transferred from the bioanalytical laboratory to the Lilly generic labs system and the TPO's system.

ECG data will be stored electronically in the central database system of Lilly's central review organization. Data will subsequently be transferred from the central review organization system to the Lilly generic labs system and the TPO's system.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

The investigator is responsible for ensuring that the subject understands the potential risks and benefits of participating in the study, including answering any questions the subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject's willingness to continue his or her participation in the trial.

The ICF will be used to explain the potential risks and benefits of study participation to the subject in simple terms before the subject is entered into the study and to document that the subject is satisfied with his or her understanding of the potential risks and benefits of participating in the study and desires to participate in the study.

The investigator is ultimately responsible for ensuring that informed consent is given by each subject before the study is started. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of the IP.

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are used at investigative sites. All ICFs must be compliant with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline on GCP.

The investigator must give assurance that the ERB was properly constituted and convened as required by 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. The ERB(s) will review the protocol as required.

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

- the current IB and updates during the course of the study
- ICF
- relevant curricula vitae

13.3. Regulatory Considerations

This study will be conducted in accordance with:

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines

2) ICH GCP Guideline (E6)

3) applicable laws and regulations

The investigator or designee will promptly submit the protocol to applicable ERB(s).

Some of the obligations of the sponsor will be assigned to a TPO.

An identification code assigned by the investigator to each subject will be used in lieu of the subject's name to protect the subject's identity when reporting AEs and/or other trial-related data.

13.3.1. Investigator Information

Site-specific contact information may be provided in a separate document.

13.3.2. 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.

13.3.3. Final Report Signature

The investigator or designee will sign the clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

The sponsor's responsible medical officer and statistician will sign/approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

14. References

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Attachment 1. Protocol AMAD Study Schedule

Study Schedule Protocol I6T-JE-AMAD

Study Day	Screening ≤28 days	–2	–1	1	2	4	8	11[a]	15	22	29	43	57	71	85	ED
Visit Window						**± 1 d**	**± 1 d**	**± 1 d**	**± 2 d**	**± 2 d**	**± 2 d**	**± 3 d**	**± 3 d**	**± 3 d**	**±3 d**	
Informed consent	X															
Admission to CRU		X														
Discharge from CRU					X											
Review/confirm I/E criteria	X		X													
Complete medical history	X															
LY3074828 or placebo administration				X												
Weight	X			X							X				X	X
Height	X															
Complete physical examination	X		X												X	X
Directed physical examination				X	X	X	X		X	X	X	X	X	X		
Chest x-ray	X															
Concomitant medications	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review preexisting conditions/AEs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (pulse rate, blood pressure, and temperature)[b,c]	X		0, EI[d], 2[e], 6	0, EI[d], 2[e], 6	24	72	168	240	336	504	672	1008	1344	1680	2016	X
12-lead ECGs[c,f]	X		0, EI[d], 2[e], 6	0, EI[d], 2[e], 6	24	72	168	240	336	504	672	1008	1344	1680	2016	X
	Laboratory Tests															
QuantiFERON-TB Gold or TST	X															
HIV/HBV/HCV testing	X															
FSH[g]	X															
Serum pregnancy test[g]	X															
Urine pregnancy test[g]				X							X		X		X	X
Serum chemistry, hematology, and urinalysis	X		X		X		X		X		X		X		X	X
Exploratory storage samples (serum, plasma, RNA)				X					X		X		X	X	X	X
Pharmacogenetics storage sample (DNA)				X												

Study Schedule Protocol I6T-JE-AMAD

Study Day	Screening ≤28 days	–2	–1	1	2	4	8	11[a]	15	22	29	43	57	71	85	ED
Visit Window						**± 1 d**	**± 1 d**	**± 1 d**	**± 2 d**	**± 2 d**	**± 2 d**	**± 3 d**	**± 3 d**	**± 3 d**	**±3 d**	
Immunogenicity				X							X				X	X
LY3074828 (PK) concentration[h]				0, EI[d], 2[e], 6	24	72	168	240	336	504	672	1008	1344	1680	2016	X

Abbreviations: 0 = predose; AE = adverse event; CRU = clinical research unit; d = day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ED = early discontinuation; EI = end of infusion; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; I/E = inclusion/exclusion; IL = interleukin; lab = laboratory; PK = pharmacokinetic; TST = tuberculin skin test.

a Day 11 required for subjects receiving subcutaneous dosing only.

b Vital signs should be taken following an approximate 5-minute rest in supine position. Vital signs on days without dosing should be taken close to the Day 1 dosing time where possible.

c Time from starting infusion in hours, with the exception of Day –1. Time-matched ECGs and vital signs on Day –1 should approximately match the times planned on Day 1. Vital signs and ECG recording should occur prior to PK sampling, except at the end of infusion, at which time PK sampling will occur first.

d Required for intravenous cohorts only. PK samples will be collected precisely at end of infusion. Vital signs and ECGs should be taken approximately 10 minutes after the end of infusion.

e Not done for Cohort 3.

f ECGs should be taken after an approximate 5-minute rest in supine position. ECGs on days without dosing should be taken close to the Day 1 dosing time, where possible. ECGs will be collected in triplicate except for screening visit.

g All female subjects of childbearing potential will have serum pregnancy test at screening. For women who are considered to be postmenopausal, FSH should be drawn to confirm postmenopausal status as defined in inclusion criterion [1b] and to be considered exempt for further pregnancy tests during the study.

h Time from starting infusion in hours. Samples are requested to be taken at the specified time and on days without dosing should be taken close to the Day 1 dosing time where possible. Actual times of doses and samples are to be recorded accurately to the minute on the appropriate forms.

Attachment 2. Protocol AMAD Clinical Laboratory Tests

Laboratory Tests

Hematology:[a]	Clinical Chemistry[a]
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Calcium
Mean cell volume	Glucose fasting
Mean cell hemoglobin	Blood urea nitrogen (BUN)
Mean cell hemoglobin concentration	Uric acid
Leukocytes (WBC)	Total cholesterol
Cell Morphology	Total protein
Absolute counts of:	Albumin
Neutrophils	Total bilirubin
Lymphocytes	Alkaline phosphatase
Monocytes	Aspartate aminotransferase (AST)
Eosinophils	Alanine aminotransferase (ALT)
Basophils	Creatinine
Platelets	
Urinalysis[a]	Ethanol testing[c,d]
Specific gravity	Urine drug screen[c,d]
pH	Hepatitis B surface antigen[c]
Protein	Hepatitis B core antibody[c]
Glucose	Hepatitis C antibody[c]
Ketones	HIV antibodies[c]
Bilirubin	Pregnancy test (serum[a] and urine)
Urobilinogen	FSH[c]
Blood	QuantiFERON-TB Gold test[a,c]
Nitrite	
Microscopic examination of sediment[b]	

Abbreviations: FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; RBC = red blood cells; WBC = white blood cells.

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

b Test only if dipstick result is abnormal.

c Performed at screening only.

d Urine drug screen and ethanol level may be repeated prior to admission to the clinical research unit as per judgment of investigator.

Attachment 3. Protocol AMAD Blood Sampling Summary

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

Protocol I6T-JE-AMAD Sampling Summary

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	45	1	45
Clinical laboratory tests[a]	12.5	7	87.5
Pharmacokinetics	2	15+3	36
Immunogenicity	10	3	30
Pharmacogenetics	10	1	10
Exploratory storage samples (serum, plasma, RNA)	14.5	6	87
Total			295.5
Total for clinical purposes			300

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

Attachment 4. Protocol AMAD Blinding/Unblinding Plan

Levels of unblinding are indicated in the table below. This table provides general guidance as to who will be allowed access to randomization codes at various steps of the trial. The information in the protocol will always take precedence over this table. For interim analysis (IA), appropriate IA team members, including statistician, programmer, and data manager will be identified and agreed upon between Lilly and the TPO.

Randomization data are kept strictly confidential and are accessible only by authorized personnel until unblinding of the trial as described below. All measures possible must be taken to maintain the blind, which means that access to the randomization code must be restricted to authorized personnel as described in the protocol and summarized in the table below.

If there is a need for unblinding of select people from Lilly and/or the TPO who are not dealing with the site, the detailed process including formation of the unblinded team, creating restricted access electronic folders, and measures taken to guard against inappropriate dissemination of treatment codes (for example, by maintaining no contact with the study team until team is unblinded) will be described in the unblinding plan or another appropriate document and approval sought from Lilly and Covance team statisticians.

Study I6T-JE-AMAD Blinding and Unblinding Plan

	Study Timelines				
Study Team Member	**Screening**	**Randomization**	**Treatment Phase**	**Follow-Up**	**Database Lock**
General					
Drug supply	NA	U	U	U	U
Randomization statisticians	NA	U	U	U	U
ECG reader (if read later)	NA	B	B	B	B
BioAnalysis lab/sample analysis	NA	U	U	U	U
Clinical Site					
Pharmacist	NA	U	U	U	U
Dosing staff	NA	B	B	B	B
Subject	NA	B	B	B	B
Investigator	NA	B	B	B	B
Study monitor	NA	U	U	U	U
Covance/CDARO					
Project integration	NA	U	U	U	U
Data management	NA	U	U	U	U
Programming	NA	U	U	U	U
Statistician	NA	U	U	U	U
Medical writing	NA	U	U	U	U
Pharmacokinetic scientist/associate	NA	U	U	U	U
Lilly					
BioPharm coordinator	NA	U	U	U	U
CPA	NA	U	U	U	U
DSA	NA	U	U	U	U
SDTM core team	NA	U	U	U	U
Statistician	NA	U	U	U	U
Medical writing	NA	U	U	U	U
Clinical pharmacologist	NA	U	U	U	U
Pharmacokinetic scientist/associate	NA	U	U	U	U

Abbreviations: B = blinded; CPA = clinical pharmacology associate; DSA = data sciences associate; ECG = electrocardiogram; NA = not applicable; SDTM = study data tabulation model; U = unblinded.

Attachment 5. Protocol Amendment I6T-JE-AMAD(a) Summary: A Single-Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of LY3074828 in Japanese and Caucasian Healthy Subjects

Overview

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

The overall changes made to this protocol are due to the implementation of Cohort 6, which contains the additional higher dose of 2400 mg IV, which will be the new maximum dose in the study. Editorial changes and formatting corrections were made throughout the protocol, but not necessarily documented below. The rationale for the changes is as follows:

The original protocol assesses the safety, tolerability, and pharmacokinetic profile up to 1200 mg IV of LY3074828 in Japanese and Caucasian healthy subjects. Single doses of up to 1200 mg IV support the highest dose of 1000 mg IV in Phase 2 studies for patients with ulcerative colitis (Study AMAC) and Crohn's disease (Study AMAG), in that the safety data to date does not reveal any dose-related safety or tolerability issues with dose regimens of up to 1000 mg IV Q4W for up to 52 weeks.

Dose levels higher than 1000 mg may be required to support the best clinical outcomes in many auto-inflammatory disease indications, including IBD. Study 20029153 (4-week repeat-dose monkey study) showed the margin of safety for 2400 mg IV to be 1.9-fold. This value is based on the predicted exposure at 2400 mg in humans after a single dose compared to the observed exposure at 100 mg/kg IV, administered once weekly in monkeys. In this study, 100 mg/kg, the highest dose tested, was the NOAEL.

The 2400-mg IV dose was selected to support potential future studies in patients with ulcerative colitis and Crohn's disease, where higher IV doses (potentially beyond 1200 mg) during induction treatment may be required to maximize efficacy. Because the drug is degraded via the catabolic pathway (same as IgG) and the amount of drug is much smaller than the endogenous IgG in the body, it is unlikely that an unexpected PK profile will be observed after implementing a 2400-mg IV dose.

The overall changes and rationale for the changes made to this protocol are described in the following table:

Amendment Summary for Protocol I6T-JE-AMAD Amendment (a)

Section # and Name	Description of Change	Brief Rationale
Cover page	Approval date removed	New date will be timestamped upon approval of protocol amendment
Cover page	Cohort 6 added with 2400-mg dosage	• Single doses of up to 1200 mg IV to date did not reveal any safety or tolerability issues. • Dose levels higher than 1000 mg may be required to support the best clinical outcomes in many auto-inflammatory disease indications, including IBD. • Because the drug is degraded via the catabolic pathway (same as IgG) and the amount of drug is much smaller than the endogenous IgG in the body, it is unlikely that an unexpected PK profile will be observed after implementing a 2400-mg IV dose.
2. Synopsis, Number of Planned Subjects	Number of planned subjects increased from 42 to 50	
2. Synopsis, Study Design	Cohort 6 added with 2400-mg dosage	
2. Synopsis, Investigational Product, Dosage, and Mode of Administration	Cohort 6 added with 2400-mg dosage	
2. Synopsis: Evaluation Methods	Cohort 6 added (n=8); number of planned subjects completing study increased from 42 to 50; added information regarding a possible interim analysis for Cohort 6 subjects	
Table of Contents: List of Attachments, Attachment 5	Protocol amendment section added	Added as per template
5.1 General Introduction	Updated per IB	Consistent with IB
7.1. Summary of Study Design	Cohort 6 added; both Cohorts 5 and 6 will be dosed after confirming the safety and PK from Cohort 1 and Cohort 5, respectively	• Single doses of up to 1200 mg IV to date did not reveal any safety or tolerability issues. • Dose levels higher than 1000 mg may be required to support the best clinical outcomes in many auto-inflammatory disease indications, including IBD. • Because the drug is degraded via the catabolic pathway (same as IgG) and the amount of drug is much smaller than the endogenous IgG in the body, it is unlikely that an unexpected
7.1. Summary of Study Design, Figure AMAD.2. Study design for Protocol I6T JE AMAD.	Cohort 6 added with details	
7.1. Summary of Study Design; Treatment	Cohort 6 description added, safety and PK assessment added between Cohort 1 and 5, then 5 and 6	
7.2. Discussion of Design and Control	Cohort 6 2400-mg dosage added	
8.1.1. Inclusion Criteria	Cohort 6 added to Exclusion Criterion [5]	
9.2. Treatment Administration;	New column added to table with	

Table AMAD. 1.	Cohort 6 description	PK profile will be observed after implementing a 2400-mg IV dose.
9.3. Rationale for Selection of Dose	Cohort 6 description added, safety and PK assessment added between Cohort 1 and 5, then 5 and 6	
9.3. Rationale for Selection of Dose, Table AMAD.2	Cohort 6 added, paragraphs moved within this same section and added to for readability. Table AMAD.2 updated with 2400-mg dosing information	
9.4. Dose Escalation 9.4.1. Dose Escalation Method	Cohort 6 description added, safety and PK assessment added between Cohort 1 and 5, then 5 and 6	
11.1. Determination of Sample Size	Cohort 6 added, sample size increased from 42 subjects to 50 subjects	
11.3 Interim Analyses	Interim analysis information added for Cohort 6	Cohort 6 added
14. References	References added	References added to reflect higher dosing

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

Amendment Summary for Protocol I6T-JE-AMAD Amendment (a)

Section # and Name	Additions and Deletions
Cover page	The study will consist of ~~5~~ 6 planned dose cohorts: ~~4~~ 5 intravenous cohorts (60 mg, 200 mg, 600 mg, ~~and~~ 1200 mg, and 2400 mg)
Cover page	~~Approval Date: 11-Aug-2015 GMT~~
2. Synopsis, Number of Planned Subjects	approximately ~~42~~50
2. Synopsis, Study Design	The study will consist of ~~5~~ 6 planned dose cohorts: ~~4~~ 5 IV cohorts (60 mg, 200 mg, 600 mg, ~~and~~ 1200 mg, and 2400 mg) and 1 SC cohort (200 mg).
2. Synopsis, Investigational Product, Dosage, and Mode of Administration	A single dose of LY3074828 will be administered IV at the planned dose levels of 60 mg, 200 mg, 600 mg, ~~and~~ 1200 mg, and 2400 mg.
2. Synopsis: Evaluation Methods	Up to 60 subjects may be enrolled in order that approximately ~~42~~ 50 subjects complete the study. It is intended that 10 subjects (6 Japanese and 4 Caucasian) will be randomized in Cohort 1, and 8 subjects (4 Japanese and 4 Caucasian) will be randomized in Cohorts 2, 3, 4,5, and ~~5~~6. … The first i~~I~~nterim analysis is scheduled to occur when safety and PK data through Day 15 become available from at least 8 subjects in Cohort 1, including at least 3 Japanese subjects on LY3074828. An additional interim analysis may occur when safety and PK data through Day 15 becomes available from at least 6 subjects in Cohort 6, including at least 3 Japanese subjects on LY3074828.
Table of Contents: List of Attachments, Attachment 5	List of Attachments Attachment 5. Protocol Amendment I6T-JE-AMAD Summary: A Single-Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of LY3074828 in Japanese and Caucasian Healthy Subjects…..58
5.1 General Introduction	… The first such biologic to demonstrate clinical benefit in autoimmune disease was ustekinumab, which is now an approved medicine for the treatment of patients with psoriasis and psoriatic arthritis (Stelara package insert, 2013) and ~~is being evaluated in Phase 3 trials for treatment of~~ CD (Toussirot et al. 2013). ... One study, Study I6T-MC-AMAA (AMAA): A Phase 1, Randomized, Placebo-Controlled Study of LY3074828, an Anti-IL-23 Humanized Antibody in Subjects With and

	Without Psoriasis, has been completed ~~conducted to date~~evaluating. This study evaluated LY3074828 in healthy volunteers and in subjects with plaque psoriasis. ... • No deaths, serious adverse events (SAEs), or discontinuations due to an adverse event (AE) were reported. • ~~Preliminary data from subjects administered single doses of up to 600 mg IV indicate that LY3074828 has linear pharmacokinetics (PK), a low IV clearance (approximately 0.02 L/h), and long half-life (~10 days), all of which are consistent with expectations for a monoclonal antibody. SC bioavailability was 40% to 50%.~~ • ~~Treatment-emergent antidrug antibodies (ADAs) developed in 3 subjects after administration of single IV doses of LY3074828, (120 mg, 2 subjects; 350 mg, 1 subject). No subject had ADAs after SC administration. There was no correlation between ADA titers and the doses of LY3074828.~~ • ~~There have not yet been any studies conducted for LY3074828 with efficacy as a primary objective. However,~~ Following single IV doses of LY3074828 in Study AMAA, the area under the curve (AUC) and maximum drug concentration (C_{max}) increased in approximately a dose-proportional manner. The mean terminal phase half-life across all IV doses was 10.5 days and did not appear to be dependent on dose, and the mean clearance is within the range expected for human monoclonal antibodies. The overall mean clearance across all doses following IV administration was approximately 0.526 L/day and is within the range expected for human monoclonal antibodies. Maximum concentrations were observed 3 days postdose following SC administration. Based on the AUC, the SC bioavailability was 40% relative to IV administration. • Immunogenicity evaluations were performed in Study AMAA. Blood samples to evaluate anti-drug antibodies (ADA) were collected at baseline and approximately 22, 43, and 85 days postdose. ADA data were available for 45 subjects, 38 who received LY3074828 and 7 who received placebo. All subjects who received placebo were ADA negative at baseline and postbaseline. Only one subject who received LY3074828 was positive at baseline. Thirty-one subjects who received LY3074828

	(81.6%) were negative at all postbaseline time points evaluated. Seven subjects who received LY3074828 had a postbaseline positive titer; however, only 3 of those subjects (7.9% of LY3074828-treated individuals) developed treatment-emergent ADA, defined as a 4-fold or greater change in titer from baseline. None of these cases of treatment-emergent anti-drug antibodies (TE-ADA) were associated with treatment-emergent adverse events (TEAEs). … Phase 2 studies investigating the efficacy of LY3074828 as a potential treatment for psoriasis (AMAF), ulcerative colitis (AMAC), and Crohn's disease (AMAG) are currently ongoing. ~~However,~~ ~~I~~in Study AMAA, clinical activity was explored… … Information on AEs expected to be related to the IP may be found in Section ~~7~~ 6 (Development Core Safety Information) of the IB.
7.1. Summary of Study Design	Subjects will be randomized to LY3074828 or placebo within 1 of ~~5~~6 cohorts, as shown in Figure AMAD.2. … Cohorts 2 through ~~5~~ 6 will consist of 8 subjects (4 Japanese and 4 Caucasian) who are randomized in a 3:1 ratio of LY3074828 to placebo. … Single doses up to 600 mg IV have been studied and shown to be well tolerated, therefore all cohorts, with the exception of Cohort 5 and Cohort 6, may be dosed in parallel if the site is able to accommodate more than 1 cohort at a time. Cohort 5 will be dosed after confirming the safety and PK data from Cohort 1. Cohort 6 will be dosed last after confirming the safety and PK data from Cohort ~~1~~ 5.
7.1. Summary of Study Design, Figure AMAD.2.	Cohort 6 added, arrow showing safety and PK assessment between Cohort 1 and 5, then 5 and 6
7.1. Summary of Study Design; Treatment	… **Treatment:** **…** Cohort 6: a single dose of LY3074828 2400 mg or placebo IV
7.2 Discussion of Design and Control	The dose levels included in this single-dose study are within the range of doses studied previously, with the exception of the planned 1200 mg and 2400 mg IV dose cohort~~, for which the expected exposure has an appropriate safety margin based on the preclinical toxicity data (see Section 9.3 for additional information)~~.
8.1.1. Inclusion Criteria	[5] have a body weight of 40.0 kg or higher for Cohorts 1 to 4 and 48.0 kg or higher for Cohort 5 and Cohort 6

9.2. Treatment Administration; Table AMAD. 1.	Cohort 6, 2400 mg IV; 25 mg/mL, 96 mL
9.3. Rationale for Selection of Dose	The 4 5 IV doses for this study are 60, 200, 600, ~~and~~ 1200, and 2400 mg and the SC dose for this study is 200 mg. … The low dose of 60 mg IV for this study is ~~was~~ chosen as one of the doses that was administered in the global… ... The 200-mg IV dose is one of the starting doses in Study AMAC and is one of the doses that was administered in Study AMAA. ~~It is also the SC dose that will~~ A dose of 200 mg SC is being administered in the maintenance period of Study AMAC. The 600-mg IV dose is the highest dose being tested in Study AMAC and is the highest dose that was administered in Study AMAA. The original highest dose of 1200 mg, IV was tested for safety and tolerability, based on the safety results at each escalation cohort of this study. Findings from these results supported the highest dose of 1000 mg IV in the Phase 2 Crohn's disease study (Study AMAG). The amended maximum dose of 2400 mg IV is selected to support potential future studies in patients with ulcerative colitis and Crohn's disease, where high IV doses (potentially beyond 1200 mg) during induction treatment may be required to maximize efficacy (Sandborn et al. 2012; Adedokun et al. 2016; Feagan et al. 2016). The margin of safety at 2400 mg IV is 1.9-fold. This value is based on the predicted exposure at 2400 mg compared to the observed exposure at 100 mg/kg IV, administered once weekly, in the 4-week, repeat-dose monkey study. In this study, 100 mg/kg was the no observed adverse-effect level (NOAEL) and also the highest dose tested. (see Table AMAD.2). … Due to a lack of a preclinical disease model, the anticipated minimally effective dose for LY3074828 is unknown. The clinical dose range for LY3074828 is not yet known, and the maximum planned LY3074828 dose level to be evaluated in ~~the Phase 2 ulcerative colitis~~ Study AMAC is 600 mg. … Therefore, this study ~~plans~~planned to evaluate the safety, tolerability, and PK of a 1200-mg IV dose of LY3074828. ~~Evaluation of this additional higher dose cohort will provide safety and PK data to support the use of a higher dose level in~~

	~~later clinical development. The 1200-mg dose cohort (Cohort 5) will be dosed after safety, tolerability, and PK data are confirmed from the 600-mg dose cohort (Cohort 1). A 2-fold dose escalation will provide the most informative PK data, as there is minimal overlap between the 600-mg and 1200-mg doses on the basis of data obtained from simulations. Other dose levels may be dosed concurrently in this study because these doses have already been shown to be well tolerated in Study AMAA. As shown in Table AMAD.2, the proposed maximum dose of 1200 mg IV infusion has a sufficient margin of safety both in terms of dose and exposure.~~ The 1200-mg IV dose cohort (Cohort 5) was dosed after safety, tolerability, and PK data were confirmed from the 600-mg dose cohort (Cohort 1). Other dose levels were~~as~~ dosed concurrently in this study because these doses have already been shown to be well tolerated in Study AMAA. Evaluation of 1200-mg IV dose cohort (Cohort 5) provided safety and PK data to support the use of a higher dose level in Study AMAC and Study AMAG. In addition to the above evaluation, this study is amended to add the evaluation of safety, tolerability, and PK of a 2400-mg IV dose of LY3074828, since there is a possibility to evaluate a higher dose level up to 2400 mg IV in later clinical development. The proposed dose of 2400 mg IV infusion has a sufficient margin of safety in terms of dose. Moreover, the clinical safety profile of LY3074828 available to date supports 2400-mg IV administration in this study. Single doses of up to 1200 mg IV were evaluated in healthy subjects from Study AMAD and no dose-related safety or tolerability issues were observed. Evaluation of the safety data available to date in the ongoing Study AMAC and Study AMAG that are evaluating higher and more frequent dose regimens of up to 1000 mg IV Q4W for up to 52 weeks has not revealed any differences in the safety profile. The PK profile of this drug was found to be approximately linear up to 1200-mg IV administration. Since the 2400-mg IV dose is only 2-fold of 1200 mg, it is unlikely that an unexpected PK profile will be observed after administration of a 2400-mg IV dose. Therefore, evaluation of this additional higher dose cohort (2400 mg) will provide safety and PK data to support the use of a higher dose level beyond 1200 mg during the clinical development of this compound.
9.3. Rationale for Selection of Dose, Table AMAD.2	[Title]: Margin of Safety for Intravenous Administration of ~~1200~~ 2400 mg Human highest dose: (~~1200~~ 2400 mg): Dose: ~~18.5~~ 36.9 (IV); $AUC_{0\text{-}672h,ss}$ ~~53800~~ 110000

	Monkey NOAEL[d] 6-month study: Dose Multiple: ~~5.4~~ 2.7; Margin of Safety: ~~1.6~~ 0.78 Monkey NOAEL[d]: Dose Multiple: ~~5.4~~ 2.7; Margin of Safety: ~~3.8~~ 1.9 Footnote c:… Human $AUC_{0\text{-}672h,ss}$ at ~~1200~~ 2400 mg IV is predicted on the basis of the average IV clearance (0.526L/day) ~~observed in~~ from Study I6T-MC-AMAA. ~~for doses between 5 mg and 350 mg.~~
9.4. Dose Escalation	All doses in this study, with the exception of the 1200-mg and 2400-mg doses, have been previously tested and shown to be well tolerated in Study AMAA. The only dose escalation decisions in this study will be made to proceed from the 600-mg cohort (Cohort 1) to the 1200-mg cohort (Cohort 5) and the ~~600~~ 1200-mg cohort (Cohort ~~1~~ 5) to the ~~1200~~ 2400-mg dose cohort (Cohort ~~5~~ 6). Safety and PK data reviewed at the time of the first interim analysis will be used for the escalation decision to the 1200-mg dose. Safety and PK data up to the 1200-mg dose cohort will be reviewed before dose escalation to 2400 mg.
9.4.1. Dose Escalation Method	… After review of the data, an agreement on the appropriate dose escalation will be made by the investigator and sponsor for ~~the 1200-mg cohort (~~Cohort ~~56). The planned dose for Cohort 5 is 1200 mg, but depending on the observations from the 600 mg cohort (Cohort 1), the magnitude of the dose escalation may be reduced following data review; the maximum dose for the study will be 1200 mg.~~ ~~If any of the following scenarios occur at 600 mg LY3074828, dose escalation to 1200 mg will not take place, and the dose for Cohort 5 may be reduced or the cohort will be canceled:~~ None of the following scenarios occurred at 1200-mg LY3074828,
11.1. Determination of Sample Size	Up to 60 subjects may be enrolled in order that approximately ~~42~~ 50 subjects complete the study. It is intended that 10 subjects (6 Japanese and 4 Caucasian) will be randomized in Cohort 1, and 8 subjects (4 Japanese and 4 Caucasian) will be randomized in Cohorts 2, 3, 4, ~~and~~ 5, and 6.
11.3 Interim Analyses	The first ~~I~~interim analysis is scheduled to occur when when safety and PK data through Day 15 become available … … The data review for dose escalation to 2400 mg will not be included in the interim review. An additional interim analysis may occur when safety and PK data through Day 15 becomes available from at least 6 subjects in Cohort 6, including at least 3 Japanese subjects. The purpose of this interim analysis is to support a future

	potential higher dosage in Study AMAG. The investigator and the Lilly study team will review the safety and tolerability data. The investigator will remain blinded and the Lilly study team will be unblinded during this interim review. If ADA follow-up described in the Protocol Addendum 1 is needed for subjects in Cohort 6, another interim analysis may occur when all procedures of the main protocol for Cohort 6 are completed, even if the ADA follow-up is in process. The investigator and the Lilly study team will review all available data. The investigator will remain blinded and the Lilly study team will be unblinded during this interim review.
14. References	Adedokun OJ, Xu Z, Gasink C, Friedman J, Szapary P, Lang Y, Johanns J, Gao L-L, Miao Y, Davis H, Hanauer S, Feagan B, Sandborn W. Pharmacokinetics and exposure-response relationships of intravenously administered ustekinumab during induction treatment in patients with Crohn's disease: results from the UNITI-1 and UNITI-2 studies. Oral presentation at: 11th Congress of European Crohn's and Colitis Organisation (ECCO): Inflammatory Bowel Diseases; Mar 16-19, 2016; Amsterdam: The Netherlands. Oral presentation (OP) 028. … Feagan BG, Sandborn W, Panés J, Ferrante M, Louis E, D'Haens GR, Franchimont D, Kaser A, Dewit O, Seidler U, Kim K-J, Neurath M, Scholl P, Visvanathan S, Padula S, Herichova I, Soaita A, Hall D, Böcher WO. Efficacy and safety of induction therapy with the selective IL-23 inhibitor BI 655066, in patients with moderate-to-severe Crohn's disease: results of a randomized, double-blind, placebo-controlled Phase II study. Gastroenterology. 2016;150(4) suppl 1:S1266. Abstract 812a. … Sandborn WJ, Gasink C, Gao LL, Blank MA, Johanns J, Guzzo C, Sands BE, Hanauer SB, Targan S, Rutgeerts P, Ghosh S, de Villiers WJ, Panaccione R, Greenberg G, Schreiber S, Lichtiger S, Feagan BG; CERTIFI Study Group. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. N Engl J Med. 2012;367(16):1519-1528.

Leo Document ID = fd22d648-6b60-4d2c-ade1-38a575f42ba1

Approver: PPD
Approval Date & Time: 23-Jan-2018 03:00:15 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 23-Jan-2018 14:08:22 GMT
Signature meaning: Approved