Protocol I6T-MC-AMAC (c)

A Phase 2, Multicenter, Randomized, Double-Blind, Parallel, Placebo-Controlled Study of LY3074828 in Subjects with Moderate to Severe Ulcerative Colitis

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Approval Date: 10-Jul-2018

1. Protocol I6T-MC-AMAC(c)
A Phase 2, Multicenter, Randomized, Double-Blind, Parallel, Placebo-Controlled Study of LY3074828 in Subjects with Moderate to Severe Ulcerative Colitis

LY3074828

Study I6T-MC-AMAC is a Phase 2, multicenter, randomized, double-blind, placebo-controlled trial of LY3074828 in subjects with moderate to severe ulcerative colitis.

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Amendment (c) Electronically Signed and Approved by Lilly on approval date provided below.

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2. Synopsis

Study Rationale

Ulcerative colitis (UC) is a chronic disease of unknown cause that is characterized by inflammation in the colon. Subjects have intermittent disease flares interspersed with periods of remission; the primary symptoms are blood in the stool, diarrhea, and abdominal pain, which reduce overall quality of life. Many subjects with UC experience a severe clinical course: approximately 30% require colectomy within 10 years of diagnosis (Ordás et al. 2012a).

Various biologic therapies that target specific immunological pathways have been studied as potential therapeutics for UC. Experimental studies suggest that blocking the interleukin-23 (IL-23)/T helper 17/interleukin-17 immune axis alone is effective to treat inflammation in UC (Monteleone et al. 2009). Agents specifically targeting the IL-23 p19 subunit, including LY3074828, are in development for many autoinflammatory diseases to determine whether improvement in efficacy can be achieved by targeting IL-23 specifically (Gaffen et al. 2014).

LY3074828 is a humanized immunoglobulin G4–variant monoclonal antibody (molecular weight approximately 144,000 Da) that is directed against the p19 subunit of IL-23 and does not bind interleukin-12.

Eli Lilly has an ongoing (database locked, clinical study report pending) Phase 1 (first-in-human) ascending-dose study in which 33 subjects with psoriasis and 5 healthy subjects have each been administered a single dose of LY3074828. No serious adverse events (SAEs) were reported, and no subject was discontinued because of an adverse event (AE).

This Phase 2 study will provide efficacy data on intravenous (IV) administration of LY3074828 (3 doses versus placebo) in subjects with moderate to severe UC.

Clinical Protocol Synopsis: Study I6T-MC-AMAC

Name of Investigational Product:
LY3074828

Title of Study: A Phase 2, Multicenter, Randomized, Double-Blind, Parallel, Placebo-Controlled Study of LY3074828 in Subjects with Moderate to Severe Ulcerative Colitis

Number of Planned Subjects:	**Phase of Development:** Phase 2
Approximately 240 subjects will be randomized.	

Length of Study: Subject participation is up to 120 weeks
Estimated first subject visit: November 2015 Estimated last subject visit: October 2019

Objectives: The primary objective of this study is to test the hypothesis that treatment with LY3074828 is superior to placebo in inducing clinical remission at Week 12 in subjects with moderate to severe ulcerative colitis (UC).

The secondary objectives are:

- To evaluate the safety and tolerability of treatment with LY3074828
- To evaluate the efficacy of treatment with LY3074828 in inducing a clinical response at Week 12
- To evaluate endoscopic remission at Week 12 and Week 52
- To evaluate the effect of maintenance treatment with LY3074828 on the durability of clinical remission, endoscopic remission, and clinical response at Week 52
- To evaluate the effect of LY3074828 on health outcomes/quality of life measures (Inflammatory Bowel Disease Questionnaire score, 36-Item Short Form Health Survey score, Patient's Global Impressions of Severity score, and Patient's Global Impressions of Improvement score)
- To characterize the pharmacokinetic (PK) profile of LY3074828

Study Design: Study I6T-MC-AMAC is a multicenter, randomized, double-blind, parallel-arm, placebo-controlled trial in which approximately 240 subjects will be randomized. Subjects must have moderate or severe UC (defined as a Mayo score of 6 to 12 with an endoscopic subscore ≥2). Approximately two-thirds (~160) of the subjects randomized to study treatment must have been exposed to at least 1 previous biologic therapy (such as tumor necrosis factor antagonists, vedolizumab, or experimental UC biologic), and approximately one-third (~80) of the subjects will be naive to biologic therapy.

Screening Period: Subjects will be evaluated for study eligibility ≤28 days before the baseline visit. At the baseline visit, subjects who fulfill the eligibility criteria will be randomized equally to 1 of 4 induction treatment arms.

Induction Period: A 12-week induction period is designed to establish the efficacy and safety of LY3074828 administered IV at Weeks 0, 4, and 8. Subjects will be stratified across the treatment arms on the basis of previous exposure to biologic therapy for treatment of UC. Subjects who discontinue the study for any reason before the end of the induction period will complete the induction period early termination visit.

Maintenance Period: The maintenance period is designed to explore the safety and durability of clinical responses and remissions to treatment with 200-mg LY3074828 administered subcutaneously (SC) every 4 weeks (Q4W) or every 12 weeks (Q12W). Subjects defined as having clinical responses at Week 12 will continue study participation in the maintenance period up to Week 104. Subjects who do not meet clinical response criteria at Week 12 will have the option to continue in a study extension period or discontinue from the study.

Responding subjects who have received LY3074828 in induction period will be re-randomized to 1 of 2 LY3074828 maintenance treatment arms (200 mg Q4W or 200 mg Q12W); these subjects will be stratified according to their Week-12 remission status. Any responding subjects in the placebo arm SC Q4W will remain on placebo. After Week 52, subjects who experience worsening of UC (partial Mayo score of 7 or more) may receive rescue treatment with LY3074828 200 mg SC Q4W. Subjects who discontinue the study for any reason during the maintenance period will complete the maintenance period early termination visit.

Maintenance Follow-Up Period: The follow-up period will include a visit every 4 weeks for a total of 16 weeks following Week 104 to assess subject safety. Subjects who discontinue the study for any reason during the maintenance follow-up period will complete the maintenance period early termination visit.

Extension Period: Subjects who complete the study induction period (through Visit 7) but do not have a clinical response may choose to participate in the unblinded study extension period following consultation with, and at the discretion of, the investigator. Subjects who discontinue the study for any reason during the extension period will complete the extension period early termination visit.
Extension Follow-Up Period: A follow-up period will include a visit every 4 weeks for a total of 16 weeks following Extension Week 92 to assess subject safety. Subjects who discontinue the study for any reason during the extension follow-up period will complete the extension period early termination visit.

Diagnosis and Main Criteria for Inclusion and Exclusions: This study will include male or female subjects ≥18 and ≤75 years of age with moderate to severe active UC (defined as a Mayo score of 6 to 12 with an endoscopic subscore ≥2).

Investigational Product, Dosage, and Mode of Administration or Intervention:
Induction Period:
50 mg, 200 mg, or 600 mg LY3074828 given as an IV infusion (Weeks 0, 4, 8)
The 50-mg and 200-mg arms will use exposure-based dosing: doses for individuals in the 50-mg and 200-mg arms may be increased at Weeks 4 and 8 if the projected trough concentrations of LY3074828 for those visits fall below prespecified thresholds. Dose level changes in these patients will be communicated to the site by the sponsor.
Maintenance Period:
Responding subjects (as defined by the protocol) will be re-randomized to receive 200 mg LY3074828 given SC either Q4W or Q12W.
Extension Period:
Nonresponding subjects (as defined by the protocol) may continue in the study and receive LY3074828.

Reference Therapy, Dose, and Mode of Administration or Comparative Intervention:
Induction Period: Placebo (0.9% normal saline) as an IV infusion (Weeks, 0, 4, 8)
Maintenance Period: Placebo given SC Q4W

Planned Duration of Treatment:
Induction period: 12 weeks
Maintenance period: 92 weeks
Extension period (for nonresponders): 92 weeks

Criteria for Evaluation:
Efficacy: The following efficacy measures will be assessed in this study: clinical remission at Week 12, clinical response at Week 12, and endoscopic remission at Week 12 and Week 52.
Safety: The following safety measures will be assessed in this study: AEs; SAEs; vital signs; electrocardiograms (ECGs); physical examinations; and laboratory safety evaluations including chemistry, hematology, and urinalysis.
Health Outcomes: The following health outcomes measures will be assessed in this study: Patient's Global Impressions of Severity score, Patient's Global Impressions of Improvement score, Inflammatory Bowel Disease Questionnaire score, and 36-Item Short Form Health Survey score.
Pharmacokinetic: Serum for the measurement of LY3074828 time-concentration profiles will be collected as specified in the visit schedule.

Statistical Methods:
Statistical: Approximately 240 subjects will be randomized to 1 of 4 double-blind treatment regimens: placebo, 50 mg LY3074828 exposure-based dosing, 200 mg LY3074828 exposure-based dosing, or the 600-mg LY3074828 fixed-dose treatment group in a 1:1:1:1 ratio (~60 subjects per arm). Approximately one-third are to be biologic-naive subjects (~20 per arm) and approximately two-thirds are to have been exposed to at least 1 previous biologic agent (~40 per arm).
Efficacy analyses will be conducted on the intent-to-treat population. Safety analyses will be conducted on the safety population. Subjects will be analyzed according to the treatment to which they were assigned.
All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05 unless otherwise stated. Summary statistics for continuous variables may include mean, standard deviation, median, and minimum and maximum

values; categorical variables will be presented as counts and percentages.

Efficacy: The rates of remission and nonremission will be summarized by dose level and previous biologic use (yes/no). For categorical measures of efficacy, the differences between each treatment arm and placebo will be tested separately via a logistic regression model that controls for previous biologic use.

Safety: Safety will be assessed by evaluating all reported AEs and changes in laboratory analytes, ECGs, and vital signs (including body weight). Duration of exposure to therapy will be calculated for each subject and summarized by treatment group.

In the analysis of treatment-emergent adverse events (TEAEs) during the induction period, all preexisting conditions recorded at screening (Visit 1) and any on-study AEs recorded at or before dosing at baseline (Visit 2) will be used as baseline. The induction period and the maintenance period will be analyzed separately. For each event classification term, the number of subjects experiencing a TEAE with that classification term will be tabulated.

Additional safety parameters include laboratory test results, ECGs, and vital-sign measurements. The baseline for computing the change in safety variables for the induction period will be data collected at or before dosing on Visit 2; the baseline for the maintenance period will be the last value collected during the induction period. The parameters will be listed and summarized with standard descriptive statistics. Change from baseline will also be summarized by randomized treatment.

Health Outcomes: Mean change from baseline in health outcomes measures will be summarized by treatment group.

Pharmacokinetics/Pharmacodynamics:

Population PK analyses will be performed to characterize the PK of LY3074828 after IV and SC dosing. These analyses will include model-based and graphical evaluations of the data. Estimates of PK model parameters and covariate effects and corresponding 90% confidence intervals will be reported.

Population PK/PD analyses will be conducted to evaluate the relationship between LY3074828 concentrations and/or dose and clinical response as measured by the primary endpoint of clinical remission, Mayo subscores, and other biomarkers and endpoints.

3. Table of Contents

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4. Abbreviations and Definitions

Term	Definition
5-ASA	5–aminosalicylic acid
6-MP	6-mercaptopurine
AE	adverse event: Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event 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.
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AZA	azathioprine
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, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s)
blinding/masking	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
clinical remission	Achievement of the following Mayo subscores at Week 12: a rectal bleeding subscore of 0, stool frequency subscore of 0 or 1 (with 1 point decrease from baseline), and endoscopy subscore of 0 or 1.
clinical research physician	individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
clinical response	Achievement of a decrease in 9-point Mayo subscore (rectal bleeding, stool frequency, and endoscopy) inclusive of ≥2 points and ≥35% from baseline with either a decrease of rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1.

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, 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
ECG	electrocardiogram
efficacy or effectiveness	Efficacy is the ability of a treatment to achieve a beneficial intended result under controlled conditions. Effectiveness is the measure of the produced effect of an intervention when carried out in a real-world clinical environment.
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 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: a board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the subjects participating in a clinical study are protected
GCP	good clinical practice
HBcAb+	tests positive for anti–hepatitis B core antibody
HBV DNA	hepatitis B deoxyribonucleic acid
IB	investigator's brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	informed consent form
ICH	International Conference on Harmonisation

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 study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	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 study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
ITT	intent-to-treat
IV	intravenous
IWRS	interactive web-response system
open-label	a study in which there are no restrictions on knowledge of treatment allocation; therefore, the investigator and the study participant are aware of the drug therapy received during the study
PASI	Psoriasis Area and Severity Index
PCR	polymerase chain reaction
PGI-I	Patient's Global Impressions of Improvement
PGI-S	Patient's Global Impressions of Severity
PK/PD	pharmacokinetics/pharmacodynamics
PPD	purified protein derivative
PRO	patient-reported outcome
Q4W	every 4 weeks
Q12W	every 12 weeks
randomize	the process of assigning subjects to an experimental group on a random basis
rescreen	to screen a subject who was previously declared a screen failure for the same study

SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
screen	the act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, diagnostic psychological tests, x-rays, 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.
SF-36	36-Item Short Form Health Survey
subject	an individual who is or becomes a participant in clinical research after confirming informed consent. A subject may be either a healthy human or a patient.
SUSARs	suspected unexpected serious adverse reactions
TB	tuberculosis
TEAE	treatment-emergent adverse event: any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
Th17	T helper 17
TNF	tumor necrosis factor
TPO	third-party organization
ULN	upper limit of normal

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5. Introduction

Ulcerative colitis (UC) is a chronic disease of unknown cause that is characterized by inflammation in the colon. Patients have intermittent disease flares interspersed with periods of remission; the primary symptoms are blood in the stool, diarrhea, and abdominal pain, which reduce overall quality of life. Many patients with UC experience a severe clinical course: approximately 30% require colectomy within 10 years of diagnosis (Ordás et al. 2012a).

The treatment goal in UC is the induction and maintenance of remission (including steroid-free remission). Conventional medications used for treatment of UC include 5- aminosalicylic acid (5-ASA), steroids, and immunosuppressive drugs such as azathioprine (AZA) and 6-mercaptopurine (6-MP). However, as many as 40% of patients with UC do not respond or maintain a response to conventional medications and require secondary drug treatment or colectomy (Burger et al. 2011). As a result, various biologics that target specific immunological pathways have been studied as potential therapeutics for UC. Anti–tumor necrosis factor α monoclonal antibodies and more recently vedolizumab, an integrin receptor antagonist, have been approved by the Food and Drug Administration and by the European Medicines Agency.

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 is shared by IL-12, and the p19 subunit, which is 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), and is critically involved in the maintenance and amplification of T helper 17 (Th17) cells. Stimulation of these cells with IL-23 induces a unique inflammatory signature that includes interleukin-17A, interleukin-17F, interleukin-6, granulocyte-macrophage-colony stimulating factor, tumor necrosis factor α, chemokine ligand 20, chemokine ligand 22, and IL-23 receptor (Langrish et al. 2005; Dong 2008). 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/inflammatory diseases including UC and Crohn's disease (CD) (Croxford et al. 2014). These cells are characterized by expression of the transcription factor retinoic acid receptor–related orphan receptor-γt (RORγt) and include subsets of γδ T cells, natural killer T cells, "natural" Th17 cells, and innate lymphoid cells (Gaffen et al. 2014).

Treatment of autoimmune/inflammatory diseases with IL-23 targeted therapy is being pursued by several companies. The first such biologic to demonstrate clinical benefit in autoimmune disease was ustekinumab, which is a Food and Drug Administration-approved monoclonal antibody for the treatment of psoriasis and psoriatic arthritis (Stelara® package insert 2013) and is now being evaluated in Phase 3 trials for the treatment of CD (Toussirot et al. 2013). Ustekinumab binds the common p40 subunit of IL-12 and IL-23; therefore, it targets both cytokines, rather than 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 alone is sufficient to treat autoimmune inflammation (Monteleone et al. 2009). Agents specifically targeting the IL-23 p19 subunit, including LY3074828, 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 UC has yet to occur, the IL-23/Th17 pathway is believed to have a significant role in this disease (Gheita et al. 2014; Globig et al. 2014; El-Bassat et al. 2014).

LY3074828 is a humanized immunoglobulin G4-variant monoclonal antibody (molecular weight approximately 144,000 Da) that is directed against the p19 subunit of IL-23 and does not bind interleukin-12. LY3074828 is being developed for the treatment of autoimmune diseases in which the IL-23 pathway is thought to have a pathogenic role. LY3074828 does not bind rodent IL-23, so a surrogate molecule was developed to neutralize murine IL-23 for preclinical studies. Neutralization of IL-23 with this surrogate antibody significantly reduced the development of arthritis and ileal inflammation in a mouse model of spondyloarthropathy with bowel inflammation (Ruutu et al. 2012). In addition, neutralization of IL-23 significantly reduced disease in a mouse model of multiple sclerosis, relapsing-remitting experimental autoimmune encephalomyelitis. Anti–IL-23 antibody also demonstrated some efficacy in preclinical arthritis models, depending on the timing of intervention (Cornelissen et al. 2013).

Study I6T-MC-AMAA (AMAA) was a multicenter, ascending-dose, parallel-group, first-in-human Phase 1 single dose administration study evaluating LY3074828 in healthy volunteers and in subjects with plaque psoriasis. Seven cohorts of subjects with active psoriasis received a single dose of intravenous (IV) LY3074828 (5, 20, 60, 120, 200, 350, or 600 mg) or placebo. A single cohort of 5 healthy subjects received a single subcutaneous (SC) dose of LY3074828 (120 mg). A total of 33 subjects with psoriasis and 5 healthy subjects were administered LY3074828.

- No serious adverse events (SAEs) were reported and no subject discontinued because of an adverse event (AE). Treatment-emergent adverse events (TEAEs) reported as related to investigational product 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 AEs were seen. No clinically important changes in vital signs, electrocardiograms (ECGs), or clinical laboratory results were observed.
- Preliminary data from subjects administered single doses of up to 600 mg IV indicate that LY3074828 has linear pharmacokinetics (PK), a low IV clearance (~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 anti-drug antibodies (ADAs) developed in 3 subjects after administration of single IV doses of LY3074828. 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, in Study AMAA, clinical activity was explored in subjects with psoriasis, with a follow-up period of approximately 12 weeks. Figure AMAC.5.1 presents data by cohort for the mean 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.

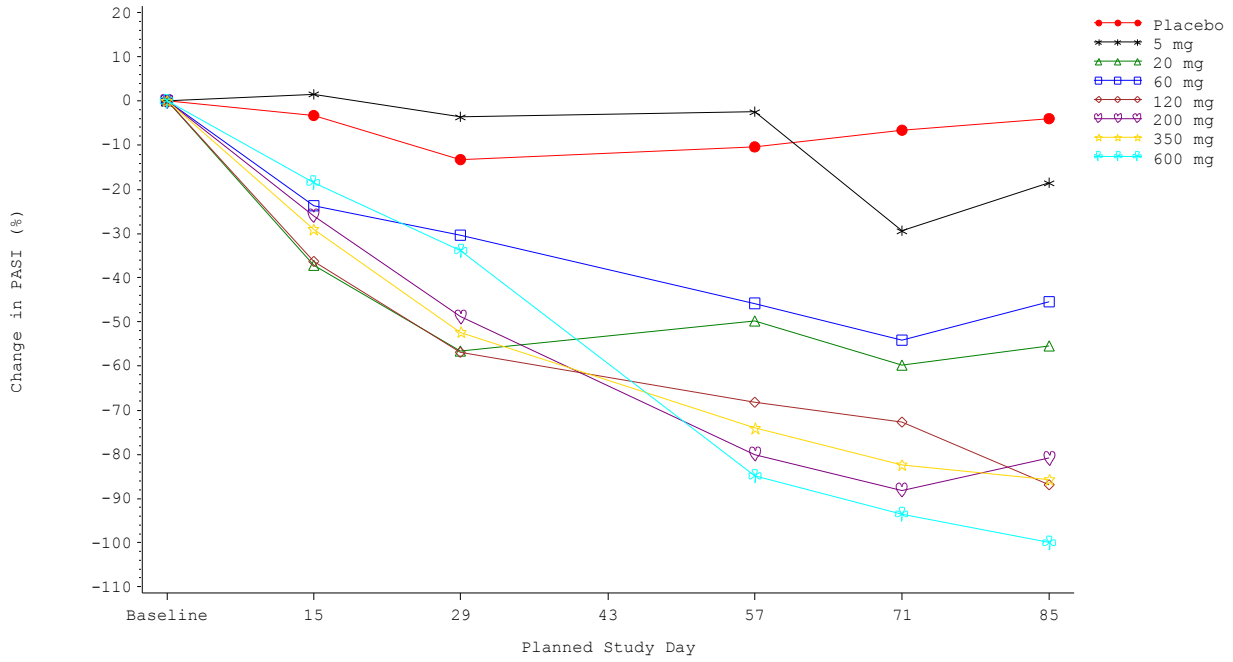


Figure AMAC.5.1. Psoriasis Area and Severity Index score (% change from baseline).

Study I6T-JE-AMAD (AMAD) is a single-site, subject- and investigator-blind, randomized, placebo-controlled, single-dose study to assess the safety, tolerability, and pharmacokinetics (PK) of LY3074828 in Japanese and Caucasian healthy subjects. The study consisted of 5 dose cohorts: 4 IV cohorts (60, 200, 600, and 1200 mg) and 1 SC cohort (200 mg). Subjects in each cohort were randomized to receive LY3074828 or placebo. As of 30 May 2016, all subjects in all cohorts, except for the 1200-mg cohort, have completed the study. Forty-three subjects were administered LY3074828 or placebo via either IV infusion or SC injection. A total of 18 TEAEs were reported in 14 subjects; one of the TEAEs (animal bite) was reported in the 1200-mg cohort. The most common TEAE was upper respiratory tract infection, reported by 4 subjects,

followed by urinary tract infection, which was reported by 2 subjects. All TEAEs were reported as mild except 1 moderate TEAE (right calf strain in the 60-mg cohort). There were no infusion reactions or injection site reactions. All TEAEs were judged not to be related to study drug. The reported TEAEs were not dose-dependent. There were no clinically significant findings in vital signs, ECGs, or clinical laboratory tests, except for 1 subject having an abnormal ECG finding that was mild and not considered to be related to study drug. Overall, in this study, no clinically significant safety concerns have been identified so far.

More information about the known and expected benefits, risks, reasonably anticipated AEs, PK, and immunogenicity of LY3074828 may be found in the investigator's brochure (IB). Information on AEs expected to be related to the investigational product may be found in Section 7 of the IB (Development Core Safety Information). Information on SAEs expected in the study population independent of drug exposure, may be found in Section 6 of the IB (Effects in Humans).

The study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements. Given these requirements, the rationale for this study is based on the following:

- published literature supporting the concept of blocking IL-23 in autoimmune/inflammatory diseases, including inflammatory bowel disease (IBD)
- the favorable safety and PK profile of LY3074828 in Study AMAA, as well as the initial clinical activity observed for LY3074828, in subjects with psoriasis

Study I6T-MC-AMAC (AMAC) will test the hypothesis that LY3074828 can induce significantly higher rates of clinical remission than placebo in subjects with moderate to severe UC. Given the safety profile of LY3074828, the potential benefits of participating in this study are expected to outweigh the potential risks.

6. Objectives

6.1. Primary Objective

The primary objective of this study is to test the hypothesis that treatment with LY3074828 is superior to placebo in inducing clinical remission at Week 12 (as defined in Section 10.1.1) in subjects with moderate to severe UC.

6.2. Secondary Objectives

The secondary objectives are:

- To evaluate the safety and tolerability of treatment with LY3074828
- To evaluate the efficacy of treatment with LY3074828 in inducing a clinical response at Week 12 (as defined in Section 10.1.2)
- To evaluate endoscopic remission at Week 12 and Week 52 (as defined in Section 10.1.2)
- To evaluate the effect of maintenance treatment with LY3074828 on the durability of clinical remission, endoscopic remission, and clinical response at Week 52
- To evaluate the effect of LY3074828 on health outcomes/quality of life measures (including: Inflammatory Bowel Disease Questionnaire [IBDQ] score, 36-Item Short Form Health Survey [SF-36] score, Patient's Global Impressions of Severity [PGI-S] score, and Patient's Global Impressions of Improvement [PGI-I] score)
- To characterize the PK profile of LY3074828

6.3. Exploratory Objectives

The exploratory objectives are:

- To assess the change from baseline in Ulcerative Colitis Endoscopic Index of Severity (completed by central reader only) scores at Weeks 12 and 52
- To assess the change from baseline in the partial Mayo score at various times during induction and maintenance
- To determine the relationship of LY3074828 exposure levels to clinical endpoints and biomarkers
- To determine the change from baseline in the biomarkers C-reactive protein and fecal calprotectin
- To explore the development of any anti-LY3074828 antibodies that are formed and their effect on safety, PK, and pharmacodynamics (PD) of LY3074828
- To explore the effect of additional (unblinded) dosing on clinical response in subjects who do not meet responder criteria at Week 12

7. Investigational Plan

7.1. Summary of Study Design

Study I6T-MC-AMAC is a multicenter, randomized, double-blind, parallel-arm, placebo-controlled trial in which approximately 240 subjects will be randomized (Figure AMAC.7.1). Subjects must have moderate or severe UC (defined as a Mayo score of 6 to 12 with an endoscopic subscore ≥2; see Attachment 5). Approximately two-thirds (~160) of the subjects randomized to study treatment must have been exposed to at least 1 previous biologic therapy (received treatment with 1 or more agents such as tumor necrosis factor [TNF] antagonists, vedolizumab, or experimental UC biologic therapy), and approximately one-third (~80) of the subjects will be naive to biologic therapy.

All procedures to be conducted during the study, including timing of all procedures, are indicated in the study schedule (Attachment 1).

Screening Period

Subjects will be evaluated for study eligibility ≤28 days before the baseline visit. At the baseline visit, subjects who fulfill the eligibility criteria will be randomized equally to 1 of 4 induction treatment arms.

Subjects may be rescreened upon review and consultation with a member of the Lilly medical team.

Induction Period

A 12-week induction period is designed to establish the efficacy and safety of LY3074828 administered IV at Weeks 0, 4, and 8 (described in Section 10.1 and Section 10.3, respectively). Approximately 240 subjects will be enrolled into 4 induction treatment arms (placebo or 50 mg, 200 mg, or 600 mg of LY3074828) to adequately evaluate the clinical response and remission endpoints. On the basis of plasma concentrations of LY3074828 during the induction period, dose levels in individual subjects within the 50-mg and 200-mg arms may by increased (Section 9.1) and will be communicated to the site by the sponsor. The 600-mg dose arm will remain at a fixed dose during the induction period. No subject will be dosed above 600 mg in this initial induction period. Subjects enrolled in the trial will be stratified across the treatment arms on the basis of previous exposure to biologic therapy for treatment of UC.

Subjects who discontinue the study for any reason before the end of the induction period will complete the induction period early termination visit (V7).

Maintenance Period:

Responding subjects who have received LY3074828 will be re-randomized to 1 of 2 LY3074828 maintenance treatment arms (200 mg every 4 weeks [Q4W] SC or 200 mg every 12 weeks [Q12W] SC); any subjects in the placebo arm achieving a clinical response will remain on placebo. The maintenance period is designed to explore the safety and durability of clinical responses and remissions to treatment with 200 mg LY3074828 administered SC Q4W or

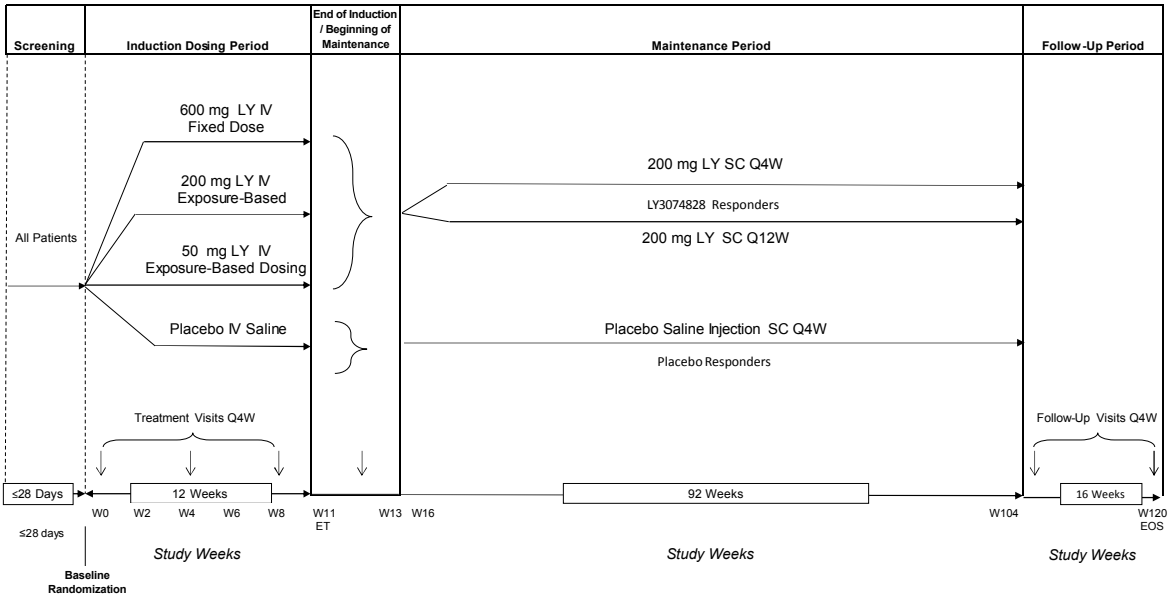
Q12W. Subjects having clinical responses (see Section 10.1.2) at Week 12 will continue study participation in the maintenance period up to Week 104. Subjects who are randomized in the induction period but do not have a clinical response at Week 12 will have the option to continue in a study extension period (Section 7.1.1) or discontinue from the study.

Subjects entering the LY3074828 maintenance dosing period will be stratified according to their Week-12 remission status. After Week 52, subjects who experience worsening of UC (partial Mayo score of 7 or more) may receive rescue treatment with LY3074828 200 mg SC Q4W.

Maintenance Follow-Up Period (16 Weeks):

The follow-up period will include a visit every 4 weeks for a total of 16 weeks following Week 104 to assess subject safety.

Subjects who discontinue the study for any reason during the maintenance or maintenance follow-up period will complete the maintenance period early termination visit (V804).



Abbreviations: EOS = end of study; ET = early termination; IV = intravenous; LY = LY3074828; n = number of subjects; Q4W = every 4 weeks; Q12W = once every 12 weeks; SC = subcutaneous; W = study week.
Note: Induction nonresponders can consider participation in the study extension period (Section 7.1.1).

Figure AMAC.7.1. Protocol I6T-MC-AMAC study design.

7.1.1. Study Extensions

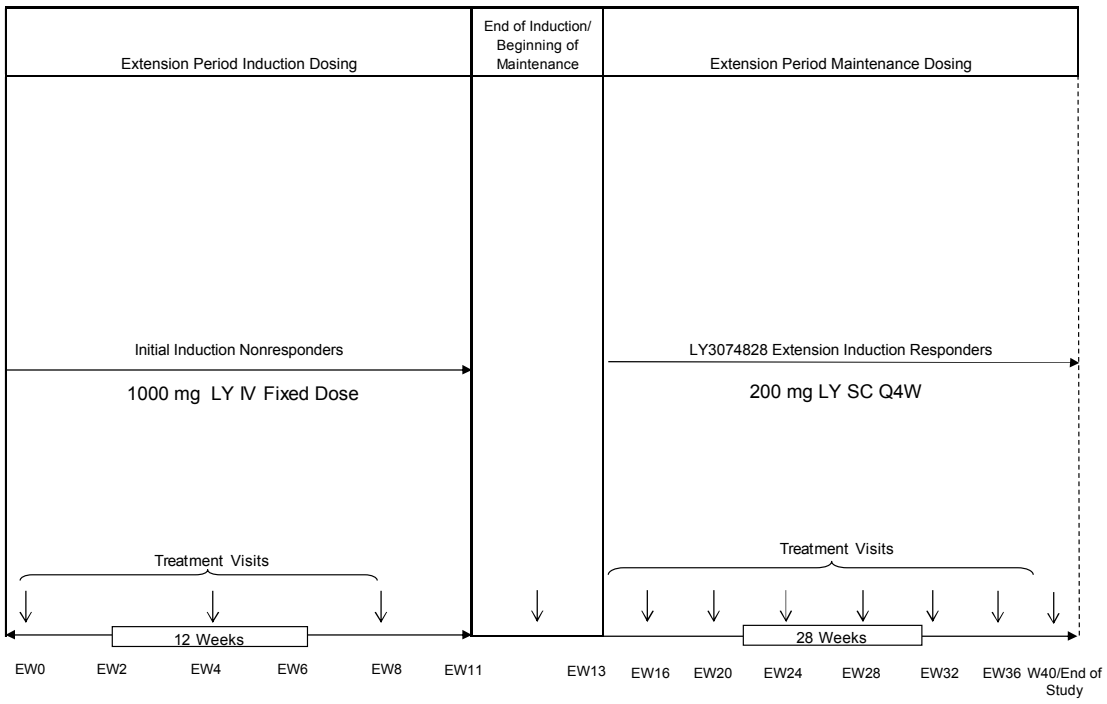
Subjects who complete the induction period (through Visit 7) but do not have a clinical response (see Section 10.1.2) may choose to participate in the unblinded study extension period following consultation with, and at the discretion of, the investigator. The extension period will consist of induction and maintenance parts that are modified versions of the induction and maintenance periods in the primary study design (Figure AMAC.7.2). For subjects who choose to participate, Extension Visit 1 (Attachment 2) should be planned to occur within 12 days of induction period Visit 7.

During the extension period induction, all subjects are planned to receive 1000 mg LY3074828 IV administered at Extension Weeks 0, 4, and 8 (the dose level and/or frequency of dosing may be reduced based on review of Study AMAC trial data). Subjects should complete all assessments according to the extension period schedule of events (Attachment 2) and should remain on permitted UC concomitant medication according to Section 9.9. Subjects who have a clinical response (Section 10.1.2) at Extension Visit 6 will have the opportunity to continue on extension period maintenance therapy, while nonresponders at Extension Visit 6 will be discontinued from the study.

Subjects who continue into the extension period maintenance treatment are planned to receive unblinded 200 mg LY3074828 administered SC Q4W for 80 weeks. Subjects should complete all assessments according to the extension period schedule of events in Attachment 2, and should remain on permitted UC concomitant medication according to Section 9.9. The dose level and frequency of dosing may be reduced based on review of Study AMAC trial data.

Extension Follow-Up Period (16 Weeks):

A follow-up period will include a visit every 4 weeks for a total of 16 weeks following Extension Week 92 to assess subject safety. Subjects who discontinue the study for any reason during the extension or extension follow-up period will complete the extension period early termination visit (V808).



Abbreviations: EOS = end of study; ET = early termination; EW = extension week; IV = intravenous; LY = LY3074828; Q4W = every 4 weeks; SC = subcutaneous.

Figure AMAC.7.2. Protocol I6T-MC-AMAC extension period study design.

7.2. Discussion of Design and Control

IL-23 is a validated target for evaluation of treatment of various autoimmune/inflammatory diseases, including UC (see Section 5).

The initial induction dosing period is designed to establish the efficacy and safety of LY3074828 versus placebo in subjects with moderate to severe UC. Subjects are to continue their background pharmacotherapies for UC as permitted per protocol; therefore, the selection of placebo as a comparator in this subject population is justified to effectively evaluate the safety and efficacy of LY3074828.

The maintenance period for responding subjects is designed to explore 2 maintenance treatment regimens (200 mg administered every 4 or every 12 weeks) to support selection of the most appropriate maintenance regimen for evaluation in future studies. No subject treated with LY3074828 during induction will be randomized to the placebo arm in the maintenance period.

The extension period provides an option for nonresponding placebo subjects to receive treatment with unblinded LY3074828 and an option for nonresponding LY3074828-treated subjects to receive higher dosing support with 1000 mg (particularly those subjects randomized to the 600-mg cohort in the induction period). Data from Study AMAD (Section 5) supports further evaluation of this dose level. No subject will receive placebo in the extension period.

Patients who are still enrolled in the study at Week 104 will continue into a 16-week follow-up period. If an open-label extension study is enrolling at the time the patient enters follow-up, the patient could consider enrolling in that study.

8. Study Population

This study will include subjects who meet the eligibility criteria outlined in Sections 8.1 and 8.2.

Study investigator(s) will review patient records and test results from screening to determine if the patient meets all inclusion and exclusion criteria to qualify for participation in the study (Attachment 1).

Subjects who do not meet the criteria for participation in this study (screen failure) may be rescreened. Subjects may be rescreened only 1 time for failure due to Criteria [2], [4], [5], [6], [7], [8], [9], [11], [14], [16], [17], [23], [25], [29], or [30]. If a patient fails screening because of administrative reasons, rescreening can occur after sponsor approval. For each rescreening, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number. Subjects who have had previous screening chest radiography and tuberculosis (TB) tests as per protocol within 90 days of their rescreening date of consent, do not need to repeat these procedures but may do so at the discretion of the investigator (see Section 10.3.2.2).

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

8.1. Inclusion Criteria

Subjects with UC are eligible for enrollment only if they meet all of the following criteria during screening:

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

[2] are male or female subjects ≥18 and ≤75 years of age at the time of initial screening

[2a] male subjects agree to use a reliable method of birth control during the study and for 3 months, which is greater than 5 half-lives, after the last dose of investigational product

[2b] female subjects:

- are women of childbearing potential whose serum pregnancy test results are negative and who agree to use a reliable method of birth control (eg, condom, sponge, or diaphragm combined with spermicidal foam, gel, or cream; ongoing hormonal contraception [oral, intramuscular, depot, or transdermal], such as Depo-Provera, Evra, or NuvaRing; an intrauterine device; or complete abstinence from sexual intercourse with men) during the study and for 3 months after the last dose of the investigational product

-or-

- are not women of childbearing potential, defined as having:
    - bilateral oophorectomy, tubal ligation, or hysterectomy at least 6 weeks before screening;
    - spontaneous amenorrhea for ≥12 months, not induced by a medical condition or medications; or
    - spontaneous amenorrhea for 6 to 12 months and a follicle-stimulating hormone level greater than 40 mIU/mL at screening

[3] venous access sufficient to allow blood sampling and IV administration (if applicable), as per the protocol

[4] have had a diagnosis of UC for ≥3 months before baseline (endoscopic evidence corroborated by a histopathology report); a biopsy for a local histopathology evaluation (to obtain a report) can be obtained during the baseline endoscopy procedure if a histopathology report is not available

[5] have moderate to severe active UC as defined by a Mayo score of 6 to 12 with an endoscopic subscore ≥2 within 14 days before the first dose of study treatment (note: a partial Mayo score of at least 4 and other eligibility criteria must have been met before endoscopy is performed as a study procedure)

[6] have evidence of UC extending proximal to the rectum (≥15 cm of involved colon)

[7] have documentation of a surveillance colonoscopy (performed according to local standard) within 12 months before baseline (may be performed during screening) for subjects with pancolitis of >8 years' duration or left-sided colitis of >12 years' duration

[7a] up-to-date colorectal cancer surveillance (performed according to local standard), for subjects with family history of colorectal cancer, personal history of increased colorectal cancer risk, age >50 years, or other known risk factor

[8] subjects must either:

[8a] be naive to biologic therapy (such as TNF antagonists, vedolizumab, or experimental UC biologics) and have at least 1 of the following:

- inadequate response or failure to tolerate current treatment with oral or IV corticosteroids or immunomodulators (6-MP or AZA) or
- history of corticosteroid dependence (an inability to successfully taper corticosteroids without return of UC)

OR

[8b] have also received treatment with 1 or more biologic agents (such as TNF antagonists, vedolizumab, or experimental UC biologics) with or without documented history of failure to respond or tolerate such treatment

- the biologic treatment must have been discontinued according to the following timelines:
    - anti-TNF therapy at least 8 weeks before baseline
    - vedolizumab treatment at least 12 weeks before baseline
    - experimental biologic UC therapy at least 8 weeks before baseline

[9] may be receiving a therapeutic dosage of the following drugs:

[9a] oral 5-ASA compounds: if the prescribed dose has been stable for at least 2 weeks before screening endoscopy

[9b] oral corticosteroid therapy (prednisone ≤20 mg/d or equivalent): if the prescribed dose has been stable for at least the 2 weeks before screening endoscopy

[9c] AZA or 6-MP: if the prescribed dose has been stable for at least 8 weeks before baseline

[10] are willing and able to complete the scheduled study assessments, including endoscopy

[11] have clinically acceptable laboratory results at screening, as assessed by the investigator, including:

[11a] hematologic: absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, hemoglobin level ≥10.0 g/dL, lymphocyte count >500 cells/μL, and total white blood cell count $\geq 3.0 \times 10^9$/L

[11b] chemistry: serum creatinine, total bilirubin level, alkaline phosphatase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels ≤2× upper limit of normal (ULN)

8.2. Exclusion Criteria

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

[12] have been diagnosed with indeterminate colitis, proctitis (distal disease involving the rectum only; less than 15 cm from the anal verge) or CD

[13] have had surgery for treatment of UC or are likely to require surgery for UC during the study

[14] have received any of the following for treatment of UC:

[14a] cyclosporine or thalidomide within 30 days of screening endoscopy

[14b] corticosteroid enemas, corticosteroid suppositories, or topical treatment with 5-ASA within 30 days of screening endoscopy

[14c] have used apheresis (eg, Adacolumn apheresis) ≤2 weeks before screening endoscopy

[15] have previous exposure to any biologic therapy targeting IL-23 (including ustekinumab), either licensed or investigational

[16] have been treated with any investigational drug for UC within 30 days or 5 half-lives of the drug (whichever is longer) before the initial screening visit (Visit 1), OR with interferon therapy within 8 weeks before baseline

[17] have evidence of abdominal abscess or toxic megacolon during screening

[18] have extensive colonic resection, subtotal or total colectomy, ileostomy, colostomy, or fixed symptomatic stenosis of the intestine

[19] have evidence of active or latent TB (refer to Section 10.3.2.2 for details on full TB exclusion criteria)

[20] have had any malignancy within 5 years of screening, except for basal cell or squamous epithelial carcinoma of the skin that has been resected with no evidence of metastatic disease for at least 3 years OR cervical carcinoma in situ with no evidence of recurrence within 5 years of screening

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

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

[23] are currently enrolled in a clinical trial involving an investigational product or nonapproved use of a drug or device, OR are concurrently enrolled in any other type of medical research not scientifically or medically compatible with this study, per investigator judgment

[24] have previously completed or withdrawn from this study or any other study investigating LY3074828. This criterion does not apply to subjects undergoing rescreening procedures

[25] have received live, attenuated vaccine(s) within 2 months of screening or intend to receive such during the study; vaccines should be avoided for 2 months after the last dose of study drug. Uses of nonlive (inactivated) vaccinations are allowed for all subjects

[26] have HIV/AIDS or test positive for human immunodeficiency virus antibodies at screening

[27] have hepatitis B or test positive for hepatitis B virus (HBV) at screening, defined as: (1) positive for hepatitis B surface antigen or (2) positive for anti–hepatitis B core antibody (HBcAb+) and positive confirmatory polymerase chain reaction (PCR) for HBV, regardless of anti–hepatitis B surface antibody status

[28] have hepatitis C or test positive hepatitis C virus at screening, defined as: positive result for hepatitis C antibody and positive confirmatory PCR test for hepatitis C virus

[29] had *Clostridium difficile* infection within 30 days of screening endoscopy or test positive at screening, or other intestinal pathogen with 30 days before screening endoscopy. Subject must not have signs of an ongoing infection related to an intestinal pathogen.

[30] have any clinically significant extra-intestinal infection or opportunistic, chronic, or recurring infection within 6 months before screening. Examples include but are not limited to infections requiring IV antibiotics, hospitalization, or prolonged treatment

[31] are unsuitable for inclusion in the study in the opinion of the investigator or sponsor for any reason that may compromise the subject's safety or confound data interpretation

[32] Exclusion Criterion [32] applies to study sites in Japan only. For study sites in Japan, see the Japan protocol addendum

[33] are pregnant, lactating, or planning pregnancy (either men or women) while enrolled in the study or within 4 months after receiving the last dose of study agent

8.2.1. Rationale for Exclusion of Certain Study Candidates

Criteria [21] and [22] prevent conflict of interest in study participants. Criteria [12] through [20] and [23] through [33] 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.

8.3. Discontinuations

8.3.1. Discontinuation of Subjects

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 sponsor clinical research physician and the investigator to determine whether the subject may continue in the study, with or without continued investigational product dosing. Inadvertently enrolled subjects may be maintained in the study and on investigational product when the Lilly clinical research physician agrees with the investigator that it is medically appropriate for that subject. The subject may not continue in the study with or without investigational product if the Lilly clinical research physician does not agree with the investigator's determination that it is medically appropriate for the subject to continue. The investigator must obtain documented approval from the Lilly clinical research physician to allow the inadvertently enrolled subject to continue in the study.

In addition, subjects will be discontinued from the study in the following circumstances:

- enrollment in any other clinical trial involving an investigational product 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
    - the subject requires treatment with a therapeutic agent that has been demonstrated to be effective for treatment of the study indication. Discontinuation from the study should occur before introduction of the new agent
    - the subject requires a protocol-prohibited change in permitted UC concomitant therapy (Section 9.9)
- subject decision
    - the subject requests to be withdrawn from the study
- sponsor decision
    - Lilly or its designee 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 GCP
- AE
    - if the investigator decides that the subject should be withdrawn because of an AE/SAE or a clinically significant laboratory value, the investigational product is to be discontinued and appropriate measures are to be taken. Lilly or its designee is to be alerted immediately. Refer to Safety Evaluations, Section 10.3.
- subject becomes pregnant
- subject experiences a systemic hypersensitivity event or anaphylaxis

Subjects who discontinue the study early will have early termination procedures performed as shown in the study schedule (Attachment 1).

8.3.2. Discontinuation of Investigational Product

Discontinuation of the investigational product for abnormal liver test results should be considered by the investigator in consultation with the Lilly-designated medical monitor when a subject meets any of the following conditions:

- ALT or AST level >8× ULN
- ALT or AST level >5× ULN for more than 2 weeks
- ALT or AST level >3× ULN and total bilirubin level >2× ULN or prothrombin time >1.5× ULN

- ALT or AST level >3× ULN with the appearance of fatigue, nausea, vomiting, right-upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Subjects who discontinue the investigational product early will have early termination procedures performed as shown in the study schedule (Attachment 1).

8.3.3. 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 attempt to contact subjects who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Site personnel or an independent third party will attempt to collect the vital status of the subject within legal and ethical boundaries for all subjects randomized, including those who did not receive investigational product. Public sources may be searched for vital status information. If vital status is determined, this will be documented, and the subject will not be considered lost to follow-up.

8.3.4. Discontinuation of Study Sites

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

8.3.5. Discontinuation of the Study

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

9. Treatment

9.1. Treatments Administered

This study involves a comparison of IV administration of LY3074828 versus placebo during a 12-week induction period followed by a maintenance period through Week 104 in which maintenance of response to LY3074828 will be explored using 2 LY3074828 SC dosing regimens. Table AMAC.1 shows the treatment regimens.

Table AMAC.1. Treatment Regimens

Treatment Group	Description
Induction Period	
LY Dose Arm 1	50 mg[a] LY given as an IV infusion (Weeks 0, 4, 8)
LY Dose Arm 2	200 mg[a] LY given as an IV infusion (Weeks 0, 4, 8)
LY Dose Arm 3	600 mg[b] LY given as an IV infusion (Weeks 0, 4, 8)
Comparator	Placebo, normal saline (0.9% sodium chloride) as an IV infusion (Weeks, 0, 4, 8)
Maintenance Period	
LY Dose Arm 1	200 mg LY given SC Q4W
LY Dose Arm 2	200 mg LY given SC Q12W (placebo given at Q4W intervals when LY is not given)
Placebo	Placebo given SC Q4W
Extension Period	
Induction LY Dose	1000 mg LY given as an IV infusion (Extension Weeks 0, 4, 8)
Maintenance LY Dose	200 mg LY given SC Q4W

Abbreviations: IV = intravenous; LY = LY3074828; Q4W = every 4 weeks; Q12W = every 12 weeks; SC = subcutaneous.

[a] Doses may be increased in individual subjects for the planned Week 4 and 8 treatments (Section 9.5). Dose increases for individual patients will be communicated to the site by the sponsor.

[b] The 600-mg arm will remain at a fixed dose during the induction period.

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Investigational product will be prepared at the site by unblinded pharmacists or other trained personnel. Investigational product will be administered at the site by blinded nurses or other trained personnel. The investigator or his/her designee is responsible for the following:

- explaining the correct administration of the investigational agent(s) to the site personnel
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing
- 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.

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

9.2. Materials and Supplies

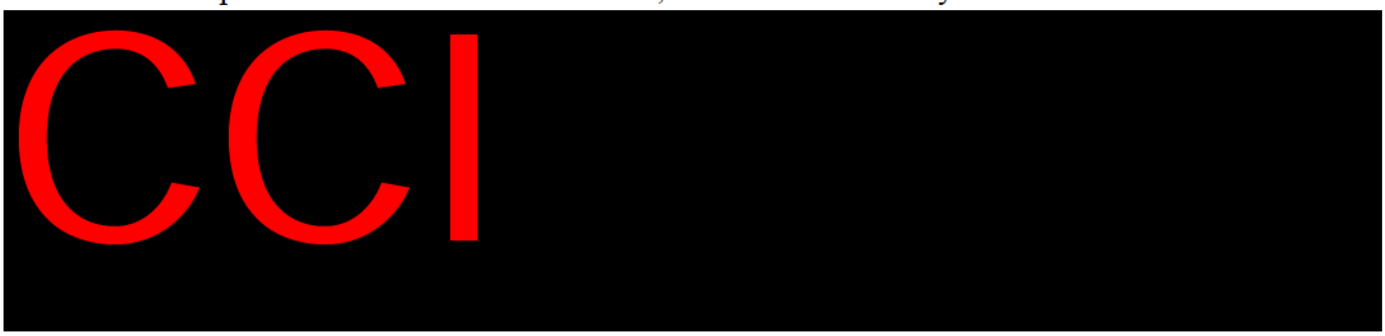
LY3074828 will be supplied to the investigator by Lilly. Clinical trial materials are manufactured in accordance with good manufacturing practices. All investigational products will be stored, inventoried, reconciled, and destroyed according to applicable regulations.

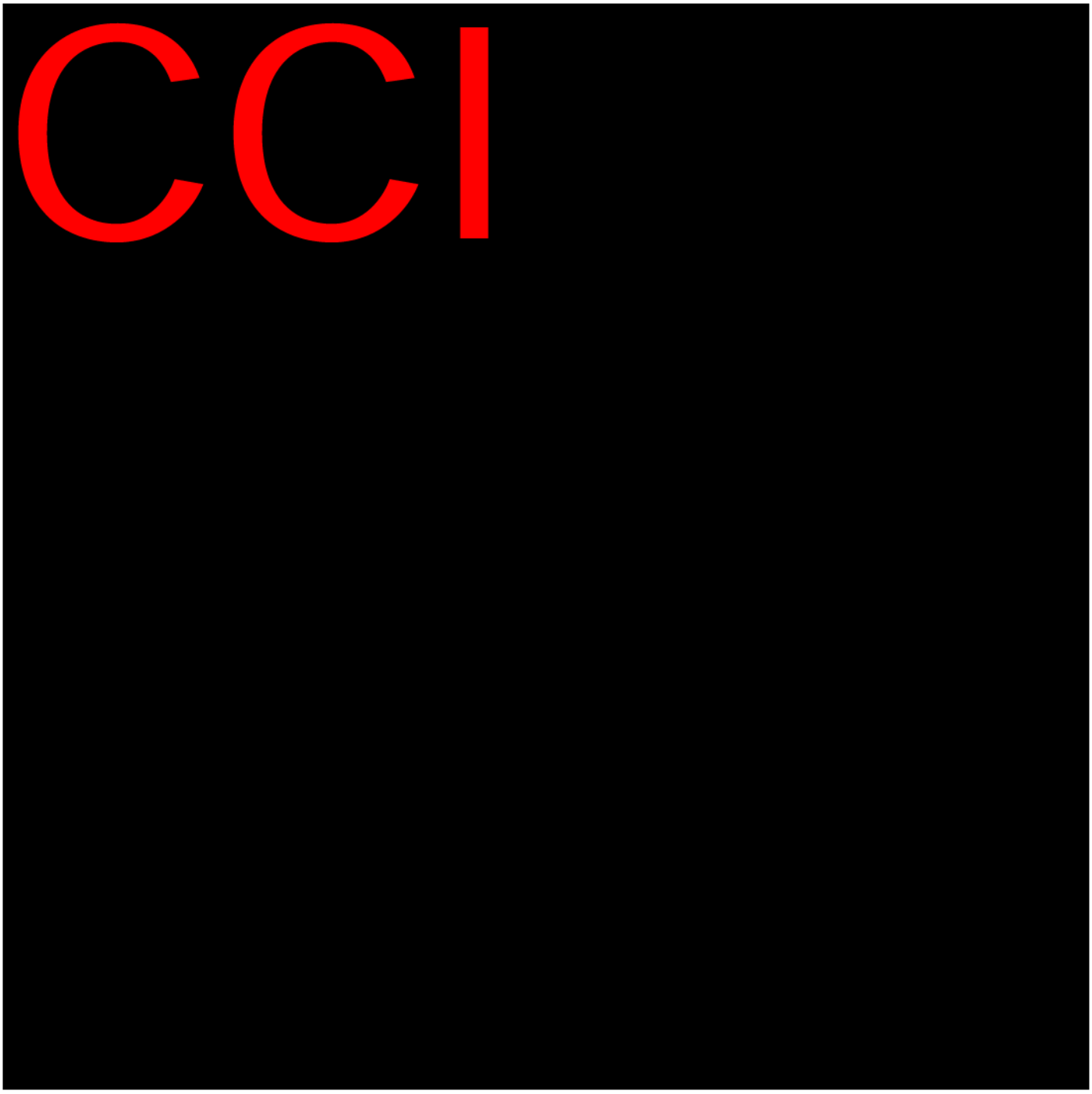
9.3. Method of Assignment to Treatment

Subjects who meet all criteria for enrollment will be randomized to treatment at the baseline visit. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS), and then the site will be responsible for administering the treatment to the subjects. Subjects who have clinical responses (Section 10.1.2) to LY3074828 at the end of the induction period will be re-randomized to 1 of 2 maintenance LY3074828 treatment arms.

9.4. Rationale for Selection of Doses in the Study

The dose levels and regimens planned for this study were selected based on analyses of PK, PD, safety, and efficacy data from the single-dose study (Study AMAA), literature information about doses and exposures for other IL-23 antibodies, and nonclinical safety data.





9.5. Therapeutic Drug Monitoring and Dose Adjustment

Experience with use of anti-TNF antibodies in treating IBD suggests that inadequate drug exposure in some subjects may be a factor contributing to lack of efficacy (Ordás et al. 2012b). The application of therapeutic drug monitoring and dose adjustment may therefore result in a higher probability of response in individual subjects who have low exposure and improved overall response rates.

Exposure-Based Dose Adjustment

In this study, subjects in the 50- and 200-mg dose groups will have their doses increased at the Week 4 (Day 29) and Week 8 (Day 57) visits if the projected trough concentrations for those visits fall below prespecified thresholds. The concentration thresholds selected for the 50- and 200-mg arms are 0.5 and 2.0 μg/mL, respectively. The concentrations of 0.5 and 2.0 μg/mL are not related to expected efficacy at these specific target concentrations but rather were selected so that only the subjects with lower than expected exposures in the 50- and 200-mg groups would have their doses increased. On the basis of PK simulations, these thresholds are estimated to result in dose increases in approximately 40% of subjects at Week 4. A smaller percentage of subjects are expected to require dose adjustment at Week 8.

The projected trough concentration for an individual subject will be estimated on the basis of concentration data collected before the date when doses will be adjusted. Application of exposure-based dose adjustment in this study will only serve to increase the dose level if drug concentrations are below the prespecified thresholds. Dose level will not be reduced on the basis of drug concentrations, and once a subject has a dose level increase, the dose will not be reduced. Dose adjustments on the basis of drug concentration levels will only be done during the induction period.

The maximum dose administered will not exceed 600 mg during the induction period regardless of the observed concentration of LY3074828. Study investigators and sites will remain blinded to concentration data. The required dose adjustments for individual subjects will be provided to the unblinded pharmacists by Lilly personnel during the study after analysis of concentration data. If Lilly is unable to provide the site with the recommended dose adjustment for a subject because of issues with sample shipment, analysis, or other unforeseen circumstances, the subject will receive the same dose he/she received at the previous administration.

9.6. Selection and Timing of Doses

Subjects will be assigned to treatment arms (see Section 9.3) and are planned to receive their assigned treatment as outlined in Section 9.1.

9.6.1. Special Treatment Considerations

9.6.1.1. 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 investigators (see Section 9.9).

Any premedication given will be documented as a concomitant therapy (see Section 9.9).

9.6.1.2. Management of Infusion Reactions

Because of the risk of an infusion reaction with any biological agent, all subjects should be monitored for 1 hour after dosing or longer according to local standard of care. Symptoms and signs that may occur as part of an infusion reaction include but are not limited to fever, chill, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash, pruritus,

myalgia, and/or dizziness. In the event that a significant infusion reaction occurs, the following guidance should be followed:

- the investigational product infusion should be slowed or stopped, depending on the symptoms or signs present

    if slowed or stopped, the infusion may be continued in accordance with signs and symptoms at the investigator's discretion

- supportive care should be employed in accordance with the symptoms or signs

9.7. Continued Access to Investigational Product

LY3074828 will not be made available to subjects after conclusion of the study.

9.8. Blinding

This is a double-blind study; 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. A study site pharmacist or other trained person will be unblinded at the site for investigational product preparation.

Emergency unblinding for AEs may be performed through the IWRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option should be used ONLY if the subject's well-being requires knowledge of the subject's treatment assignment. All notifications resulting in an unblinding event are recorded and reported by the IWRS.

If an investigator, a member of site personnel performing assessments, or a subject is unblinded to a subject's treatment, that subject must be discontinued from the study. In cases in which there are ethical reasons to have the subject remain in the study, the investigator must obtain specific approval from a Lilly clinical research physician for the subject to continue in the study.

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 a subject's treatment assignment is unblinded, Lilly must be notified immediately.

Nonresponder subjects entering the extension period will receive study drug in an unblinded fashion.

9.9. Concomitant Therapy

All concomitant medication taken during the study must be recorded on the concomitant medication case report form (CRF).

All subjects should maintain their usual medication regimens for concomitant conditions or diseases throughout the study unless those medications are specifically excluded in the protocol.

Subjects taking concomitant medications should be on stable dosages at the time of baseline and should remain at stable dosages throughout the study unless changes need to be made because of AEs. Additional systemic drugs are to be avoided during the study, unless required to treat AEs. Other medications may be allowed if they are approved by the sponsor or its designee.

Uses of nonlive (inactivated) vaccinations are allowed for all subjects. Use of live, attenuated vaccines is prohibited. Chronic use of nonsteroidal anti-inflammatory drugs during the study is excluded. Chronic use of opioid drugs during the study is excluded. Occasional use of acetaminophen in over-the-counter dose ranges for headache, menstrual pain, or other transient conditions is acceptable but should be held on study visit days until after assessments have been completed, as much as possible; use of prophylactic daily aspirin (up to 162.5 mg) is permitted.

Concomitant therapies for treatment of UC during the study are permitted only as outlined in Table AMAC.3.

Table AMAC.3. Permitted Medications for Treatment of Ulcerative Colitis

Drug Class	Conditions for Use
Oral 5-ASA or sulfasalazine	Subjects were receiving the medications at baseline and the prescribed dose was stable for at least 2 weeks before screening endoscopy. Dosages should remain stable throughout the study unless the medication is discontinued because of toxicity. If stopped, the medication should not be restarted during the study.
Azathioprine or 6-mercaptopurine	Subjects were receiving the medications at baseline and the prescribed dose was stable for at least 8 weeks before baseline. Dosages should remain stable throughout the study unless the medication is discontinued because of toxicity. If stopped, the medication should not be restarted during the study.
Oral corticosteroid therapy (prednisone at a stable dosage ≤20 mg/d or equivalent oral steroid)	Oral steroids are allowed during the study up to 20 mg/d of prednisone or equivalent, providing that the prescribed dose has not been changed within 2 weeks of screening endoscopy. Decrease of the steroid dosage due to tapering regimen is allowed during the study per investigator judgment, except during the induction period. If the steroid tapering is commenced, the daily dose of prednisone or equivalent is recommended to be decreased by 2.5 mg every week until dose 0. • Equivalent of oral budesonide is up to 9 mg/d and must be stable within 2 weeks of endoscopy. Decrease of the steroid dosage due to tapering regimen is allowed during the study per investigator judgment, except during the induction period. If the steroid tapering is commenced, is recommended to be decreased 3mg every week until dose 0. • Equivalent for oral beclomethasone is up to 5 mg/d and must be stable within 2 weeks of endoscopy Dosages should remain stable throughout the study unless the medication is discontinued because of toxicity. If stopped, the medication should not be restarted during the study.

Abbreviation: 5-ASA = 5–aminosalicylic acid.

9.10. Treatment Compliance

Every attempt will be made to select subjects who have the ability to understand and comply with study instructions. The investigator is responsible for discussing methods to ensure high treatment compliance with the subject before randomization.

All doses of study medication will be administered at the study site. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

If a subject is noncompliant with study procedures and/or investigational product administration, the investigator should assess the subject to determine the reason for noncompliance and educate and/or manage the subject as appropriate to improve compliance. If, in consultation with Lilly or its designee, the noncompliance is deemed to be significant or if further noncompliance occurs, the subject should be discontinued from the study. A subject will be considered significantly

noncompliant if he or she fails to attend for administration of study medication within the required treatment window as defined in the study schedules (Attachment 1 and Attachment 2).

10. Efficacy, Health Outcome/Quality of Life Measures, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Study procedures and their timing (including tolerance limits for timing) are summarized in the study schedules (Attachment 1 and Attachment 2). A list of the specific planned laboratory tests to be performed for this study is provided in Attachment 3.

10.1. Efficacy Measures

10.1.1. Primary Efficacy Measure

The primary efficacy endpoint is clinical remission at Week 12. Clinical remission is defined as having achieved the following Mayo subscores at Week 12: a rectal bleeding subscore of 0, stool frequency subscore of 0 or 1 (with 1 point decrease from baseline), and endoscopy subscore of 0 or 1.

10.1.2. Secondary Efficacy Measures

Secondary efficacy endpoints are clinical response at Week 12 and endoscopic remission at Week 12 and Week 52. Clinical response is defined as having achieved at Week 12 a decrease in 9-point Mayo subscore (rectal bleeding, stool frequency, and endoscopy) inclusive of ≥2 points and ≥35% from baseline with either a decrease of rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1. Endoscopic remission is defined as having achieved a Mayo endoscopic subscore of 0.

10.1.3. Subject Diary

Subjects will be provided with a diary tool during screening in order to record information such as:

- number of stools per day
- presence of blood in the stools (if any)

Diary data will be assessed at the clinic, at each visit defined in the study schedule. Diary information will be used to calculate the subject's Mayo score. Data will include information collected over 3 days prior to each study visit. Three days of subject diary data must exclude data from days when bowel preparation or endoscopic exam (flexible proctosigmoidoscopy/colonoscopy) occur and exclude data from the day after the endoscopic exam.

Subjects should enter diary data continuously throughout the study.

The study data completion guidelines and study data management plan will provide detailed information on use of patient-reported outcome (PRO) measures and the subject diary.

10.1.4. Endoscopy/Histopathology

To ensure quality data and standardization, endoscopy will be performed locally at clinical sites per the study schedules (Attachment 1 and Attachment 2) and using the same endoscopist throughout the trial wherever possible.

Endoscopy images will be obtained during each endoscopy and will be sent for independent central reading and determination of the Mayo endoscopy subscore. A detailed image review charter from the central reading laboratory will outline the endoscopic procedures, video recordings, and equipment to be used for video capture and transmission of endoscopic recordings. For each subject, video recording of the entire endoscopic procedure will be performed using a storage medium provided by the sponsor or designee. The endoscopic recordings will be read centrally in a blinded manner by a qualified gastroenterologist according to the image review charter. The Mayo score used for clinical endpoints in the trial will use the Mayo endoscopy subscore derived from the central reader.

To ensure quality data and standardization, colonic tissue histopathologic scoring will be performed by the central reading laboratory. A detailed image review charter from the central reading laboratory will outline the histopathologic procedures to be used for secure specimen transfer, processing, slide preparation, and digitization of slides for histopathologic scoring. The histologic images will be read centrally in a blinded manner by a qualified pathologist according to the image review charter.

10.2. Health Outcome/Quality of Life Measures

The self-reported questionnaires will be administered according to the study schedule in countries where the questionnaires have been translated into the native language of the region and linguistically validated. The health outcome measures in this trial will be the PGI-S, PGI-I, IBDQ, and the SF-36.

PGI-S: The PGI-S is a 1-item subject-rated questionnaire designed to assess the subject's impression of their disease symptoms at baseline (Guy 1976; Yalcin and Bump 2003). Responses are graded on a 7-point scale in which a score of 1 indicates that the subject's symptom(s) are "normal," a score of 2 indicates that the subject feels "borderline ill," a score of 3 indicates that the subject feels "mildly ill," a score of 4 indicates that the subject(s) feel "moderately ill," and scores of 5, 6, and 7 indicate that the subject feels "markedly ill," "severely ill," and "extremely ill," respectively.

PGI-I: The PGI-I scale is a subject-rated instrument designed to assess the subject's impression of change in their symptom(s) (Guy 1976; Yalcin and Bump 2003). Responses are graded on a 7-point Likert scale in which a score of 1 indicates that the subject's symptom(s) is "very much better," a score of 4 indicates that the subject's symptom(s) has experienced "no change," and a score of 7 indicates that the subject's symptom(s) is "very much worse."

IBDQ: The IBDQ is a 32-item subject-completed questionnaire that measures 4 aspects of subjects' lives: symptoms directly related to the primary bowel disturbance, systemic symptoms, emotional function, and social function (Guyatt et al. 1989). Responses are graded on a 7-point

Likert scale in which 7 denotes "not a problem at all" and 1 denotes "a very severe problem." Scores range from 32 to 224; a higher score indicates a better quality of life.

SF-36: The SF-36 is a 36-item subject-completed measure designed to be a short, multipurpose assessment of health in the areas of physical functioning, role-physical, role-emotional, bodily pain, vitality, social functioning, mental health, and general health (Ware and Sherbourne 1992; Ware et al. 1993; McHorney et al. 1994). The 2 overarching domains of mental well-being and physical well-being are captured by the mental and physical component summary scores. Responses are graded on Likert scales of varying lengths/points. The summary scores range from 0 to 100; higher scores indicate better levels of function and/or better health.

10.3. 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.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to the 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 judgment of the investigator.

10.3.1. Adverse Events

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

Lack of drug effect is not an AE in clinical studies because the purpose of the clinical study is to establish drug effect.

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

Study site personnel will record the occurrence and nature of each subject's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

After the 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 its designee. All AEs occurring after the subject receives the first dose of investigational product must be reported to Lilly or its designee via CRF.

Any clinically significant findings from ECGs, laboratory test results, vital-sign measurements, and other procedures should be reported to Lilly or its designee.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure, studied disease state, or investigational product via CRF.

Study site personnel must alert Lilly or its designee within 24 hours of the investigator **unblinding** a subject's treatment assignment for any reason (see Section 9.8).

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

Subjects will be evaluated for AEs at each visit and should be instructed to call their physicians to report any AEs between visits.

The investigator will decide whether he or she interprets the observed AE as related to disease, to the study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to investigational product or study procedure, the following terms are defined:

- probably related: the study treatment/procedure is more likely than another etiology to be the cause of the AE
- possibly related: the study treatment/procedure is at least as likely as another etiology to be the cause of the AE
- not related: the study treatment/procedure is less likely than another etiology to be the cause of the AE

Lilly will classify all "probably related" and "possibly related" AEs and SAEs as related to investigational product or study procedure.

10.3.1.1. Serious Adverse Events

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

Planned surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study, necessitating a change in the extent, type, or date of planned surgery.

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.

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 serious adverse drug events when, according to 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.

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.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the subject summary CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

Information on SAEs that are 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.

10.3.1.1.1. 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 investigational product 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.

10.3.2. Other Safety Measures

10.3.2.1. Physical Examination

One complete physical examination (excluding pelvic, rectal, and breast examinations) will be performed at screening (Visit 1) and during the extension period as detailed in Attachment 2. This examination will determine whether the subject meets the criteria required to participate in the study and will also serve as a monitor for preexisting conditions and as a baseline for TEAE assessment. All physical examinations throughout the study should include a symptom-directed evaluation as well as examination of the heart, lungs, and abdomen and a visual examination of the skin.

10.3.2.2. Chest Radiography and Tuberculosis Testing

Posterior-anterior view and lateral view chest radiography will be obtained at screening (Visit 1) (unless local standards dictate 1 view), unless the radiographs or medical report from chest radiography performed within 3 months before initial screening (per local standard of care for TB evaluation) are available to the investigator for review.

In addition, subjects will be tested as indicated in the study schedule for evidence of active or latent TB. A positive TB test result is indicated by a purified protein derivative (PPD) skin test response ≥5 mm induration documented approximately 48 to 72 hours after test application (regardless of Bacillus Calmette-Guerin vaccination history). In countries where the QuantiFERON®-TB Gold test (or equivalent) is available and is preferred (in the judgment of the investigator) as an alternative to the PPD skin test for the evaluation of TB infection in a subject, that test may be used instead of the PPD test. If the QuantiFERON-TB Gold test is indeterminate, 1 retest is allowed. If the retest is indeterminate, then the subject is excluded from the study.

Subjects with documentation of negative TB test results within 3 months before initial screening may not need to repeat TB testing at screening (Visit 1) based on judgment of the investigator. Documentation of this previous test result must include a record of the size (in millimeters) of the induration response. A PPD test recorded as "negative" without documenting the size of induration (in millimeters) will not be acceptable and will require a retest.

However, subjects with a PPD skin test response ≥5 mm induration or a positive interferon-γ release test (eg, QuantiFERON-TB Gold or T-SPOT®) result at screening and no other evidence of active TB may be rescreened once and enrolled according to the following requirements:

- after receiving at least 4 weeks of appropriate ongoing prophylactic therapy for latent TB as per local standard of care
- no evidence of treatment hepatotoxicity (ALT and AST levels must remain ≤2× ULN) upon retesting of serum ALT and AST levels before randomization)

Such subjects must continue and complete appropriate latent TB therapy during the course of the study to remain eligible and must continue to meet all other inclusion and exclusion criteria for participation.

Subjects who have a documented history of completing an appropriate TB prophylaxis regimen with no history of reexposure since their treatments were completed and no evidence of active TB are eligible to participate in the study; these subjects should not undergo PPD testing.

Subjects who have had household contact with a person with active TB must be excluded unless appropriate and documented prophylaxis for TB has been given, as described above.

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

10.3.2.3. Vital Signs

Blood pressure and heart rate will be measured as specified in the study schedules (Attachment 1 and Attachment 2) and as clinically indicated.

Blood pressure and heart rate should be measured after the subject has been supine for at least 5 minutes.

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, only supine vital signs 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 if clinically warranted.

10.3.2.4. Electrocardiograms

For each subject, 12-lead digital ECGs will be collected according to the study schedules (Attachment 1 and Attachment 2). Subjects should be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

ECGs may be obtained at additional times when deemed clinically necessary. Collection of additional ECGs at a particular time point is allowed when needed to ensure high quality records.

ECGs 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 and for immediate subject management should any clinically relevant findings be identified.

After enrollment, if a clinically significant increase in the QT interval or corrected QT interval or other clinically significant quantitative or qualitative change from baseline is present, the investigator will assess the subject for symptoms (eg, palpitations, near syncope, syncope) and to determine if the subject can continue in the study. The investigator or qualified designee is responsible for determining if any change in subject management is needed and must document his/her review of the ECG printed at the time of evaluation. Clinically significant increase in the QT interval or corrected QT interval should be recorded as an AE.

10.3.3. Safety Monitoring

The Lilly clinical research physician will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly clinical research physician will, as appropriate, consult with the functionally independent global patient safety therapeutic area physician or clinical scientist and periodically review:

- trends in safety data
- laboratory analytes
- AEs/SAEs

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of a sponsor assessment committee (an advisory group for this study formed to protect the integrity of data; refer to Section 12.2.10) should conduct additional analyses of the safety data.

Hepatic monitoring: If a subject experiences elevated ALT or AST level >3× ULN or elevated total bilirubin level >2× ULN, clinical and laboratory monitoring should be initiated by the investigator. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure subject safety and compliance with regulatory guidance, the investigator is to consult with the Lilly-designated medical monitor regarding collection of specifically recommended clinical information and follow-up laboratory tests (see Attachment 4).

Any enrolled subject who is HBcAb+ will undergo periodic monitoring of hepatitis B deoxyribonucleic acid (HBV DNA) per the study schedule.

In addition to the above, any enrolled subject who is HBcAb+ or tests positive for hepatitis B surface antibody and who experiences an elevated ALT or AST level >3× ULN must undergo HBV DNA testing. If the HBV PCR test is negative, the investigator should consult with the Lilly-designated medical monitor regarding further management of the subject.

If the result of any HBV PCR test is positive at any time, the subject must be discontinued from the study and should receive appropriate follow-up medical care, including consideration for antiviral therapy. A specialist physician in the care of patients with hepatitis (for example, infectious disease or hepatologist subspecialists) should be consulted and potentially start antiviral therapy.

10.3.4. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

For blinded studies, all product complaints associated with material packaged, labeled, and released by Lilly or delegate 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.

10.4. Sample Collection and Testing

Attachment 1 and Attachment 2 list the schedules for sample collections in this study.

Attachment 3 lists the laboratory tests that will be performed for this study.

Attachment 4 lists the hepatic monitoring tests that will be performed for this study.

10.4.1. Samples for Study Qualification and Health Monitoring

As applicable blood and urine samples will be collected to determine whether subjects meet inclusion and exclusion criteria and to monitor subject health during the study.

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 will be 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.

Laboratory test or analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel.

10.4.2. Samples for Pharmacogenetic Evaluation

There is growing evidence that genetic variation may affect a subject's response to therapy. Variable response to therapy may be caused by genetic determinants that impact drug absorption, distribution, metabolism, and excretion; the mechanism of action of the drug; the disease etiology; and/or the molecular subtype of the disease being treated. Therefore, where local regulations and ERBs allow, blood samples will be collected for pharmacogenetic analysis. This will be a one-time collection, as specified in the study schedule (Attachment 1).

In the event of an unexpected AE or the observation of unusual response, the pharmacogenetic samples may be genotyped and analysis may be performed to evaluate a genetic association with response to LY3074828. These investigations may be limited to a focused candidate gene study, or, if appropriate, genome-wide analysis may be performed to identify regions of the genome associated with the variability observed in drug response. The pharmacogenetic samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

The samples will be coded with the subject number and stored for up to a maximum 15 years after the last subject visit for the study at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the study subject by investigator site personnel. The storage duration allows the sponsor to respond to regulatory requests related to the investigational product.

10.4.3. Samples for Immunogenicity Research

Blood samples for immunogenicity testing will be collected to determine antibody production against the investigational product. Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of the investigational product(s). Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the investigational product.

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

10.4.4. Samples for Drug Concentration Measurements Pharmacokinetics/Pharmacodynamics

At the visits and times specified in the study schedule (Attachment 1 and Attachment 2), venous blood samples of approximately 2 mL each will be collected to determine the serum concentrations of LY3074828.

A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon by the investigator and sponsor. In case of early termination, a PK sample will be taken at the end-of-study visit. 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. It is essential that the actual times of doses and samples are recorded accurately.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel.

Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 1 year after last subject visit for the study.

10.4.5. Samples for Exploratory Evaluations

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

Whole blood, serum, plasma, colonic tissue and, fecal matter will be collected at the times specified in the study schedule (Attachment 1 and Attachment 2). 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.

10.5. Appropriateness of Measurements

The clinical safety parameters in this study are routine elements of clinical health assessment and Phase 2 drug development. The disease activity measurements are used in clinical practice and UC clinical trials.

11. 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 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, its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

11.1. Data Capture System

A source document is the first record of data. These can be paper (for example, ECG tracing or subject 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.

An electronic data capture system will be used in this study. The process will be documented and communicated by the sponsor to the investigator site before the first subject visit. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

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.

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. After 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.

PRO measures (eg, a rating scale) or other data reported directly by the subject (eg, daily dosing schedule, event diary) are entered into a PRO instrument (eg, in a personal digital assistant, on paper, or by electronic means) at the time that the information is obtained. In these instances where there is no previous written or electronic source data at the site, the PRO instrument record will serve as the source.

The study data completion guidelines and study data management plan will provide detailed information on use of PRO measures and the subject diary.

Any data for which paper documentation provided by the subject will serve as the source document will be identified and documented by each site in that site's study file.

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

Approximately 240 subjects will be randomized to 1 of 4 double-blind treatment regimens to evaluate the primary endpoint. Subjects will be randomized to placebo, 50 mg LY3074828 exposure-based dosing, 200 mg LY3074828 exposure-based dosing, or the 600-mg LY3074828 fixed-dose treatment group in a 1:1:1:1 ratio (60 subjects per arm). The randomized subjects will comprise approximately one-third biologic-naive subjects (~20 per arm) and approximately two-thirds previous biologic therapy subjects (received treatment with 1 or more agents such as TNF antagonists, vedolizumab, or experimental UC biologics) (~40 per arm).

Assuming LY3074828 and placebo clinical remission rates of 30% and 7.5% respectively (a difference of 22.5%) and given 60 subjects per treatment arm, each pairwise comparison testing the superiority of LY3074828 to placebo will have 89% power via chi-square test with a two-sided 0.05 significance level.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

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

The subject populations to be analyzed for this study are defined in Table AMAC.4.

Table AMAC.4. Analysis Populations

Population	Definition
Screening	all subjects who signed informed consent and participated in the screening period (Visit 1)
Safety Population	all randomized patients who receive at least 1 dose of study treatment. maintenance period: only subjects who received LY3074828 during the induction phase, met the protocol definition of clinical response at Week 12, and then received any amount of investigational product in the maintenance phase
Intent-to-Treat (ITT)	all randomized patients, even if the patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol
PK-Evaluable	all subjects who received at least 1 dose of investigational product and have sufficient blood sampling to allow for PK evaluation

Efficacy analyses will be conducted on the intent-to-treat (ITT) population. Safety analyses will be conducted on the safety population. Subjects will be analyzed according to the treatment to which they were assigned, regardless of any errors of dosing.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05 unless otherwise stated. Unless otherwise specified, no multiplicity adjustment will be considered for all planned analyses.

Summary statistics for continuous variables may include mean, standard deviation, median, and minimum and maximum values; categorical variables will be presented as counts and percentages.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol and the justification for making the change will be described in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

Unless otherwise specified, variables will be analyzed in the original scale on which they are measured. However, if it is deemed more statistically appropriate, a transformation, such as to the logarithmic scale, may be applied before analysis. The parametric approach will be employed by default for statistical analysis except when nonparametric analysis, such as by a rank-based method, is assessed to be more fitting.

12.2.2. Subject 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.

Counts and percentages of subjects entered and subjects failing screening before randomization will be summarized overall, and counts and percentages of subjects randomized, discontinued, and completed will be summarized by treatment group. The reasons for discontinuation from treatment and from the study will be summarized by treatment group.

12.2.3. Subject Characteristics

The subject's year of birth, sex, weight, height, smoking habits, previous biologic treatment, and other demographic characteristics will be recorded. Age and body mass index will be calculated. Demographic and baseline characteristics will be summarized for each treatment group. Certain characteristics, such as weight, that are collected after baseline, will be reported as a listing.

12.2.4. Concomitant Therapy

Concomitant therapy will be collected at each visit, and the reported term will be classified by the World Health Organization drug dictionary. Previous concomitant therapy (reported before randomization) and current concomitant therapy (reported after randomization) will be presented separately in frequency tables by drug name for all randomized subjects.

12.2.5. Treatment Compliance

Subjects who are noncompliant according to the definition in Section 9.10 will be listed by treatment. A contingency table of numbers of noncompliant subjects by treatment will be provided.

12.2.6. Efficacy and Health Outcome Analyses

12.2.6.1. Primary Analyses

Rates of clinical remission at Week 12, as defined in Section 10.1.1, will be analyzed.

Subjects who do not achieve clinical remission or who do not reach the Week 12 assessment will be considered to be nonremitters.

The rates of clinical remission and nonremission will be summarized by dose level and previous biologic use (yes/no). The differences between each treatment arm and placebo will be tested separately via a logistic regression model that controls for previous biologic use.

The primary analysis will be based on the ITT population.

12.2.6.2. Secondary Efficacy Analyses

The proportions of subjects with endoscopic remission at Week 12, endoscopic remission at Week 52, clinical response at Week 12, durability of remission at Week 52, durability of endoscopic remission at Week 52, and durability of response at Week 52 will be calculated. The differences between each treatment arm and the placebo arm will be tested via a logistic regression model that controls for previous biologic use. More information on the definition of secondary endpoints can be found in Section 10.1.2.

For continuous efficacy measures, mean change from baseline to Week 12 and Week 52, as appropriate, will be summarized by treatment group in the ITT population.

Unless otherwise specified, the secondary analyses will be based on the ITT population.

12.2.6.3. Health Outcome Analyses

The effect of LY3074828 on quality of life will be quantified by using the IBDQ, SF-36, PGI-S, and PGI-I measures.

The ITT population will be used for change-from-baseline analyses such as analyses of IBDQ and SF-36 scores. Subjects in this population will be analyzed according to the treatments they were randomized to receive regardless of any errors of dosing.

Mean change from baseline will be summarized by treatment group.

12.2.7. Pharmacokinetic/Pharmacodynamic Analyses

The PK-evaluable population will be used for all PK analyses. Analysis will be performed using a nonlinear mixed-effect modeling approach as implemented in NONMEM software on a computer that meets or exceeds the minimum system requirements for this program. It is possible that other validated equivalent PK software programs may be used if appropriate. The version of any software used for the analysis will be documented.

Population PK analyses will be performed to characterize the PK of LY3074828 after IV and SC dosing. These analyses will include model-based and graphical evaluations of the data. Estimates of PK model parameters and covariate effects and corresponding 90% confidence intervals will be reported.

Population PK/PD analyses will be conducted to evaluate the relationship between LY3074828 concentrations and/or dose and clinical response as measured by the primary endpoint of clinical remission, Mayo subscores, and other biomarkers and endpoints. These analyses may include analyses of relationships at specific time points as well as the development of longitudinal exposure-response models. Additional analyses may be conducted if they are deemed appropriate.

12.2.8. Safety Analyses

Safety will be assessed by evaluating all reported AEs and changes in laboratory analytes, ECGs, and vital signs (including body weight).

Duration of exposure to therapy will be calculated for each subject and summarized by treatment group.

AEs will be coded according to the *Medical Dictionary for Regulatory Activities* and summarized by system organ class, preferred term, severity, and relationship to investigational product. A TEAE is defined as an event that first occurred or worsened in severity after baseline. In the analysis of TEAEs during the induction period, all preexisting conditions recorded at screening (Visit 1) and any on-study AEs recorded at or before baseline (Visit 2) will be used as baseline. In the analysis of TEAEs during the maintenance period, any on-study AEs recorded at Week 12 will be used as baseline. The induction period and the maintenance period will be analyzed separately. For each event classification term, the number of subjects experiencing a TEAE with that classification term will be tabulated. Treatment-related TEAEs are defined as events that are indicated by the investigator on the CRF to be related to treatment. If a subject reports the occurrence of a particular event more than once, the most severe of those events will be included in the summary tables of TEAEs, and the most severe of the most related of those events will be included in the summary tables of treatment-related events. TEAEs of interest will be presented.

Additional safety parameters include laboratory test results, ECGs, and vital-sign measurements. The baseline for computing the change in safety variables for the induction period will be data collected at or before dosing on Visit 2; the baseline for the maintenance period will be the last value collected during the induction period. The parameters will be listed and summarized with standard descriptive statistics. Change from baseline will also be summarized by randomized treatment.

12.2.9. Subgroup Analyses

Analyses of population subgroups of interest (for example previous biologic treatment versus biologic naive) will be performed if deemed appropriate. Full details of subgroup analyses will be described in the statistical analysis plan (SAP).

12.2.10. Interim Analyses

One interim analysis will be conducted to assess the primary efficacy results when approximately half (~120) of the subjects have completed the induction phase (or discontinued

study treatment). The interim efficacy results will be used for internal decision making to trigger planning activities associated with the investigational product and to aid development of PK/PD modeling. No adjustment of Type I error will be performed. The assessment will be conducted by a sponsor assessment committee with a limited number of preidentified team members who do not have direct site contact or data entry/validation responsibilities, or by an Independent Data Monitoring Committee. To minimize any bias being introduced into the analysis of the study results, the SAP and PK/PD analysis plan will be finalized and approved before the efficacy interim analysis begins. Unblinding details are specified in the unblinding plan section of the SAP or in a separate unblinding plan document. Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until the study has been unblinded.

Ongoing monitoring of safety data (including AEs, SAEs, and selected laboratory measurements) will continue throughout the study using blinded data. Interim safety analyses may be conducted to review unblinded safety data; the analyses will be conducted and reviewed by an internal assessment committee composed of personnel who do not have direct site contact, data entry responsibilities, or data validation responsibilities. Details are specified in the trial level safety review plan or a separate document.

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 risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that written, informed consent is given by each subject or legal representative. This includes obtaining the appropriate signatures and dates on the ICF before the performance of any protocol procedures including administration of investigational product.

As used in this protocol, the term "informed consent" includes all consent given by subjects.

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are used at investigative sites(s). All ICFs must be compliant with the International Conference on Harmonisation (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(s). 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 International Ethical Guidelines

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

The investigator with the most enrolled subjects will serve as the coordinating investigator for the clinical study report. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the coordinating investigator.

The sponsor's responsible medical officer and statistician will 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 I6T-MC-AMAC Study Schedule

Study Schedule, Protocol I6T-MC-AMAC

Screening, Baseline, and Induction Dosing Period (1 of 4)

		Induction Dosing Period					
	Screening	**Baseline**					
Visit No. (V)	V1	V2	V3	V4	V5	V6	V7
Study Week (W)		W0	W2	W4	W6	W8	W11-W12[a] ET
Day (D)	≤28 from V2	D1	D15 ± 2d	D29 ± 2d	D43 ± 2d	D57 ± 2d	D78-85
Informed consent	X						
Physical examination[b] and weight	X	X					X
Complete medical/surgical history and habits[c]	X						
Demographics	X						
Height[c]	X						
Chest radiography	X[d]						
Randomization (Section 9.3)		X					
Concomitant medications	X	X	X	X	X	X	X
Vital signs (BP and heart rate)[e] Body temperature only at V1 and V2, unless clinically indicated	X	X	X	X		X	X
AEs	X	X	X	X	X	X	X
Dosing[f]		X		X		X	
Partial Mayo score (all subjects)	X	X	X	X		X	
Endoscopy[g] (baseline: only subjects who meet the partial Mayo score and I/E criteria will undergo endoscopy)	X						X
Colon biopsy sample collection (occurs at time of endoscopy)	X						X
Full Mayo score (only patients who meet eligibility criteria for endoscopy will have a full Mayo score)		X					X
Subject diary instruction	X						
Subject diary data review & collection		X	X	X	X	X	X
IBDQ		X		X		X	X

Study Schedule, Protocol I6T-MC-AMAC
Screening, Baseline, and Induction Dosing Period (2 of 4)

		Induction Dosing Period					
	Screening	**Baseline**					
Visit No (V)	V1	V2	V3	V4	V5	V6	V7
Study Week (W)		W0	W2	W4	W6	W8	W11-W12[a]/ET
Day (D)	≤28 from V2	D1	D15 ± 2d	D29 ± 2d	D43 ± 2d	D57 ± 2d	D78-85
SF-36		X		X		X	X
PGI-S		X					X
PGI-I				X		X	X
PPD/T-SPOT®/QuantiFERON®-TB Gold[h]	X						
Read PPD (48-72 hrs after PPD is administered)	X						
ECG[i]	X	X					X
HIV, HBV and HCV testing	X						
HBV PCR (only if HBcAb+ with negative HBV PCR test at screening)	X						X
Serum pregnancy test[j]	X						
Urine pregnancy test[j]		X		X		X	X
FSH[k]	X						
Serum chemistry	X	X	X	X		X	X
Hematology	X	X	X	X		X	X
LY3074828 PK samples		X[l]	X	X[l]	X	X[l]	X
Urinalysis	X	X		X			X
NGAL and MMP-9[m]		X		X		X	X
CRP		X	X	X		X	X
Samples for exploratory biomarkers (whole blood, serum, plasma)		X		X			X
Pharmacogenetics storage sample (DNA)		X					
Immunogenicity samples[n]		X	X	X		X	X
Fecal sample (collection instructions in laboratory manual) for *Clostridium difficile* and biomarker testing	X			X		X	X

Study Schedule, Protocol I6T-MC-AMAC
Maintenance Dosing Period (3 of 4)

	Maintenance Dosing Period												
Visit No (V)	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20
Study Week (W)	W12-W13	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W56	W60
Day (D)	D85-92	D113 ± 7d	D141 ± 7d	D169 ± 7d	D197 ± 7d	D225 ± 7d	D253 ± 7d	D281 ± 7d	D309 ± 7d	D337 ± 7d	D365 ± 7d	D393 ± 7d	D421 ± 7d
Randomization	X[o]												
Physical examination[b] and weight		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (BP and heart rate)	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X
Dosing[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
Partial Mayo score (all subjects)		X	X	X	X	X	X	X	X	X		X	X
Endoscopy											X[p]		
Colon biopsy sample collection (occurs at time of endoscopy)											X[p]		
Full Mayo score (only patients who meet eligibility criteria for endoscopy will have a full Mayo score)											X		
Subject diary data review/collection		X	X	X	X	X	X	X	X	X	X	X	X
IBDQ, SF-36, and PGI-I				X		X					X		
ECG						X					X		
HBV PCR[q] (only if HBcAb+ with negative HBV PCR test at screening)				X			X			X			X
Urine pregnancy test[j]		X	X	X	X	X	X	X	X	X	X	X	X
Blood draws for hematology and serum chemistry		X	X	X	X	X	X	X	X	X	X	X	
NGAL and MMP-9				X							X		
LY3074828 PK samples[n]	X	X	X	X		X		X		X		X	
LY3074828 postdose samples	X[r] (2-10 days postdose)												
Urinalysis		X		X		X		X		X			
CRP		X	X	X	X	X	X	X	X	X	X		
Samples for exploratory biomarkers (whole blood, serum, plasma)				X							X		
Immunogenicity samples[n]		X		X		X		X		X		X	
Fecal sample (eg, fecal calprotectin)											X		

Study Schedule, Protocol I6T-MC-AMAC
Maintenance Dosing and Follow-Up Periods (4 of 4)

	Maintenance Dosing Period											Follow-Up Period			
Visit No (V)	V21	V22	V23	V24	V25	V26	V27	V28	V29	V30	V31	V801	V802	V803	V804
Study Week (W)	W64	W68	W72	W76	W80	W84	W88	W92	W96	W100	W104	W108	W112	W116	W120[s]/ EOS/ET
Day (D)	D448 ± 7d	D476 ± 7d	D504 ± 7d	D532 ± 7d	D560 ± 7d	D588 ± 7d	D616 ± 7d	D644 ± 7d	D672 ± 7d	D700 ± 7d	D728 ± 7d	D756 ± 7d	D784 ± 7d	D812 ± 7d	D840 ± 7d
Physical examination[b] and weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (BP and heart rate)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dosing[f]	X	X	X	X	X	X	X	X	X	X	X				
Partial Mayo score (all subjects)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject diary data review/collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IBDQ, SF-36, PGI-S, and PGI-I															X
ECG					X						X				X
HBV PCR[q] (only if HBcAb+ with negative HBV PCR test at screening)			X			X			X			X			X
Urine pregnancy test[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood draws for hematology and serum chemistry	X		X		X		X		X		X		X		X
LY3074828 PK samples[n]	X		X		X		X		X		X		X		X
Urinalysis	X				X				X						X
CRP	X		X		X		X		X		X		X		X
Immunogenicity samples[n]	X		X		X		X		X		X		X		X
Fecal sample (eg, fecal calprotectin)															

Study Schedule, Protocol I6T-MC-AMAC

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; C_{max} = maximum concentration; CRP = C-reactive protein; d = days; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EOS = end of study; ET = early termination; FSH = follicle-stimulating hormone; HBcAb+ = positive for anti–hepatitis B core antibody; HBsAb = anti–hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IBDQ = Inflammatory Bowel Disease Questionnaire; I/E = inclusion/exclusion; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; MMP-9 = matrix metalloproteinase-9; NGAL = neutrophil gelatinase-associated lipocalin; PCR = polymerase chain reaction; PGI-I = Patient's Global Impressions of Improvement; PGI-S = Patient's Global Impressions of Severity; PPD = purified protein derivative; PK = pharmacokinetic; Q4W = every 4 weeks; SF-36 = 36-Item Short Form Health Survey; ULN = upper limit of normal; V = study visit; W = study week.

Note: Study visits will occur at least Q4W during the maintenance dosing period.

[a] For subjects discontinued during the induction period, Visit 7 (Week 12) will serve as the ET visit.

[b] One complete physical examination (excluding pelvic, rectal, and breast examinations) will be performed at screening. All physical examinations throughout the study should include a symptom-directed evaluation as well as examination of heart, lungs, and abdomen and visual examination of the skin.

[c] Subject to remove shoes prior to measurement of height. Habits include recording of caffeine, alcohol, and tobacco use.

[d] Chest radiography (posterior-anterior and lateral views) will be performed at screening unless such radiography has been performed within 3 months before initial screening (provided the radiographs and/or formal report are available for the investigator's review).

[e] Blood pressure and heart rate should be measured after the subject has been supine for at least 5 minutes. If orthostatic measurements are required, subjects should be supine for at least 5 minutes and stand for at least 3 minutes.

[f] All subjects should be monitored for 1 hour after dosing or longer according to investigator practice/local standard of care.

[g] See Section 10.1.4 for a description of the endoscopy procedures.

[h] See Section 10.3.2.2 for detailed description of QuantiFERON-TB Gold and PPD T-SPOT testing. PPD should be read approximately 48 to 72 hours after placement and response recorded in mm of induration.

[i] ECGs should be performed before any blood is drawn. Subjects should be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

[j] To be performed only for women of childbearing potential.

[k] FSH test is to be performed at screening for women who have had spontaneous amenorrhea for 6 to 12 months to confirm lack of childbearing potential.

[l] On the day of dosing, PK samples should be drawn before each intravenous infusion (trough) and at the end of the infusion (C_{max}).

[m] MMP-9 and NGAL as blood biomarker in addition to fecal calprotectin as quick response marker of LY3074828 treatment.

[n] A single sample is to be drawn prior to investigational product administration if occurring on a dosing day.

[o] See Section 7.1 for a detailed description of the randomization process during the maintenance period.

[p] Subjects will not need to undergo an endoscopy/biopsy at the EOS visit if they discontinued the study due to reasons specified in Section 8.3.1.

[q] Any enrolled subject who is HBcAb+ will undergo monitoring of HBV DNA according to schedule of events. Any subject with a positive HBV DNA test at any time must be discontinued from the study and receive appropriate follow-up medical care, including consideration for antiviral therapy.

[r] An additional PK sample will be drawn 2 to 10 days after the first SC dosing in the maintenance period.

[s] Visit V804 (Week 120) will serve as the EOS visit or ET visit if a subject prematurely discontinues from the study at any time during the maintenance or maintenance follow-up period.

Attachment 2. Protocol I6T-MC-AMAC Extension and Follow-Up Periods Study Schedule

Study Schedule, Protocol I6T-MC-AMAC

Extension Period—Induction (1 of 3)

	Extension Period - Induction					
Extension Visit No. (EV)	EV1	EV2	EV3	EV4	EV5	EV6
Extension Study Week (EW)	EW0	EW2	EW4	EW6	EW8	EW11-EW12[a]
Extension Day (ED)	ED1	ED15 ± 2d	ED29 ± 2d	ED43 ± 2d	ED57 ± 2d	ED78-ED85
Physical examination[b] and weight	X					X
Concomitant medications	X	X	X		X	X
Vital signs (BP and heart rate)[c] Body temperature only at V1 and V2, unless clinically indicated	X	X	X		X	X
AEs	X	X	X	X	X	X
Dosing[d]	X		X		X	
Partial Mayo score (all subjects)	X	X	X		X	
Endoscopy[e]						X
Colon biopsy sample collection (occurs at time of endoscopy)						X
Full Mayo score (only patients who meet eligibility criteria for endoscopy will have a full Mayo score)						X
Subject diary instruction						
Subject diary data review and collection	X	X	X	X	X	X
IBDQ	X		X		X	X
SF-36	X		X		X	X
PGI-S	X					X
PGI-I	X		X		X	X
ECG[f]	X					X
HBV PCR (only if HBcAb+ with negative HBV PCR test at screening)						X
Urine pregnancy test[g]	X		X		X	X
Serum chemistry	X	X	X		X	X
Hematology	X	X	X		X	X
LY3074828 PK samples	X[h]	X	X[h]	X	X[h]	X
Urinalysis	X		X			X
NGAL and MMP-9[i]	X		X		X	X
CRP	X	X	X		X	X
Samples for exploratory biomarkers (whole blood, serum, plasma)	X		X			X
Immunogenicity samples[l]	X	X	X			X
Fecal sample (collection instructions in laboratory manual)	X		X		X	X

Study Schedule, Protocol I6T-MC-AMAC
Extension Period—Maintenance (2 of 3)

	Extension Period - Maintenance										
Extension Visit No (EV)	EV7	EV8	EV9	EV10	EV11	EV12	EV13	EV14	EV15	EV16	EV17
Extension Study Week (EW)	EW12-13	EW16	EW20	EW24	EW28	EW32	EW36	EW40	EW44-45	EW48	EW52
Extension Day (ED)	ED85-92	ED113 ± 7d	ED141 ± 7d	ED169 ± 7d	ED197 ± 7d	ED225 ± 7d	ED253 ± 7d	ED281 ± 7d	ED309 ± 7d	ED337 ± 7d	ED365 ± 7d
Physical examination[b] and weight		X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Vital signs[c] (BP and heart rate)	X	X	X	X	X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X	X	X	X	X
Dosing[d]	X	X	X	X	X	X	X	X	X	X	X
Partial Mayo score (all subjects)		X	X	X	X	X	X	X	X	X	X
Endoscopy								X[j]			
Colon biopsy sample collection (occurs at time of endoscopy)								X[j]			
Full Mayo score (only patients who meet eligibility criteria for endoscopy will have a full Mayo score)								X			
Subject diary data review/collection		X	X	X	X	X	X	X	X	X	X
IBDQ, SF-36, and PGI-I				X		X		X			
ECG						X		X			
HBV PCR[k] (only if HBcAb+ with negative HBV PCR test at screening)				X			X			X	
Urine pregnancy test[g]		X	X	X	X	X	X	X	X	X	X
Blood draws for hematology and serum chemistry		X	X	X	X	X	X	X		X	X
NGAL and MMP-9[i]				X				X			
LY3074828 PK samples[l]	X	X	X	X		X		X		X	
LY3074828 postdose samples	X[m] (2-10 days postdose)										
Urinalysis		X		X		X		X			X
CRP		X	X	X	X	X	X	X		X	
Samples for exploratory biomarkers (whole blood, serum, plasma)				X				X			
Immunogenicity samples[l]		X		X		X		X		X	
Fecal sample (eg, fecal calprotectin)								X			

Study Schedule, Protocol I6T-MC-AMAC

Extension Period—Maintenance and Follow-Up (3 of 3)

	Extension Period - Maintenance										Extension Period - Follow-Up			
Extension Visit No (EV)	EV18	EV19	EV20	EV21	EV22	EV23	EV24	EV25	EV26	EV27	V805	V806	V807	V808
Extension Study Week (EW)	EW56	EW60	EW64	EW68	EW72	EW76	EW80	EW84	EW88	EW92	EW96	EW100	EW104	EW108[n] EOS/ET
Extension Day (ED)	ED393 ± 7d	ED421 ± 7d	ED449 ± 7d	ED477 ± 7d	ED505 ± 7d	ED533 ± 7d	ED561 ± 7d	ED589 ± 7d	ED617 ± 7d	ED645 ± 7d	ED673 ± 7d	ED701 ± 7d	ED729 ± 7d	ED757 ± 7d
Physical examination[b] and weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[c] (BP and heart rate)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dosing[d]	X	X	X	X	X	X	X	X	X	X				
Partial Mayo score (all subjects)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject diary data review/collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IBDQ, SF-36, PGI-S, and PGI-I														X
ECG					X					X				X
HBV PCR[k] (only if HBcAb+ with negative HBV PCR test at screening)		X			X			X			X			X
Urine pregnancy test[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood draws for hematology and serum chemistry	X		X			X			X	X		X		X
LY3074828 PK samples[l]	X		X		X		X			X		X		X
Urinalysis	X				X					X				X
CRP	X		X		X		X			X		X		X
Immunogenicity samples[l]	X		X		X		X			X		X		X

Study Schedule, Protocol I6T-MC-AMAC Extension Period

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; C_{max} = maximum concentration; CRP = C-reactive protein; d = days; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ED = Extension Day; EOS = end of study; ET = early termination; EV = Extension Visit; EW = Extension Week; FSH = follicle-stimulating hormone; HBcAb+ = positive for anti–hepatitis B core antibody; HBsAb = anti–hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IBDQ = Inflammatory Bowel Disease Questionnaire; I/E = inclusion/exclusion; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; MMP-9 = matrix metalloproteinase-9; NGAL = neutrophil gelatinase-associated lipocalin; PCR = polymerase chain reaction; PGI-I = Patient's Global Impressions of Improvement; PGI-S = Patient's Global Impressions of Severity; PPD = purified protein derivative; PK = pharmacokinetic; Q4W = every 4 weeks; SF-36 = 36-Item Short Form Health Survey; ULN = upper limit of normal; V = study visit; W = study week.

[a] For subjects who are nonresponders at the end of the extension induction period (Extension Visit 6 [Extension Week 12]), Extension Visit 6 (Extension Week 12) will serve as the end of study visit.

[b] All physical examinations throughout the study should include a symptom-directed evaluation as well as examination of heart, lungs, and abdomen and visual examination of the skin.

[c] Blood pressure and heart rate should be measured after the subject has been supine for at least 5 minutes. If orthostatic measurements are required, subjects should be supine for at least 5 minutes and stand for at least 3 minutes.

[d] All subjects should be monitored for 1 hour after dosing or longer according to investigator practice/local standard of care.

[e] See Section 10.1.4 for a description of the endoscopy procedures.

[f] ECGs should be performed before any blood is drawn. Subjects should be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

[g] To be performed only for women of childbearing potential.

[h] On the day of dosing, PK samples should be drawn before each intravenous infusion (trough) and at the end of the infusion (C_{max}).

[i] MMP-9 and NGAL as blood biomarker in addition to fecal calprotectin as quick response marker of LY3074828 treatment.

[j] Subjects will not need to undergo an endoscopy/biopsy at the EOS visit if they discontinued the study due to reasons specified in Section 8.3.1.

[k] Any enrolled subject who is HBcAb+ will undergo monitoring of HBV DNA according to schedule of events. Any subject with a positive HBV DNA test at any time must be discontinued from the study and receive appropriate follow-up medical care, including consideration for antiviral therapy.

[l] A single sample is to be drawn prior to investigational product administration if occurring on a dosing day.

[m] An additional PK sample will be drawn 2 to 10 days after the first SC dosing in the extension maintenance period.

[n] In the extension period, visit V808 (Extension Week 108) will serve as the EOS visit or ET visit if a subject prematurely discontinues from the study at any time during the maintenance extension or extension follow-up period.

Attachment 3. Protocol I6T-MC-AMAC Laboratory Tests

Clinical Laboratory Tests

Hematology[a]:	**Clinical Chemistry**[a]:
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count	Chloride
Mean cell volume	Bicarbonate
Mean cell hemoglobin concentration	Potassium
Leukocytes	Total bilirubin
Neutrophils, segmented	Direct bilirubin
Lymphocytes	Alkaline phosphatase
Monocytes	Alanine aminotransferase
Eosinophils	Aspartate aminotransferase
Basophils	Gamma-Glutamyl Transferase (GGT)
Platelets	Blood urea nitrogen
Cell morphology	Creatinine
	Uric acid
Urinalysis[a]:	Calcium
Specific gravity	Glucose (random)
pH	Albumin
Protein	Total Protein
Glucose	Total cholesterol
Ketones	Creatine phosphokinase (CPK)
Blood	
Urine leukocyte esterase	
nitrite	
Other Tests:	
QuantiFERON®-TB Gold or PPD	LY3074828 concentration (PK)
C-reactive protein	MMP-9
Pregnancy[b]	
FSH	NGAL
Human immunodeficiency virus antibody[c]	Fecal calprotectin
Hepatitis B surface antigen[c]	Exploratory storage samples (whole blood, serum, plasma, colonic tissue, fecal matter, and DNA)
Anti–hepatitis B surface antibody[c]	Anti-LY3074828 antibodies (immunogenicity)
Anti–hepatitis B core antibody[c]	*Clostridium difficile*[c]
Hepatitis B PCR[d]	
Anti–hepatitis C antibody and PCR[e]	

Abbreviations: FSH = follicle-stimulating hormone; MMP-9 = matrix metalloproteinase-9; NGAL = neutrophil gelatinase-associated lipocalin; PCR = polymerase chain reaction; PK = pharmacokinetic; PPD = purified protein derivative.

a Unscheduled blood chemistry, hematology, and urinalysis panels may be performed at the discretion of the investigator as needed.

b Serum pregnancy test.

c Test required only at screening (Visit 1) to determine eligibility of subject for the study. Visit 1 stool sample will be used for *Clostridium difficile* and biomarker testing.

Clinical Laboratory Tests

[d] Hepatitis B PCR testing will be performed in subjects who test positive for anti–hepatitis B core antibody (at protocol-specified intervals).

[e] Hepatitis C PCR testing will be performed in subjects who test positive for anti–hepatitis C antibody at screening.

Attachment 4. Protocol I6T-MC-AMAC Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests from the list below may be obtained in the event of a treatment-emergent hepatic abnormality per judgment of the investigator and may be required for subject follow-up as determined after consultation with the Lilly clinical research physician or designee.

Hepatic Monitoring Tests

Hematology[a]	**Hepatic Coagulation[a]**
Hemoglobin	Partial prothrombin time
Hematocrit	Prothrombin time, INR
RBC	
WBC	**Other Labs[a,b]**
Neutrophils, segmented	Hepatitis A antibody, total
Lymphocytes	Hepatitis A antibody, IgM
Monocytes	Hepatitis B surface antigen
Eosinophils	Hepatitis B surface antibody
Basophils	Hepatitis B Core antibody
Platelets	Hepatitis C antibody
	Hepatitis E antibody, IgG
Chemistry[a]	Hepatitis E antibody, IgM
Total bilirubin	Haptoglobin[a]
Direct bilirubin	LDH
Alkaline phosphatase	Antinuclear antibody[a]
ALT	Alkaline phosphatase isoenzymes
AST	Anti–smooth muscle antibody[a]
Total protein	CPK
GGT	
Albumin	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = γ-glutamyl transferase; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; labs = laboratory tests; LDH = lactate dehydrogenase; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated or local laboratory.

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

Attachment 5. Protocol I6T-MC-AMAC Mayo Scoring System for the Assessment of Ulcerative Colitis Activity

Stool Frequency	**Score**
Normal number of stools for subject	0
1 to 2 stools more than normal	1
3 to 4 stools more than normal	2
5 or more stools than normal	3
Rectal Bleeding	**Score**
No blood seen	0
Streaks of blood with stool less than half of the time	1
Obvious blood with stool most of the time	2
Blood alone passed	3
Endoscopic Findings	**Score**
Normal or inactive disease	0
Mild disease (erythema, decreased vascular pattern)	1
Moderate disease (marked erythema, absent vascular pattern, friability, erosions)	2
Severe disease (spontaneous bleeding, ulceration)	3
Physician's Global Assessment	**Score**
Normal	0
Mild disease	1
Moderate disease	2
Severe disease	3
Mayo Score = Stool Frequency + Rectal Bleeding + Endoscopic Findings + Physician's Global Assessment	

Note: The Mayo score ranges from 0 to 12, with higher scores indicating more severe disease. Partial Mayo score excludes endoscopy and ranges from 0 to 9.

Adapted from: Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med*. 1987;317(26):1625-1629.

Attachment 6. Protocol Amendment I6T-MC-AMAC(c) Summary

Overview

Protocol I6T-MC-AMAC, *A Phase 2, Multicenter, Randomized, Double-Blind, Parallel, Placebo-Controlled Study of LY3074828 in Subjects with Moderate to Severe Ulcerative Colitis*, has been amended. The new protocol is indicated by amendment (c) and will be used to conduct the study in place of any preceding version of the protocol.

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

- This amendment is to align with updated Investigator's Brochure, which states that subjects will be discontinued from the study if they experience a systemic hypersensitivity event or anaphylaxis.

Revised Protocol Sections

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

8.3.1. Discontinuation of Subjects

In addition, subjects will be discontinued from the study in the following circumstances:

- enrollment in any other clinical trial involving an investigational product 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
    - the subject requires treatment with a therapeutic agent that has been demonstrated to be effective for treatment of the study indication. Discontinuation from the study should occur before introduction of the new agent
    - the subject requires a protocol-prohibited change in permitted UC concomitant therapy (Section 9.9)
- subject decision
    - the subject requests to be withdrawn from the study
- sponsor decision
    - Lilly or its designee 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 GCP
- AE
    - if the investigator decides that the subject should be withdrawn because of an AE/SAE or a clinically significant laboratory value, the investigational product is to be discontinued and appropriate measures are to be taken. Lilly or its designee is to be alerted immediately. Refer to Safety Evaluations, Section10.3.
- subject becomes pregnant
- subject experiences a systemic hypersensitivity event or anaphylaxis

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