Protocol I6T-MC-AMAG(b)

A Phase 2, Multicenter, Randomized, Parallel-Arm, Placebo-Controlled Study of LY3074828 in Subjects with Active Crohn's Disease (SERENITY)

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A Phase 2, Multicenter, Randomized, Parallel-Arm, Placebo-Controlled Study of LY3074828 in Subjects with Active Crohn's Disease (SERENITY)

Mirikizumab (LY3074828)

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol Electronically Signed and Approved by Lilly: 21 July 2016
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Amendment (b) Electronically Signed and Approved by Lilly
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1. Synopsis

Title of Study:

A Phase 2, Multicenter, Randomized, Parallel-Arm, Placebo-Controlled Study of LY3074828 in Subjects with Active Crohn's Disease

Rationale:

Study I6T-MC-AMAG (AMAG) is a Phase 2 study designed to determine whether LY3074828, a humanized immunoglobulin G4 (IgG4)–variant monoclonal antibody that binds to the p19 subunit of interleukin 23 (IL-23), is safe and efficacious in subjects with moderate to severe Crohn's disease. This study will help evaluate safety and determine the clinical activity defined by improvement in Crohn's disease activity measures and key patient-reported outcomes (PRO) measures.

Objectives/Endpoints:

Objectives	Endpoints
Primary	
• To test the hypothesis that treatment with LY3074828 is superior to placebo in the proportion of subjects with endoscopic response at Week 12, defined as 50% reduction from baseline in SES-CD Score	• Proportion of subjects achieving endoscopic response at Week 12
Secondary	
• To evaluate the safety and tolerability of treatment with LY3074828	• AEs and discontinuation rates; mean change vital signs; laboratory values
• To evaluate the effect of LY3074828 on the proportion of subjects with endoscopic response at Week 52, defined as 50% reduction from baseline in SES-CD score	• Proportion of subjects achieving endoscopic response at Week 52
• To evaluate the efficacy of treatment with LY3074828 as superior to placebo in endoscopic remission (defined as an SES-CD score of <4 ileal-colonic or <2 for isolated ileal disease, and no subscore >1) at Week 12	• Proportion of subjects achieving endoscopic remission at Week 12
• To evaluate the effect of LY3074828 on the proportion of subjects with endoscopic remission (defined as an SES-CD score of <4 ileal-colonic or <2 for isolated ileal disease, and no subscore >1) at Week 52	• Proportion of subjects achieving endoscopic remission at Week 52
• To evaluate the efficacy of treatment with LY3074828 as superior to placebo in PRO remission (defined as SF ≤2.5 and AP ≤1) at Week 12	• Proportion of subjects achieving PRO remission at Week 12
• To evaluate the effect of LY3074828 on the proportion of subjects with PRO remission (defined as SF ≤2.5 and AP ≤1) at Week 52	• Proportion of subjects achieving PRO remission at Week 52
• To evaluate the effect of LY3074828 on health outcomes/quality-of-life measures (including: PGRS score, PGRC score, IBDQ score, SF-36 score, and FACIT-Fatigue) at Weeks 12 and 52	• The mean change from baseline for PGRS score, IBDQ score, FACIT-Fatigue, and SF-36, and the mean PGRC at Weeks 12 and 52
• To characterize the PK of LY3074828	• Clearance and volume of distribution

Abbreviations: AE = adverse event; AP = abdominal pain; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy–Fatigue; IBDQ = Inflammatory Bowel Disease Questionnaire; PGRC = Patient's Global Rating of Change; PGRS = Patient's Global Rating of Severity; PK = pharmacokinetics; PRO = patient-reported outcomes; SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey.

Summary of Study Design:

Study AMAG is a multicenter, randomized, parallel-arm, placebo-controlled trial in which approximately 180 subjects will be randomized. All subjects in the study will have had loss of response or intolerance to conventional medication used to treat Crohn's disease.

Study Periods:

Screening (Approximately 4 Weeks): Subjects will be evaluated for study eligibility ≤28 days before the baseline visit.

Period 1 (Weeks 0 to 12): A 12-week dosing period is designed to evaluate the efficacy and safety of LY3074828 administered intravenously (IV) at Weeks 0, 4, 8. At baseline, subjects will be randomized with a 2:1:1:2 allocation across the 4 treatment arms (1000, 600, 200 mg LY3074828, and placebo) and stratified on the basis of previous exposure to biologic therapy for treatment of Crohn's disease.

Period 2 (Weeks 12 to 52): Patients will receive both intravenous (IV) and subcutaneous (SC) dosing to maintain blinding from Weeks 12 through 48. All patients who received LY3074828 treatment in Period 1 and who achieved an improvement in their Simple Endoscopic Score for Crohn's Disease (SES-CD) score from baseline at Week 12 (determined by the central reader) will be randomized evenly to either (i) continue Period 1 treatment assignment (IV LY3074828 1000 mg, 600 mg, or 200 mg every 4 weeks [Q4W]) with placebo administered subcutaneously Q4W OR (ii) IV placebo Q4W with SC LY3074828 300 mg Q4W.

All patients who received LY3074828 treatment in Period 1 and who did not achieve an improvement from baseline SES-CD score at Week 12 will receive IV LY3074828 1000 mg and SC placebo Q4W.

All patients who received placebo in Period 1 will receive IV LY3074828 1000 mg and SC placebo Q4W.

Randomization will be stratified based on endoscopic response (i.e. achieving a 50% reduction in SES-CD score from baseline).

- Period 3 (Weeks 52 to 104): All subjects having clinical benefit per investigator and continuing on study treatment may proceed to Period 3 and receive 300 mg SC LY3074828 Q4W open-label starting at Week 52 through Week 104. Patients not receiving clinical benefit at Week 52 will discontinue treatment and will enter the Follow-Up period.

Follow-Up (Weeks 104 to 120): At Week 104, subjects will stop treatment and be followed for safety for an additional 16 weeks.

Number of Subjects:

Approximately 180 subjects will be randomized.

Statistical Analysis:

The primary endpoint is Week 12 endoscopic response rate (defined as a 50% reduction in SES-CD). For endoscopic response, the assumed LY3074828 and placebo rates are 35% and 15%, respectively.

Treatment comparisons of the primary endpoint and other categorical efficacy variables will be conducted using a logistic regression analysis with treatment, geographic region, and prior biologic Crohn's disease therapy use (yes/no) in the model. Unless otherwise specified, efficacy and health outcomes analyses will be conducted on the intent-to-treat population (ITT).

2. Schedule of Activities

Screening and Period 1 [V1–V7] Schedule of Activities								
Visit Number:	**V1** Screening	**V2** Baseline/ Randomization	**V3**	**V4**	**V5**	**V6**	**V7**	**Comments**
Week Relative to Study Drug Start	**-4**	**0**	**2**	**4**	**6**	**8**	**11-12**	All activities should be completed prior to any study drug administration unless otherwise stated below.
Visit Tolerance Interval (days)	**≤28 from V2**	**1± 3**	**15± 3**	**29 ± 3**	**43 ± 3**	**57 ± 3**	**78-85**	Visit 1 procedures may be conducted over more than 1 day as long as all tasks are completed within the allowable visit tolerance (at least 3 days should be allowed for receipt of laboratory test results).
Obtain Informed Consent	X							
Physical Examination	X	X					X	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.
Height	X							
Weight	X	X	X	X	X	X	X	According to standard medical practice.
Vital Signs (BP and HR) at all marked visits; body temp. only at V1 and V2, unless clinically indicated	X	X		X		X	X	Sitting BP and pulse, to be obtained at approximately the same time as ECG measurements or blood sampling. When multiple assessments are scheduled for the same time point, the order of completion should be as follows: ECG, vital signs, and then blood sampling.
Preexisting Conditions	X							
Adverse Events	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	

Screening and Period 1 [V1–V7] Schedule of Activities								
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Visit Tolerance Interval (days)	**≤28 from V2**	**1± 3**	**15± 3**	**29 ± 3**	**43 ± 3**	**57 ± 3**	**78-85**	Visit 1 procedures may be conducted over more than 1 day as long as all tasks are completed within the allowable visit tolerance (at least 3 days should be allowed for receipt of laboratory test results).
Randomization		X						
Dosing		X		X		X		
CDAI	X	X	X	X	X	X	X	Patient-reported items of CDAI (Q1–Q3) will be recorded daily (see Section 9.1.3). Clinician-reported items of CDAI (Q4–Q8) will be recorded at every visit (see Section 9.1.3).
CCI	X	X	X	X	X	X	X	CCI
BMC	X	X	X	X	X	X	X	Subjects will record BMC daily (as measured by subject diary; see Section 9.1.3).
Colonoscopy/ SES-CD	X						X	Screening colonoscopy must occur within 14 days of baseline, and should occur no fewer than within 5 days of baseline. Biopsies will be taken during all colonoscopy time points; instruction for collection will be provided in a laboratory manual.
PGRC				X			X	
PGRS	X	X	X	X	X	X	X	Subjects will record daily (as measured by subject diary; see Section 9.1.3).
IBDQ	X	X		X			X	
SF-36	X	X		X			X	
FACIT-Fatigue	X	X		X			X	
QIDS-SR16	X	X					X	
CCI	X	X	X	X	X	X	X	

Screening and Period 1 [V1–V7] Schedule of Activities								
Visit Number:	**V1** Screening	**V2** Baseline/ Randomization	**V3**	**V4**	**V5**	**V6**	**V7**	**Comments**
Week Relative to Study Drug Start	**-4**	**0**	**2**	**4**	**6**	**8**	**11-12**	All activities should be completed prior to any study drug administration unless otherwise stated below.
Visit Tolerance Interval (days)	**≤28 from V2**	**1± 3**	**15± 3**	**29 ± 3**	**43 ± 3**	**57 ± 3**	**78-85**	Visit 1 procedures may be conducted over more than 1 day as long as all tasks are completed within the allowable visit tolerance (at least 3 days should be allowed for receipt of laboratory test results).
CCI	X	X					X	
Chest Radiography (CXR)	X							Chest radiography (see Section 9.5.4.1) 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).
PPD, T-SPOT®, or QuantiFERON-TB Gold	X							Subjects will return 2 to 3 days after Visit 1 to read their PPD test results.
ECG	X	X					X	This should be completed prior to any study dose administration or blood draw. Subjects should be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
Serum Chemistry/ Hematology	X	X	X[b]	X	X[b]	X	X	Unscheduled blood chemistry and hematology panels may be performed at the discretion of the investigator.
Urinalysis	X	X		X		X	X	
FSH	X							FSH test is to be performed at screening for women who have had spontaneous amenorrhea for 6 to 12 months to confirm lack of child-bearing potential.
Serum Pregnancy Test	X							To be performed only on women of child-bearing potential.

Screening and Period 1 [V1–V7] Schedule of Activities								
Visit Number:	**V1** Screening	**V2** Baseline/ Randomization	**V3**	**V4**	**V5**	**V6**	**V7**	**Comments**
Week Relative to Study Drug Start	**-4**	**0**	**2**	**4**	**6**	**8**	**11-12**	All activities should be completed prior to any study drug administration unless otherwise stated below.
Visit Tolerance Interval (days)	**≤28 from V2**	**1± 3**	**15± 3**	**29 ± 3**	**43 ± 3**	**57 ± 3**	**78-85**	Visit 1 procedures may be conducted over more than 1 day as long as all tasks are completed within the allowable visit tolerance (at least 3 days should be allowed for receipt of laboratory test results).
Urine Pregnancy Test		X		X		X		To be performed only on women of child-bearing potential.
HIV, HBV, HCV Testing	X							
HBV PCR	X						X	Perform only if subject was HBcAb+ with negative HBV PCR test at screening. Any enrolled subject who is HBcAb+ will undergo monitoring of HBV PCR at specified intervals. Any subject with a positive HBV PCR test at any time must be discontinued from the study and receive appropriate follow-up medical care, including consideration for antiviral therapy.
LY3074828 PK Samples		Pre-dose and end of infusion	X	Pre-dose & end of infusion	X	Pre-dose & end of infusion	X	Additional immunogenicity, PK, and hypersensitivity markers samples may be collected. See Section 7.8.2.2.
Immunogenicity Samples		X	X	X		X	X	Additional immunogenicity, PK, and hypersensitivity markers samples may be collected. See Section 7.8.2.2.
hsCRP		X		X		X	X	
CCI								

Screening and Period 1 [V1–V7] Schedule of Activities								
Visit Number:	**V1** Screening	**V2** Baseline/ Randomization	**V3**	**V4**	**V5**	**V6**	**V7**	**Comments**
Week Relative to Study Drug Start	**-4**	**0**	**2**	**4**	**6**	**8**	**11-12**	All activities should be completed prior to any study drug administration unless otherwise stated below.
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CCI								
Stool Samples	X	X		X		X	X[d]	CCI
Supply Stool Collection Kit						X		Patients need to collect stool samples up to 3 days prior to beginning bowel prep for endoscopy at V7 and V18.

Period 2 [V8–V18] Schedule of Activities												
Visit Number:	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**Comments**
Week Relative to Study Drug Start	**12-13**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	All activities should be completed prior to any study dose administration unless otherwise stated below.
Day with Visit Tolerance Interval	**86-92**	**113 ± 5**	**141± 5**	**169 ± 5**	**197 ± 5**	**225 ± 5**	**253 ± 5**	**281 ± 5**	**309 ± 5**	**337 ± 5**	**365 ± 5**	
Physical Examination				X			X			X		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.
Weight	X	X	X	X	X	X	X	X	X	X	X	According to standard medical practice.
Randomization	X											
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs (BP and HR) at all marked visits; body temp. only at V1 and V2, unless clinically indicated				X			X			X		Sitting BP and pulse, to be obtained at approximately the same time as ECG measurements or blood sampling. When multiple assessments are scheduled for the same time point, the order of completion should be as follows: ECG, vital signs, and then blood sampling.
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	
Dosing	X	X	X	X	X	X	X	X	X	X	X	Week 52 dosing begins dosing for Period 3 and is open label.
Colonoscopy/ SES-CD											X	Week 52 colonoscopy may occur within 12 days of the Week 52 visit but must occur 3 days prior to the visit to determine centrally read SES-CD score. Biopsies will be taken during all colonoscopy time points; instruction for collection will be provided in a laboratory manual.

Period 2 [V8–V18] Schedule of Activities												
Visit Number:	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**Comments**
Week Relative to Study Drug Start	**12-13**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	All activities should be completed prior to any study dose administration unless otherwise stated below.
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CDAI		X	X	X	X	X	X	X	X	X	X	Patient-reported items of CDAI (Q1–Q3) will be recorded daily (see Section 9.1.3). Clinician-reported items of CDAI (Q4–Q8) will be recorded at every visit (see Section 9.1.3).
CCI		X	X	X	X	X	X	X	X	X	X	CCI
BMC		X	X	X	X	X	X	X	X	X	X	Subjects will record BMC daily (as measured by subject diary; see Section 9.1.3).
PGRC		X		X		X			X		X	
PGRS		X	X	X	X	X	X	X	X	X	X	Subjects will record daily (as measured by subject diary; see Section 9.1.3).
IBDQ		X		X		X			X		X	
SF-36		X		X		X			X		X	
FACIT-Fatigue		X		X		X			X		X	
QIDS-SR16											X	
ECG											X	ECG should be completed prior to any study dose administration or blood draw. Subjects should be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
Serum Chemistry/ Hematology		X	X	X	X	X	X	X	X	X	X	Unscheduled blood chemistry and hematology panels may be performed at the discretion of the investigator.
LY3074828 PK Samples	X	X	X	X	X		X		X		X	Additional immunogenicity, PK, and hypersensitivity markers samples may be collected. See Section 7.8.2.2.

Period 2 [V8–V18] Schedule of Activities												
Visit Number:	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**Comments**
Week Relative to Study Drug Start	**12-13**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	All activities should be completed prior to any study dose administration unless otherwise stated below.
Day with Visit Tolerance Interval	**86-92**	**113 ± 5**	**141± 5**	**169 ± 5**	**197 ± 5**	**225 ± 5**	**253 ± 5**	**281 ± 5**	**309 ± 5**	**337 ± 5**	**365 ± 5**	
Immunogenicity Samples	X	X		X			X				X	CCI
Urinalysis				X		X			X			
hsCRP		X			X	X			X		X	
CCI												
HBV PCR				X			X			X		Perform only if subject was HBcAb+ with negative HBV PCR test at screening. Any enrolled subject who is HBcAb+ will undergo monitoring of HBV PCR at specified intervals. Any subject with a positive HBV PCR test at any time must be discontinued from the study and receive appropriate follow-up medical care, including consideration for antiviral therapy.
Urine Pregnancy Test	X	X	X	X	X	X	X	X	X	X	X	To be performed only on women of child-bearing potential.
CCI	CCI											
					X						X	
Stool Samples		X			X				X		X[d]	CCI

Period 2 [V8–V18] Schedule of Activities												
Visit Number:	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**Comments**
Week Relative to Study Drug Start	**12-13**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	All activities should be completed prior to any study dose administration unless otherwise stated below.
Day with Visit Tolerance Interval	**86-92**	**113 ± 5**	**141± 5**	**169 ± 5**	**197 ± 5**	**225 ± 5**	**253 ± 5**	**281 ± 5**	**309 ± 5**	**337 ± 5**	**365 ± 5**	
Supply Stool Collection Kit										X		Patients need to collect stool samples up to 3 days prior to beginning bowel prep for endoscopy at V7 and V18.

Period 3 [V19–V31] Schedule of Activities														
Visit Number:	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**V30**	**V31**	**Comments**
Week Relative to Study Drug Start	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	All activities should be completed prior to any study drug administration unless otherwise stated below.
Day with Visit Tolerance Interval	**393 ± 5**	**421 ± 5**	**449 ± 5**	**477 ± 5**	**505 ± 5**	**533 ± 5**	**561 ± 5**	**589 ± 5**	**617 ± 5**	**645 ± 5**	**673 ± 5**	**701 ± 5**	**729 ± 5**	
Physical Examination		X			X			X			X		X	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.
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	According to standard medical practice.
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs (BP and HR) at all marked visits; body temp. only at V1 and V2, unless clinically indicated		X			X				X				X	Sitting BP and pulse, to be obtained at approximately the same time as ECG measurements or blood sampling. When multiple assessments are scheduled for the same time point, the order of completion should be as follows: ECG, vital signs, and then blood sampling.
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dosing	X	X	X	X	X	X	X	X	X	X	X	X	X	

Period 3 [V19–V31] Schedule of Activities														
Visit Number:	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**V30**	**V31**	**Comments**
Week Relative to Study Drug Start	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	All activities should be completed prior to any study drug administration unless otherwise stated below.
Day with Visit Tolerance Interval	**393 ± 5**	**421 ± 5**	**449 ± 5**	**477 ± 5**	**505 ± 5**	**533 ± 5**	**561 ± 5**	**589 ± 5**	**617 ± 5**	**645 ± 5**	**673 ± 5**	**701 ± 5**	**729 ± 5**	
CDAI	X	X	X	X	X	X	X	X	X	X	X	X	X	Patient-reported items of CDAI (Q1–Q3) will be recorded daily. Clinician-reported items of CDAI (Q4–Q8) will be recorded at every visit (see Section 9.1.3).
CCI	X	X	X	X	X	X	X	X	X	X	X	X	X	CCI
BMC	X	X	X	X`	X	X	X	X	X	X	X	X	X	Subjects will record BMC daily (as measured by subject diary; see Section 9.1.3).
PGRC	X				X				X				X	
PGRS	X	X	X	X	X	X	X	X	X	X	X	X	X	Subjects will record daily (as measured by subject diary; see Section 9.1.3).
IBDQ	X				X				X				X	
SF-36	X				X				X				X	
FACIT-Fatigue	X				X				X				X	
QIDS-SR16													X	
ECG													X	ECG should be completed prior to any study dose administration or blood draw. Subjects should be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Period 3 [V19–V31] Schedule of Activities														
Visit Number:	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**V30**	**V31**	**Comments**
Week Relative to Study Drug Start	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	All activities should be completed prior to any study drug administration unless otherwise stated below.
Day with Visit Tolerance Interval	**393 ± 5**	**421 ± 5**	**449 ± 5**	**477 ± 5**	**505 ± 5**	**533 ± 5**	**561 ± 5**	**589 ± 5**	**617 ± 5**	**645 ± 5**	**673 ± 5**	**701 ± 5**	**729 ± 5**	
Serum Chemistry/ Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	Unscheduled blood chemistry and hematology panels may be performed at the discretion of the investigator.
LY3074828 PK Samples		X		X		X		X		X			X	Additional immunogenicity, PK, and hypersensitivity markers samples may be collected. See Section 7.8.2.2.
Immunogenicity Samples		X		X		X		X		X			X	CCI
Urinalysis		X				X				X			X	
hsCRP													X	
CCI													X	
HBV PCR		X			X			X			X			Only if HBcAb+ with negative HBV PCR test at screening. Any enrolled subject who is HBcAb+ will undergo monitoring of HBV PCR. Any subject with a positive HBV PCR test at any time must be discontinued from the study and receive appropriate follow-up medical care, including consideration for antiviral therapy.
Urine Pregnancy Test	X	X	X	X	X	X	X	X	X	X	X	X	X	To be performed only on women of child-bearing potential.

Period 3 [V19–V31] Schedule of Activities														
Visit Number:	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**V30**	**V31**	**Comments**
Week Relative to Study Drug Start	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	All activities should be completed prior to any study drug administration unless otherwise stated below.
Day with Visit Tolerance Interval	**393 ± 5**	**421 ± 5**	**449 ± 5**	**477 ± 5**	**505 ± 5**	**533 ± 5**	**561 ± 5**	**589 ± 5**	**617 ± 5**	**645 ± 5**	**673 ± 5**	**701 ± 5**	**729 ± 5**	
CCI													X	
													X	
Stool Samples													X	CCI

Unscheduled Visit / Follow-Up Period						
Visit Number:	**UV[c]**	**V801**	**V802**	**V803**	**V804/ET[a]**	**Comments**
Week Relative to Study Drug Start	**N/A**	**108**	**112**	**116**	**120**	
Visit Tolerance Interval (days)	**N/A**	**757 ± 5**	**785 ± 5**	**813 ± 5**	**841 ± 5**	
Physical Examination	X				X	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.
Weight		X	X	X	X	According to standard medical practice.
Concomitant Medications	X	X	X	X	X	
Adverse Events	X	X	X	X	X	
Vital Signs (BP and HR), body temp. only at V1 and V2, unless clinically indicated	X	X	X	X	X	Sitting BP and pulse, to be obtained at approximately the same time as ECG measurements or blood sampling. When multiple assessments are scheduled for the same time point, the order of completion should be as follows: ECG, vital signs, and then blood sampling.
ECG					X	Subjects should be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
Colonoscopy/ SES-CD					X[a]	Performed only at early termination visit if the visit occurs 16 weeks after last colonoscopy. For patients who discontinue treatment but continue in the study perform colonoscopy within 4 weeks of last dose of study drug. Colonoscopy/SES-CD is not to be performed at Period 1, Period 3 or Visit 804.
LY3074828 PK Samples		X	X	X	X	Additional immunogenicity, PK, and hypersensitivity markers samples may be collected. See Section 7.8.2.2.
Immunogenicity Samples		X	X	X	X	Additional immunogenicity, PK, and hypersensitivity markers samples may be collected. See Section 7.8.2.2.
CDAI		X	X	X	X	Patient-reported items of CDAI (Q1–Q3) will be recorded daily (see Section 9.1.3). Clinician-reported items of CDAI (Q4–Q8) will be recorded at every visit (see Section 9.1.3).
CCI					X	
BMC					X	
IBDQ					X	
SF-36					X	

FACIT-Fatigue					X	
QIDS-SR16					X	
Serum Chemistry/Hematology	X[b]	X	X	X	X	Unscheduled blood chemistry panel or other tests may be performed at the discretion of the investigator. Complete blood count will be performed an unscheduled visit to obtain hematocrit value needed for CDAI.
Urinalysis		X			X	
Urine Pregnancy Test					X	To be performed only on women of child-bearing potential.

Abbreviations: BMC = bowel movement count; BP = blood pressure; C diff = *Clostridium difficile*; CBC = complete blood count; CDAI = Crohn's Disease Activity Index; CCI [redacted]; CXR = chest X-ray; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ET = Early Termination; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy–Fatigue; FSH = follicle-stimulating hormone; HBcAb = anti-hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; HR = heart rate; IBDQ = Inflammatory Bowel Disease Questionnaire; CCI [redacted] NRS = Numeric Rating Scale; PCR = polymerase chain reaction; PK = pharmacokinetic; PGRC = Patient's Global Rating of Change; PGRS = Patient's Global Rating of Severity; PPD = purified protein derivative; Q = Question; QIDS-SR16 = Quick Inventory of Depressive Symptomatology–Self Report (16 Items); RNA = ribonucleic acid; SES-CD = Simple Endoscopic Score for Crohn's Disease; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; temp. = temperature; TB = tuberculosis; UV = unscheduled visit; V = visit.

a Subjects who discontinue early (before V804) should have all of the V804 procedures completed at the last visit attended.

b At V3 and V5, collect a hematology sample for CBC only, do not collect serum chemistries. Complete blood count is also collected at all unscheduled visits.

c Use this visit for patients who are seen by the investigator or site staff at a time point not required by the protocol (i.e., an unscheduled visit) due to disease exacerbation or an adverse event. Procedures or laboratory tests may be performed at unscheduled visits at the discretion of the investigator.

d Stool samples should not be collected on days of bowel prep or endoscopy/colonoscopy. The stool samples may be collected up to 3 days before bowel prep at Visits 7 and 18.

3. Introduction

3.1. Study Rationale

Study I6T-MC-AMAG (AMAG) is a Phase 2 study designed to determine whether LY3074828, a humanized immunoglobulin G4 (IgG4)–variant monoclonal antibody that binds to the p19 subunit of interleukin (IL)-23, is safe and efficacious in subjects with moderate to severe Crohn's disease. Despite an influx of new biologic therapies, many subjects with Crohn's disease experience primary or secondary treatment failure; thus, a significant unmet need remains (Gordon et al. 2015). IL-23 is a validated target for evaluation of treatment of various autoimmune/inflammatory diseases, including Crohn's disease (see Section 3.2). This Phase 2 study will help evaluate safety and determine the clinical activity defined by improvement in Crohn's disease activity measures and key patient-reported outcomes (PRO) measures.

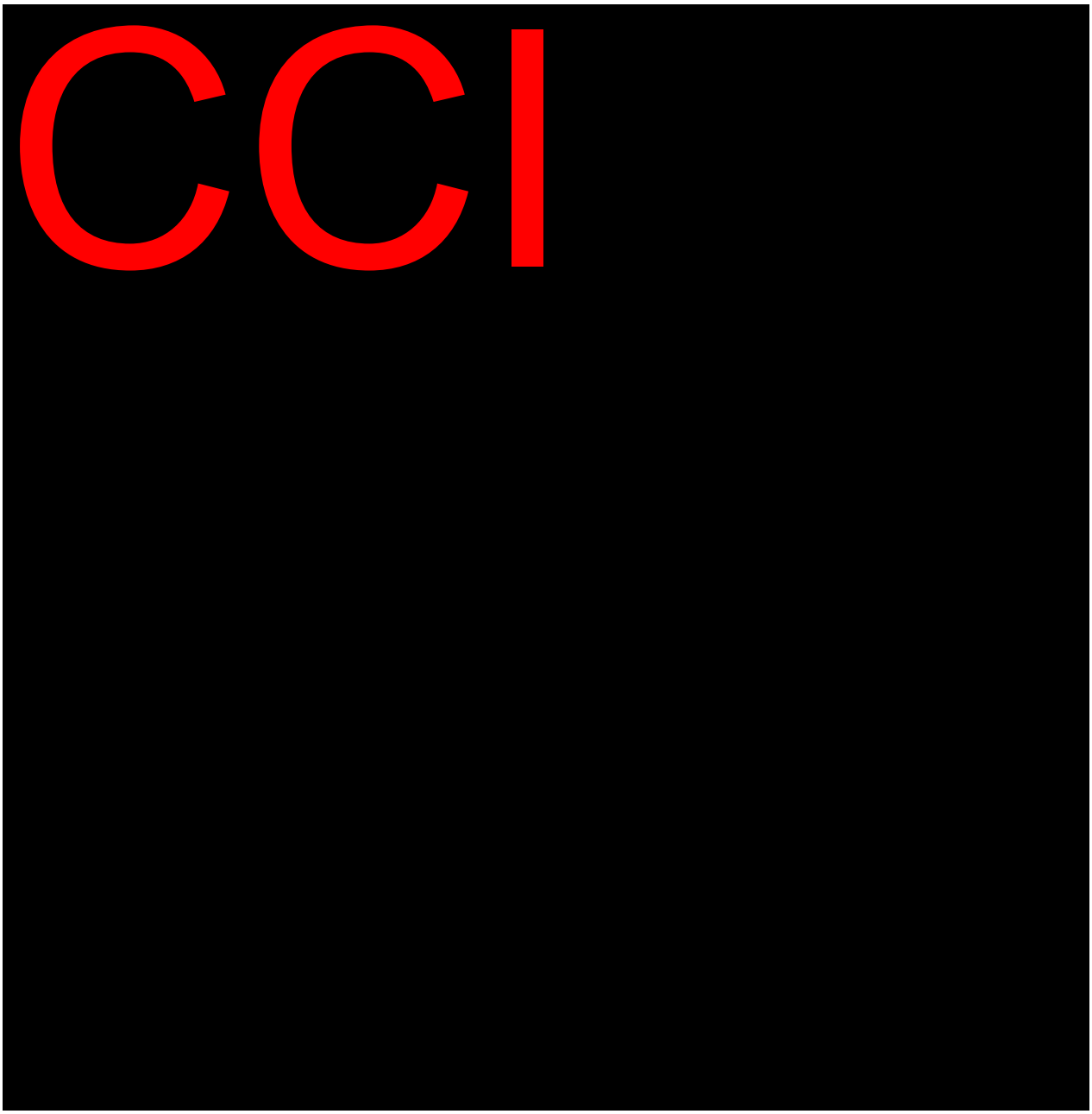
3.2. Background

LY3074828 is being developed for the treatment of autoimmune diseases where the IL-23 pathway is thought to have a significant pathogenic role. LY3074828 neutralizes IL-23 activity by binding the p19 subunit.

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 (FDA)–approved monoclonal antibody for the treatment of psoriasis and psoriatic arthritis (Stelara® prescribing information 2014) as well as Crohn's disease (Feagan et al. 2016;Stelara® prescribing information 2016). 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/IL-17 immune axis alone is sufficient to treat autoimmune inflammation (Monteleone et al. 2009). Agents specifically targeting the IL-23 p19 subunit have demonstrated clinical activity in psoriasis (including LY3074828 in Study AMAA) and Crohn's disease (Sofen et al. 2014 ; Kopp et al. 2015; Krueger et al. 2015). IL-23 p19-specific antibodies have also demonstrated clinical activity in Crohn's disease (Sands et al. 2015; Feagan et al. 2016). 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. 2015).

Eli Lilly and Company (hereafter Lilly) has one completed study (AMAA) and 2 ongoing studies (AMAD and AMAC) summarized below based upon status at the time of the AMAG protocol approval date. The most updated information about these studies (see following details) can be found in the Investigator's Brochure (IB).

CCI



Study I6T-MC-AMAC is an ongoing, multicenter, randomized, double-blind, parallel-arm, placebo-controlled trial in subjects with moderate to severe ulcerative colitis (UC). Approximately 240 subjects will be randomized to evaluate the safety and efficacy of LY3074828 in subjects with UC (NCT02589665).

3.3. Benefit/Risk Assessment

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

4. Objectives and Endpoints

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

Table AMAG.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To test the hypothesis that treatment with LY3074828 is superior to placebo in the proportion of subjects with endoscopic response at Week 12, defined as 50% reduction from baseline in SES-CD Score	• Proportion of subjects achieving endoscopic response at Week 12
Secondary	
• To evaluate the safety and tolerability of treatment with LY3074828	• AEs and discontinuation rates; mean change vital signs; laboratory values
• To evaluate the effect of LY3074828 on the proportion of subjects with endoscopic response at Week 52, defined as 50% reduction from baseline in SES-CD score	• Proportion of subjects achieving endoscopic response at Week 52
• To evaluate the efficacy of treatment with LY3074828 as superior to placebo in endoscopic remission (defined as an SES-CD score of <4 ileal-colonic or <2 for isolated ileal disease, and no subscore >1) at Week 12	• Proportion of subjects achieving endoscopic remission at Week 12
• To evaluate the effect of LY3074828 on the proportion of subjects with endoscopic remission (defined as an SES-CD score of <4 ileal-colonic or <2 for isolated ileal disease, and no subscore >1) at Week 52	• Proportion of subjects achieving endoscopic remission at Week 52
• To evaluate the efficacy of treatment with LY3074828 as superior to placebo in PRO remission (defined as SF ≤2.5 and AP ≤1) at Week 12	• Proportion of subjects achieving PRO remission at Week 12
• To evaluate the effect of LY3074828 on the proportion of subjects with PRO remission (defined as SF ≤2.5 and AP ≤1) at Week 52	• Proportion of subjects achieving PRO remission at Week 52
• To evaluate the effect of LY3074828 on health outcomes/quality-of-life measures (including: PGRS score, PGRC score, IBDQ score, SF-36 score, and FACIT-Fatigue) at Weeks 12 and 52	• The mean change from baseline for PGRS score, IBDQ score, FACIT-Fatigue, and SF-36, and the mean PGRC at Weeks 12 and 52
• To characterize the PK of LY3074828	• Clearance and volume of distribution
Tertiary/Exploratory	
• To evaluate the efficacy of treatment with LY3074828 as superior to placebo in PRO2 response (defined as a PRO2 reduction of at least 5 points) at Week 12	• Proportion of subjects achieving PRO2 response at Week 12
• To evaluate the effect of LY3074828 on the proportion of subjects with PRO2 response (defined	• Proportion of subjects achieving PRO2 response at Week 52

Objectives	Endpoints
as a PRO2 reduction of at least 5 points) at Week 52	
• To evaluate the efficacy of treatment with LY3074828 as superior to placebo in PRO2 remission (defined as a PRO2 <8) at Week 12	• Proportion of subjects achieving PRO2 remission at Week 12
• To evaluate the effect of LY3074828 on the proportion of subjects with PRO2 remission (defined as a PRO2 <8) at Week 52	• Proportion of subjects achieving PRO2 remission at Week 52
• To evaluate the effect of LY3074828 on durability of endoscopic response at Week 52	• Proportion of subjects achieving endoscopic response at Week 52 who also had endoscopic response at Week 12
• To evaluate the effect of LY3074828 on durability of endoscopic remission at Week 52	• Proportion of subjects achieving endoscopic remission at Week 52 who also had endoscopic remission at Week 12
• To evaluate the effect of LY3074828 on durability of PRO2 response at Week 52	• Proportion of subjects achieving PRO2 response at Week 52 who also had PRO2 response at Week 12
• To evaluate the effect of LY3074828 on durability of PRO2 remission at Week 52	• Proportion of subjects achieving PRO2 remission at Week 52 who also had PRO2 remission at Week 12
• To evaluate the efficacy of treatment with LY3074828 as superior to placebo in the composite of endoscopic remission and PRO remission at Week 12	• Proportion of subjects achieving both endoscopic remission and PRO remission at Week 12
• To evaluate the effect of LY3074828 on the proportion of subjects with composite endoscopic remission and PRO remission at Week 52	• Proportion of subjects achieving both endoscopic remission and PRO remission at Week 52
• To evaluate the effect of LY3074828 on durability of composite endoscopic remission and PRO remission at Week 52	• Proportion of subjects achieving both endoscopic remission and PRO remission at Week 52 who also had both endoscopic remission and PRO remission at Week 12
• To evaluate the relationships between LY3074828 exposure and clinical endpoints	• Proportion of subjects achieving a 50% reduction from baseline in SES-CD score at Weeks 12 and 52 at specific LY3074828 exposure intervals (e.g., quartiles). EC_{50} and E_{max} for probability of subjects achieving a 50% reduction from baseline in SES-CD score at Weeks 12 and 52. EC_{50} and E_{max} of longitudinal relationships between LY3074828 exposure and CDAI score and PRO2, SF, and AP subcomponents of CDAI.
[redacted]	
reported using the BMC scale	all time points evaluated

Objectives	Endpoints
• To evaluate the effect of LY3074828 on QIDS-SR16 at Weeks 12 and 52 • To explore the development of any anti-LY3074828 antibodies that are formed and their effect on safety, PK, and PD of LY3074828	• Change from baseline in reported QIDS-SR16 score at Weeks 12 and 52 • Proportion of subjects who are ADA+. Proportion of ADA+ subjects who experience certain immunogenicity-specific AEs. PK/PD subgroup analyses on ADA+ subjects
• To evaluate changes in CDAI from baseline	• Change from baseline in CDAI
CCI	

• To evaluate the elimination of neutrophils from the mucosa by histopathology at Week 52	• Absence of lamina propia and epithelial neutrophils at Week 52 assessed by
	  ○ GHAS
	  ○ RHI

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; AP = abdominal pain; BMC = bowel movement count; CDAI = Crohn's Disease Activity Index; CCI CRP = C-reactive protein; EC_{50} = drug concentration that produces 50% of E_{max}; E_{max} = maximum effect; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy–Fatigue; FCP = fecal calprotectin; GHAS = Global Histologic Disease Activity Score; IBDQ = Inflammatory Bowel Disease Questionnaire; Pain NRS = Numeric Rating Scale; PD = pharmacodynamics; PK = pharmacokinetics; PGRC = Patient's Global Rating of Change; PGRS = Patient's Global Rating of Severity; PRO = patient-reported outcomes; PRO2 = Patient Reported Outcome2; QIDS-SR16 = Quick Inventory of Depressive Symptomatology–Self Report (16 Items); RHI = Robarts Histologic Index; SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency; SF-36 = Medical Outcomes 36-Item Short Form Health Survey.

5. Study Design

5.1. Overall Design

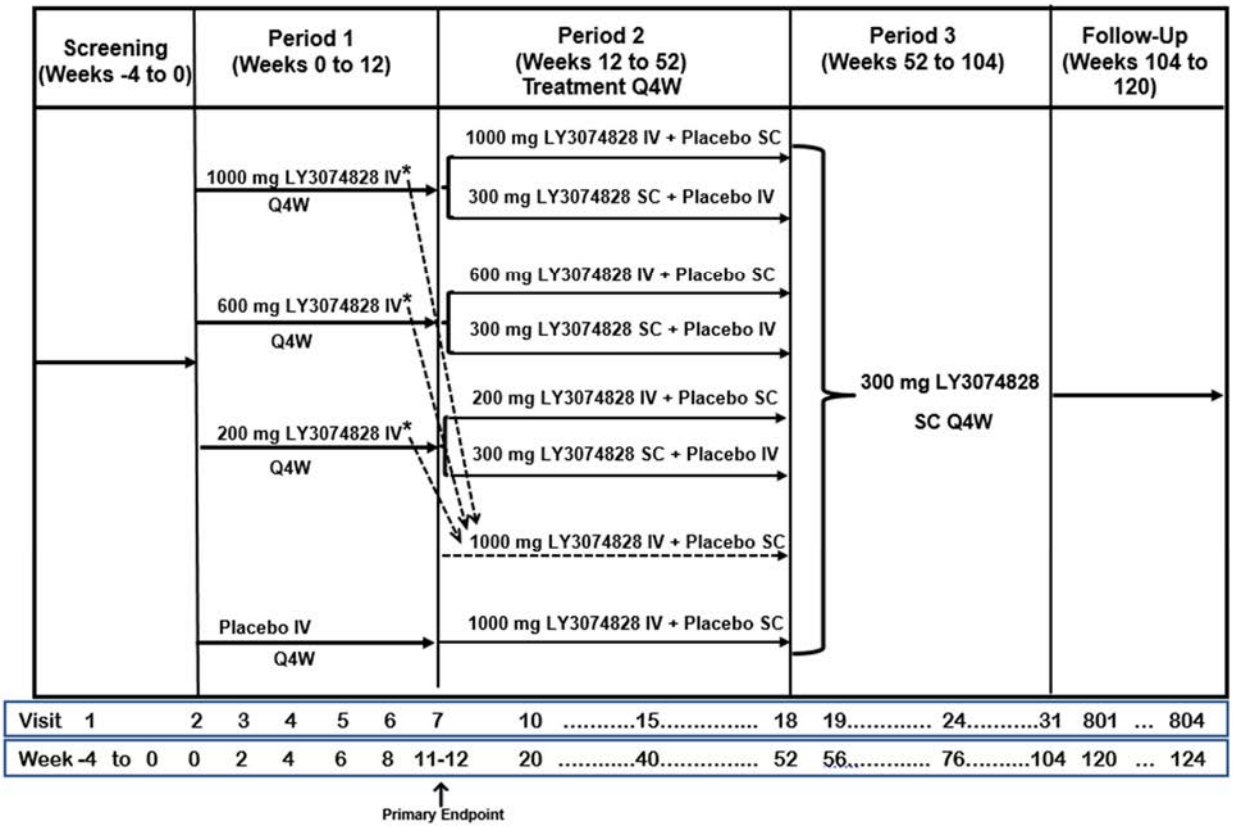
Study AMAG is a multicenter, randomized, parallel-arm, placebo-controlled trial in which approximately 180 subjects will be randomized. Subjects will be stratified to the following categories, and the exact number enrolled in either group will be dependent upon the enrollment rate of each subject population:

- A minimum of approximately 30% of subjects will be naive to biologic Crohn's disease therapy (including experimental biologic Crohn's disease therapy) (Inclusion Criterion 4a; Section 6.1).
- At least 50% of the subjects will be prior biologic Crohn's disease therapy-experienced (including experience with experimental biologic Crohn's disease therapy) (Inclusion Criterion 4b; Section 6.1).

Study Periods:

- Screening (Approximately 4 Weeks): Subjects will be evaluated for study eligibility ≤28 days before the baseline visit.
- Period 1 (Weeks 0 to 12): A 12-week dosing period is designed to evaluate the efficacy and safety of LY3074828 administered intravenously (IV) at Weeks 0, 4, 8. At baseline, subjects will be randomized with a 2:1:1:2 allocation across the 4 treatment arms (1000, 600, 200 mg LY3074828, and placebo) and stratified on the basis of previous exposure to biologic therapy for treatment of Crohn's disease.
- Period 2 (Weeks 12 to 52): Patients will receive both IV and SC dosing to maintain blinding from Weeks 12 through 48. All patients who received LY3074828 treatment in Period 1 and who achieved an improvement in their Simple Endoscopic Score for Crohn's Disease (SES-CD) score from baseline at Week 12 (determined by the central reader) will be randomized evenly to either (i) continue Period 1 treatment assignment (IV LY3074828 1000 mg, 600 mg, or 200 mg every 4 weeks [Q4W]) with placebo administered subcutaneously OR (ii) IV placebo Q4W with SC LY3074828 300 mg Q4W.
- All patients who received LY3074828 treatment in Period 1 and who did not achieve an improvement from baseline SES-CD score at Week 12 will receive IV LY3074828 1000 mg and SC placebo Q4W.
  All patients who received placebo in Period 1 will receive IV LY3074828 1000 mg and SC placebo Q4W.
  Randomization will be stratified based on endoscopic response (i.e. achieving a 50% reduction in SES-CD score from baseline).

- Period 3 (Weeks 52 to 104): All subjects having clinical benefit per investigator and continuing on study treatment may proceed to Period 3 and receive 300 mg SC LY3074828 Q4W open-label starting at Week 52 through Week 104. Patients not receiving clinical benefit at Week 52 will discontinue treatment and will enter the Follow-Up period.
- Follow-Up (Weeks 104 to 120): At Week 104, subjects will stop treatment and be followed for safety for an additional 16 weeks.
- Figure AMAG.1 illustrates the study design.



Abbreviations: IV = intravenous; Q4W = every 4 weeks; SC = subcutaneous; SES-CD = Simple Endoscopic Score for Crohn's Disease.
*Subjects who have not had any improvement in SES-CD score from baseline at Week 12, as determined by the central reader, will receive IV LY3074828 1000 mg + SC placebo.

Figure AMAG.1. Illustration of study design for Clinical Protocol I6T-MC-AMAG.

5.2. Number of Participants

Approximately 180 participants will be randomized with a 2:1:1:2 allocation across the 4 treatment arms (1000, 600, 200 mg LY3074828, and placebo).

5.3. End of Study Definition

End of the trial is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last subject.

5.4. Scientific Rationale for Study Design

IL-23 is a validated target for evaluation of treatment of various autoimmune/inflammatory diseases, including Crohn's disease (see Section 3.2). Period 1 is designed to establish the efficacy (endoscopic changes and key PRO) and safety of LY3074828 versus placebo in subjects with moderate to severe Crohn's disease. Subjects may continue background pharmacotherapies for Crohn's disease 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. Period 2 (Weeks 12 to 52) will allow for continued evaluation of efficacy and safety with baseline treatment regimens and exploration of SC dosing—except for all subjects in the placebo group and subjects in the LY3074828 treatment groups who have not had any improvement in SES-CD score from baseline at Week 12. Period 3 is intended to provide extension therapy for subjects considered to be demonstrating clinical benefit and will provide longer term evaluation of safety and durability of clinical benefit.

5.5. Justification for Dose

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

On the basis of simulations conducted using the PK data collected in Study AMAA, a Q4W dosing frequency is not expected to result in any accumulation and the planned doses of 200, 600, and 1000 mg Q4W during the induction period (Period 1) are projected to produce mean trough concentrations of 2.7 to 13 μg/ml. The projected exposures for the planned doses are similar to those that have been evaluated and found to be effective induction regimens in Crohn's disease for the IL-12/IL-23 antibody ustekinumab (Sandborn et al. 2012; Adedokun et al. 2016; and the IL-23 antibody BI-655066 (Feagan et al. 2016).

In Period 2, patients will be randomized to continue their induction regimen or be reduced to a 300 mg SC LY3074828 Q4W regimen. In Period 3, all subjects will be administered 300 mg subcutaneously Q4W. Based on the SC bioavailability of LY3074828, a 300 mg SC dose will produce an exposure area under the plasma concentration versus time curve (AUC) approximately 40% lower and a trough concentration (3.2 μg/ml) that is slightly higher than the lowest induction dose (IV 200 mg). Therefore, data from Period 2 will allow evaluation of response with continued treatment at the induction dose levels versus reduction to a lower exposure level. Experience with anti-tumor necrosis factor (anti-TNF) antibodies in inflammatory bowel disease (IBD) suggests that the exposure required to maintain response in subjects with IBD may be lower than the exposure required to induce response (Rutgeerts et al. 2004).

The margin of safety for the high dose of IV 1000 mg relative to the no-observed-adverse-effect level (NOAEL) observed in the 6-month nonclinical toxicology study in cynomolgus monkeys is 8 based on dose and 1.9 based on AUC (Table AMAG.2). No adverse effects were observed in the 6-month nonclinical toxicology study in cynomolgus monkeys at the highest tested dose (100 mg/kg subcutaneously Q4W).

Table AMAG.2. Margin of Safety for LY3074828 Based on Administered Dose and Predicted Exposure

	Dose (mg/kg)	Dose Multiple[a]	$AUC_{0\text{-}672h,ss}$ (µg*h/mL)	Margin of Safety[b]
Human highest dose (1000 mg IV)[c]	12.5 (IV)	8	45600	1.9
Monkey NOAEL[d]	100 (SC)		85800[e]	

Abbreviations: AUC = area under the plasma concentration versus time curve; $AUC_{0–672h,ss}$ = AUC over 672 hours at steady state; IV = intravenous; NOAEL = no-observed-adverse-effect level; SC = subcutaneous.

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

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

c Highest proposed dose in this study; a body weight of 80 kg is assumed. Human $AUC_{0–672h,ss}$ at IV 1000 mg is predicted on the basis of the average IV clearance observed in Study AMAA for doses between 5 and 600 mg.

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

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

6. Study Population

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

6.1. Inclusion Criteria

Subjects will be eligible for the study only if they meet all of the following criteria within the screening period, which is ≤28 days prior to the start of study treatment, unless specifically defined:

Type of Subject and Disease Characteristics

[1] have had a diagnosis of Crohn's disease for ≥3 months before baseline

[2] have active Crohn's disease as defined absolute SF ≥4 (loose and watery stools defined as Bristol Stool Scale Category 6 or 7) AND/OR AP ≥2 at baseline (refer Section 9.1.2 for details)

[3] have a SES-CD score ≥7 (centrally read) for subjects with ileal-colonic or ≥4 for subjects with isolated ileal disease within 14 days before the first dose of study treatment

Prior IBD Treatment

[4] must have received prior treatment for Crohn's disease (according to either "a)" or "b)" below or combination of both):

a) history of inadequate response to, or failure to tolerate treatment with aminosalicylates, 6-mercaptopurine (6-MP) or azathioprine (AZA), oral or IV corticosteroids or history of corticosteroid dependence (an inability to successfully taper corticosteroids without return of Crohn's disease)

OR

b) have received treatment with ≥1 biologic agents (such as TNF antagonists, vedolizumab, experimental biologic Crohn's disease therapeutics) with or without documented history of failure to respond to or tolerate such treatment:

- The treatment must have been discontinued according to the following timeline:
  - anti-TNF therapy at least 8 weeks before baseline
  - vedolizumab treatment at least 12 weeks before baseline
  - experimental biologic Crohn's disease therapy at least 8 weeks before baseline.

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

- Oral 5-aminosalicylic (ASA) compounds: if the prescribed dose has been stable for at least 3 weeks before screening colonoscopy or stopped treatment at least 3 weeks prior to screening colonoscopy.
- Oral corticosteroids must be at a prednisone-equivalent dose of ≤20 mg/day, or ≤9 mg/day of budesonide, and have been at a stable dose for at least 3 weeks prior to the screening colonoscopy. If stopping oral corticosteroid treatment prior to baseline, they must be stopped at least 3 weeks prior to screening colonoscopy.
- AZA, 6-MP, or methotrexate (MTX): if the prescribed dose has been stable for at least 4 weeks before screening endoscopy. Subjects who have discontinued therapy with AZA, 6-MP, or MTX must have stopped the medication at least 4 weeks prior to screening endoscopy to be considered eligible for enrollment.
- Crohn's disease-specific antibiotics: if the prescribed dose has been stable 4 weeks prior to baseline or stopped treatment at least 3 weeks prior to screening endoscopy.

Subject Characteristics

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

[7] Women of child-bearing potential must agree to either remain abstinent or use effective methods of contraception for the entirety of the study. Abstinence or contraception must continue 3 months following completion of study drug administration which is greater than 5 half-lives:

- Women of child-bearing potential must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to exposure.
- Two effective methods of contraception will be used. The subject may choose to use a double barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide (that is, condom with spermicide, diaphragm with spermicide, female condom with spermicide). It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.

[8] Women not of child-bearing potential may participate and include those who are:

- infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as Müllerian agenesis; or
- post-menopausal – defined as either
  - a woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had either

        - cessation of menses for at least 1 year, or
        - at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone (FSH) >40 mIU/mL; or
    - a woman ≥55 years of age not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea; or
    - a woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

[9] venous access sufficient to allow blood sampling and IV administration as per the protocol

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

[11] have an adequate organ function, including:

- hematologic: absolute neutrophil count ≥1.5 x 10^9/L (≥1.5 x 10^3/μL or ≥1.5 GI/L), platelet count ≥100 x 10^9/L (≥100 x 10^3/μL or ≥100 GI/L), hemoglobin level ≥10.0 g/dL (≥100 g/L), absolute lymphocyte count >500 cells/μL (>0.50 x 10^3/μL or >0.50 GI/L, and total white blood cell count ≥3.0 x 10^9/L (≥3.0 x 10^3/μL or ≥3.0 GI/L)
- chemistry: serum creatinine, total bilirubin level (TBL; subjects with Gilbert's syndrome must have serum direct bilirubin <1.5 mg/dL), alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels less than or equal to 2 times the upper limit of normal (≤2X ULN).

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

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

6.2. Exclusion Criteria

Subjects will be excluded from study enrollment if they meet any of the following criteria within the screening period, which is ≤28 days prior to the start of study treatment, unless specifically defined:

Study Disease Conditions or Treatments

[14] have complications of Crohn's disease such as strictures, stenoses, or any other manifestation for which surgery might be indicated or could confound the evaluation of efficacy

[15] diagnosis of conditions affecting the digestive tract, such as UC, indeterminate colitis, fistulizing disease, abdominal or perianal abscess, adenomatous colonic polyps not excised, colonic mucosal dysplasia, and short bowel syndrome

[16] have had any kind of bowel resection, diversion, or placement of a stoma within 6 months or any other intra-abdominal surgery within 3 months prior to screening

[17] have received any of the following for treatment of Crohn's disease:

- 6-thioguanine (6-TG), cyclosporine, tacrolimus, sirolimus, pentoxifylline, or mycophenolate mofetil within 8 weeks prior to baseline
- corticosteroid enemas, IV corticosteroids, corticosteroid suppositories, or topical treatment within 3 weeks prior to screening colonoscopy
- rectal 5-ASA within 3 weeks prior to screening colonoscopy
- have used apheresis (for example, Adacolumn apheresis) ≤2 weeks prior to screening.

[18] have previous exposure to any biologic therapy targeting IL-23 p19 either licensed or investigational, or prior exposure to ustekinumab

[19] have received natalizumab or agents that deplete B or T cells (for example, rituximab, alemtuzumab, or visilizumab) within 12 months of screening, or, if after receiving these agents, evidence is available at screening of persistent depletion of the targeted lymphocyte population

[20] have been treated with any investigational drug for Crohn's disease within 8 weeks prior to baseline or 5 half-lives of the drug (whichever is longer), OR with interferon therapy within 8 weeks before baseline

General Eligibility Criteria

[21] have evidence of active or latent tuberculosis (TB) (refer Section 9.5.4.1 for details on full TB exclusion criteria)

[22] 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

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

[24] increases the risks associated with participating in the study if the presence or history within 12 months prior to screening of significant uncontrolled cerebrocardiovascular (for example, myocardial infarction, unstable angina, unstable arterial hypertension, moderate-to-severe heart failure [New York Heart Association class III/IV], or cerebrovascular accident); presence of respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, or abnormal laboratory values at screening that, in the opinion of the investigator, pose an unacceptable risk to the subject if participating in the study or of interfering with the interpretation of data

[25] presence of significant uncontrolled neuropsychiatric disorder, have history of a suicide attempt or have a score of 3 on Item 12 (Thoughts of Death or Suicide) of the Quick Inventory of Depressive Symptomatology–Self Report (16 Items) (QIDS-SR16) at screening (Visit 1) or baseline (Week 0; Visit 2)

[26] 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.

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

[28] 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

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

[30] 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.

[31] have human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) or test positive for antibodies at screening

[32] 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

[33] 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

[34] had Clostridium difficile (C diff) infection within 60 days of screening 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.

[35] 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.

[36] have received a systemic (including oral) anti-infective agent for an infection within 28 days of baseline

[37] are pregnant, lactating, or planning pregnancy (both men and women) while enrolled in the study, or within 3 months after receiving the last dose of study agent

[38] have significant allergies to humanized monoclonal antibodies or any components of the LY3074828 product formulation

[39] history of alcohol or other drug abuse within the last year

[40] 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.

6.3. Lifestyle Restrictions

Study participants should be instructed not to donate blood or blood products during the study or for 16 weeks following their last dose.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Subjects may be rescreened due to the following criteria [1], [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13], [14], [16], [17], [19], [20], [21], [22], [23], [24], [26], [27], [28], [29], [30], [34], [35], [36], [37],or [39]. Individuals may be rescreened up to 2 times. Each time rescreening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number.

7. Treatments

7.1. Treatments Administered

Table AMAG.3 shows the treatment regimens.

Table AMAG.3. Treatment Regimens

Treatment Group	Description
Period 1 (Double Blind)	
LY Dose Arm 1	1000 mg IV LY Q4W
LY Dose Arm 2	600 mg IV LY Q4W
LY Dose Arm 3	200 mg IV LY Q4W
Placebo	Placebo given IV Q4W
Period 2 (Double Blind and Double Dummy)	
LY Dose Arm 1	1000 mg IV LY Q4W* or 300 mg SC LY Q4W*
LY Dose Arm 2	600 mg IV LY Q4W* or 300 mg SC LY Q4W*
LY Dose Arm 3	200 mg IV LY Q4W* or 300 mg SC LY Q4W*
LY Subjects with no Week 12 SES-CD improvement	1000 mg IV Q4W + SC Placebo Q4W
Placebo	1000 mg IV Q4W+ SC Placebo Q4W
Period 3 (Open Label)	
LY Dose Arm 1	300 mg SC LY Q4W
LY Dose Arm 2	300 mg SC LY Q4W
LY Dose Arm 3	300 mg SC LY Q4W
Placebo	300 mg SC LY Q4W

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

* Also administer the placebo by the appropriate route; for example, if active LY is administered intravenously, then administer placebo via SC route, and vice versa. Administer IV preparation first, followed by SC preparation.

Intravenous infusion of mirikizumab or placebo will occur over at least 2 hours. All patients receiving IV infusion should be monitored for 1 hour or longer (per investigator discretion or local standard of care) after IV dosing is complete. Sites must have resuscitation equipment, emergency medications, and appropriately trained staff available during the infusion and monitoring period. Detailed instructions for investigational product administration will be provided separately by the sponsor.

Subcutaneous administration of mirikizumab or placebo will be given in 3 injections. Detailed instructions regarding supplies and preparation and handling of LY3074828 will be provided by the sponsor.

The investigator or his/her designee is responsible for the following:

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

- at the end of the study, returning all unused medication to Lilly, or its designee, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law.

7.1.1. Packaging and Labeling

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.

LY3074828 is supplied for clinical trial use as lyophilized powder in a glass vial and should be stored in refrigerated conditions (2ºC to 8ºC). The vial is manufactured to deliver 75 mg of LY3074828 and will be reconstituted with sterile water for injection and further diluted with normal saline (0.9% sodium chloride) before administration. Placebo will be sterile normal saline (0.9% sodium chloride for injection).

When reconstituted and in a syringe, LY3074828 cannot be distinguished visually from placebo.

Detailed instructions regarding supplies and preparation and handling of LY3074828 will be provided by the sponsor.

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

7.2. Method of Treatment Assignment

Subjects who meet all criteria for enrollment will be randomized to treatment at Visit 2. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). To achieve between-group comparability, subjects will be stratified to these arms based upon their prior therapy (below); this stratification will be controlled by IWRS.

- A minimum of approximately 30% of subjects will be naive to biologic Crohn's disease therapy (including experimental biologic Crohn's disease therapy).
- At least 50% of the subjects will be prior biologic Crohn's disease therapy-experienced (including experience with experimental biologic Crohn's disease therapy).
- For Period 2, subjects assigned to LY3074828 at baseline will be randomized to either baseline treatment assignment or 300 mg SC LY3074828 Q4W —except for all subjects in the placebo group, and subjects in the LY3074828 treatment groups who have not had any improvement in SES-CD score from baseline at Week 12 (determined by the central reader), who will receive 1000 mg IV LY3074828 Q4W. All subjects will receive IV and SC administration of either LY3074828 or placebo during Period 2 in a double-dummy design. The randomization will be stratified based on endoscopic response (as defined for the primary endpoint).

7.2.1. Selection and Timing of Doses

The actual time of all dose administrations will be recorded in the subject's case report form (CRF). All study procedures (including blood tests) are to be performed predose unless otherwise specified in the Schedule of Activities.

7.3. 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. Only 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, site personnel performing assessments, or subject is unblinded, the subject must be discontinued from the study. In cases where there are ethical reasons to have the subject remain in the study, the investigator must obtain specific approval from a Lilly clinical research physician (CRP) 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 the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly CRP prior to unblinding a subject's treatment assignment unless this could delay emergency treatment of the subject. If a subject's treatment assignment is unblinded, Lilly must be notified immediately.

7.4. Dosage Modification

Dose adjustments are not permitted in this study, except as noted in Section 7.8.2.

7.5. Preparation/Handling/Storage/Accountability

Detailed instructions regarding supplies and preparation and handling of LY3074828 will be provided by the sponsor.

7.6. 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 noncompliant if he or she fails to attend for administration of study medication within the required treatment window as defined in the Schedule of Activities (Section 2).

7.7. Concomitant Medications

All concomitant medication taken during the study must be recorded on the concomitant medication 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.

Use of nonlive (inactivated) vaccinations are allowed for all subjects. Use of live, attenuated vaccines is prohibited. 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 Crohn's disease during the study are permitted only as outlined in Table AMAG.4. The corticosteroid tapering regimen is outlined in Table AMAG.4.

Table AMAG.4. Permitted Concomitant Therapies for Crohn's Disease

Drug Class	Conditions for Use
Oral 5-aminosalicylic (ASA) or sulfasalazine	Subjects were receiving the medications at baseline and the prescribed dose was stable for at least 3 weeks before screening colonoscopy. 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 (AZA) or 6-mercaptopurine (6-MP)	Subjects were receiving the medications at baseline and the prescribed dose was stable for at least 4 weeks before screening colonoscopy. 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.
Methotrexate (MTX)	Subjects were receiving the medications at baseline and the prescribed dose was stable for at least 4 weeks before screening colonoscopy. 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 they must be stable for 3 weeks prior to the screening colonoscopy. Decrease of the steroid dosage due to tapering regimen is allowed during the study per investigator judgment, except during Period 1. 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 up to 9 mg/d must be stable for 3 weeks prior to the screening colonoscopy. Decrease of the steroid dosage due to tapering regimen is allowed during the study per investigator judgment, except during Period 1. If the steroid tapering is commenced, is recommended to be decreased by 3 mg every week until dose 0. 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.

7.8. Treatment after the End of the Study

7.8.1. Continued Access

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

7.8.2. Special Treatment Considerations

7.8.2.1. 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.

Any premedication given will be documented as a concomitant therapy.

7.8.2.2. Management of Hypersensitivity Events, Fever Associated Reactions, and Infusion/Injection Site Reactions

During and after study drug administration, patients should be closely monitored for signs or symptoms of AEs, including hypersensitivity events, other fever associated reactions and infusion or injection site reactions.

Systemic Hypersensitivity Events

If a patient experiences a systemic hypersensitivity event involving the skin or mucous membranes, respiratory, cardiovascular, gastrointestinal, or urinary systems, during or up to 6 hours after an infusion of study drug, the following guidance should be followed (see Appendix 6 for additional information):

- Study drug infusion should be stopped immediately and appropriate supportive care provided according to local standard practice (for example, administration of epinephrine, anti-histamine, systemic steroids, and/or bronchodilators).

- After the patient's stabilization, additional immunogenicity, PK, and hypersensitivity markers samples should be collected as follows:
    - As soon as possible after the event occurs
    - 4 weeks after the event
    - 12 weeks after the event
- The patient should continue to be monitored until resolution or stabilization of the symptoms, as clinically appropriate.
- Permanently discontinue the study drug after a systemic drug administration reaction.
- If the patient discontinues study drug but remains in the study, management should follow as outlined in Section 8.1.1, and immunogenicity, PK, and hypersensitivity markers should be collected at 4 and 12 weeks after the event.
- If the patient discontinues participation in the study, the patient should proceed to early termination procedures. The patient will need to return after early termination procedures for 4 and 12 week immunogenicity, PK, and hypersensitivity markers collections.
- The medical monitor should be notified as soon as feasible.

Fever-Associated Reactions

If a patient experiences a fever-associated reaction consisting of headache, rigors and/or temperature >38°C (in the absence of signs or symptoms of a systemic hypersensitivity event) during or up to 6 hours after an infusion of study drug, the following guidance should be followed:

- Study drug infusion should be interrupted and appropriate medical care should be administered (for example, nonsteroidal anti-inflammatory drugs [NSAIDS], anti-pyretics or antihistamines).
- Additional immunogenicity, PK, and hypersensitivity markers samples should be collected as follows:
    - As soon as possible after the event occurs
    - 4 weeks after the event
    - 12 weeks after the event
- Resumption of study drug infusion after interruption, possibly at a slower rate of administration, can be considered if symptoms resolve and it is deemed to be medically appropriate based on the investigator's discretion, and considering the risk/benefit of readminstration.
- Patient should remain in observation, as is clinically appropriate for the patient's symptoms.
- Premedication prior to subsequent study drug administration may be considered, if judged by the investigator to be appropriate for the individual patient.
- If the patient discontinues study drug but remain in the study, management should follow as outlined in Section 8.1.1, and immunogenicity, PK, and hypersensitivity markers should be collected at 4 and 12 weeks after the event.

- If the patient discontinues from the study early for any reason, they should return to complete 4 and 12 week follow-up immunogenicity, PK, and hypersensitivity markers collections.
- If the patient develops systemic hypersensitivity symptoms or signs, they should be managed as described above for a systemic hypersensitivity event.

Infusion Site Reactions

If a patient experiences an infusion site reaction, including urticaria, pruritus, or angioedema localized to the IV infusion site (in the absence of systemic hypersensitivity signs or symptoms), during or up to 6 hours after an infusion of study drug, the following guidance should be followed:

- Study drug infusion should be interrupted and appropriate medical care should be administered (for example, NSAIDS, anti-pyretics or antihistamines).
- Additional immunogenicity, PK, and hypersensitivity markers samples should be collected as follows:
    - As soon as possible after the event occurs
    - 4 weeks after the event
    - 12 weeks after the event
- Resumption of study drug infusion after interruption, possibly at a slower rate of administration, can be considered if symptoms resolve and it is deemed to be medically appropriate based on the investigator's discretion, and considering the risk/benefit of readminstration.
- Patient should remain in observation, as is clinically appropriate for the patient's symptoms.
- Premedication prior to subsequent study drug administration may be considered, if judged by the investigator to be appropriate for the individual patient.
- If the patient discontinues from the study early for any reason, they should return to complete 4 and 12 week follow-up immunogenicity, PK, and hypersensitivity markers collections.
- If the patient develops systemic hypersensitivity symptoms or signs, they should be managed as described above for a systemic hypersensitivity event.

Injection Site Reactions

If a patient experiences an injection site reaction, including pain, erythema, urticaria, pruritus, or angioedema localized to the SC injection site (in the absence of systemic hypersensitivity signs or symptoms), the following guidance should be followed:

- Patient should be instructed to contact the study site to report any symptoms experienced following a SC injection.
- Premedication prior to subsequent study drug administration may be considered as appropriate for the individual patient.
- If the patient develops systemic hypersensitivity symptoms, they should be managed as described above for a systemic hypersensitivity event.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

Discontinuation of the investigational product for abnormal liver tests should be considered by the investigator when a subject meets one of the following conditions after consultation with the Lilly designated medical monitor:

- ALT or AST >8xULN
- ALT or AST >5xULN for more than 2 weeks
- ALT or AST >3xULN and TBL >2xULN or prothrombin time >1.5xULN
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP >3xULN
- ALP >2.5xULN and TBL >2xULN
- ALP >2.5xULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

Subjects may discontinue treatment for any of the reasons noted above, or for other reasons such as the development of a serious adverse event. To better communicate patient flow throughout the study, different study period situations are provided below:

- Subjects who discontinue the investigational product in Period 1 or Period 2 may continue in the study according to the visit schedule (Section 2).
- At Week 52/Visit 18, subjects who have previously discontinued the investigational product will continue to Visit 801 of the Follow-up Period.
- Subjects who discontinue the investigational product in Period 3 may continue in Period 3 and then proceed to Week 104/Visit 801 of the Follow-up Period.

Investigational product is to be discontinued for patients who experience clinically significant systemic hypersensitivity events (such as anaphylaxis) following administration of investigational product.

8.1.2. Discontinuation of Inadvertently Enrolled Subjects

If the sponsor or investigator identify a subject who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the sponsor CRP and the investigator to determine if the subject may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled subject to continue in the study with or without treatment with investigational product.

8.2. Discontinuation from the Study

Some possible reasons that may lead to permanent discontinuation include:

- 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
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- investigator decision
    - the investigator decides that the subject should be discontinued from the study
    - if the subject, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
- subject decision
    - the subject requests to be withdrawn from the study
- 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, Sections 9.5.5 and 10.3.4.
- subject becomes pregnant.

Subjects who discontinue the study early will have end-of-study procedures as outlined in Visit 804 in the Schedule of Activities (Section 2). Any medical data and biological samples collected through the early termination visit will still be evaluated in an anonymized manner.

8.3. Lost to Follow-Up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact subjects who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Lilly personnel will not be involved in any attempts to collect vital status information.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, with the study procedures and their timing (including tolerance limits for timing).

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

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

9.1. Efficacy Assessments

9.1.1. Primary Efficacy Assessments

The primary efficacy outcome measure is endoscopic response of LY3074828 versus placebo at Week 12. Endoscopic response is defined as having 50% reduction from baseline in SES-CD Score (Vuitton et al. 2015).

The SES-CD (Daperno et al. 2004) tool will be utilized by central readers to evaluate endoscopy video that is collected during subject endoscopic (colonoscopy) examination

9.1.2. Secondary Efficacy Assessments

Secondary efficacy assessments will include an assessment of the SES-CD score using centrally read endoscopy at Weeks 12 and 52, and an assessment of SF and AP at Weeks 12 and 52, using patient-reported data recorded in the patient diary, as detailed below. Changes in health outcome measures/quality-of-life measures from baseline to Weeks 12 and 52, and the PK properties of LY3074828 will also be assessed. Effects on safety parameters will also be assessed (see Section 9.5).

- Endoscopic remission is defined as an SES-CD score of <4 for ileal-colonic disease or <2 for isolated ileal disease, and no subscore >1.
- PRO scores will be determined as an average of 7 days of data recorded by the subject within a 12-day period prior to a specified visit. Fewer than 4 days of data within a 12-day period prior to a specified visit will constitute a missing data score. Data will be excluded from score calculation when collected on day(s) of colonoscopy prep, day of colonoscopy procedure, and 2 days after colonoscopy procedure. PRO remission is defined as having an average daily AP score ≤1 and an average daily SF ≤2.5 (absolute number of liquid or very soft stools defined using the Bristol Stool Scale Category 6 or 7 [Lewis and Heaton 1997], that is, liquid or watery stools).

9.1.3. Subject Diary

Subjects will be provided with a diary tool during screening in order to record information pertaining to subjects' signs and symptoms on a daily basis:

1. Patient Global Rating of Severity (PGRS)
2. Crohn's Disease Activity Index (CDAI)
    a. CCI
    b. absolute number of liquid or soft stools (Bristol Stool Scale Category 6 or 7 [Lewis and Heaton 1997] that is, liquid or watery stools).
    c. general well-being (5-point scale)
3. CCI
4. Bowel movement count (BMC; that is, absolute number of stools irrespective of quantity and consistency).

Diary data will be assessed at the clinic, at each visit defined in the Schedule of Activities. Information regarding CCI ; number of liquid or very soft stools; and general well-being score (5-point scale: 0=generally well, 1=slightly under par, 2=poor, 3=very poor, 4=terrible) will be collected daily to calculate the subjects' PRO2 and CDAI scores (see Section 9.1.5).

Data will include information collected over 7 days during a 12-day period prior to each study visit (<4 days of data within a 12-day period prior to a specified visit will constitute a missing data score). During visits when colonoscopy is required, subject diary data from colonoscopy preparation day(s), day of the colonoscopy procedure, and two days after the colonoscopy procedure will be excluded from score calculations.

In order to encourage consistent diary recording, subject should enter daily diary data continuously throughout the study.

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

9.1.4. Endoscopy

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

During the study, the SES-CD will be evaluated by both the investigator/endoscopist and by a central reader blinded to study treatment. However, only the SES-CD score from the central reader will be used to determine study eligibility and endoscopic efficacy evaluation. A detailed imaging 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.

Biopsies will be collected during the endoscopy procedure. The details of biopsy sample collection will be provided in the laboratory manual. Biopsies will be used for CCI and histopathological assessment (Appendix 5). To ensure quality data and standardization, bowel 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 images will be read centrally in a blinded manner by a qualified pathologist according to the image review charter.

9.1.5. Other Assessments

Crohn's Disease Activity Index (CDAI): CDAI is an 8-item disease activity measure comprised of 3 patient-reported and 5 physician-reported/laboratory items. Subject responses are summed over a 7-day period and subsequently weighted, yielding a total score range of 0 to 600 points with a score of <150 points defined as remission. A score of 220 to 450 points indicates moderate to severe disease activity, and a score of >450 points indicates severe disease activity.

Patient Reported Outcome 2 (PRO2) is a 2-item index comprised of the SF and AP items from the CDAI. The total PRO2 comprises the average daily scores over 7 days and is weighted using the CDAI multiplication factors for SF and AP items.

For both of these items (**CDAI and PRO2**), 7 days of subject-reported data within a 12-day period prior to a visit will be utilized to calculate scores. Data will be excluded from score calculation when collected on day(s) of colonoscopy prep, day of colonoscopy procedure, and 2 days after colonoscopy procedure.

9.1.6. Appropriateness of Assessments

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

9.2. Health Outcomes/Quality of Life

Patient's Global Rating of Severity (PGRS) (daily): The PGRS is a 1-item patient-rated questionnaire designed to assess the subjects' rating of their disease symptom severity over the past 24 hours. Responses are graded on a 6-point scale in which a score of 1 indicates the subject has no symptoms (that is, "none") and a score of 6 indicates that the subject's symptom(s) are "very severe."

Patient's Global Rating of Change (PGRC): The PGRC scale is a patient-rated instrument designed to assess the subjects' rating of change in their symptom(s). 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 has experienced "no change," and a score of 7 indicates that the subject's symptom(s) is "very much worse."

Inflammatory Bowel Disease Questionnaire (IBDQ): The IBDQ is a 32-item patient-completed questionnaire that measures 4 aspects of subjects' lives: symptoms directly related to the primary bowel disturbance, systemic symptoms, emotional function, and social function. 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.

Medical Outcomes 36-Item Short Form Health Survey (SF-36): The SF-36 is a 36-item patient-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. 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.

Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue): FACIT-Fatigue is a 13-item instrument developed to measure fatigue in chronic illness patients. It has been validated for use in IBD patients. Total score ranges from 0 to 52 based on a rating of 4-point Likert scale.

Bowel Movement Count (BMC): Due to the significant impact of SF on subjects' lives, Lilly plans to measure and validate "stool frequency in the past 24 hours" using an electronic daily diary approach. Seven days of subject diary data during a 12-day period prior to the visit must be completed and assessed, excluding colonoscopy preparation day(s), day of the colonoscopy procedure, and 2 days after colonoscopy procedure. In order to encourage consistent diary recording, subjects should enter daily diary data continuously throughout the study.

Quick Inventory of Depressive Symptomatology–Self Report (16 Items) (QIDS-SR16): The QIDS-SR16 is a self-administered, 16-item instrument intended to assess the existence and severity of symptoms of depression as listed in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM-IV) (APA 1994). A subject is asked to consider each statement as it relates to the way they have felt for the past 7 days. There is a 4-point scale for each item ranging from 0 to 3. The 16 items corresponding to 9 depression domains are summed to give a single score ranging from 0 to 27, with higher scores denoting greater symptom severity. The domains assessed by the instrument include: (1) sad mood, (2) concentration, (3) self-criticism, (4) suicidal ideation, (5) interest, (6) energy/fatigue, (7) sleep disturbance (initial, middle, and late insomnia or hypersomnia), (8) decrease/increase in appetite/weight, and (9) psychomotor agitation/retardation. Additional information and the QIDS-SR16 questions may be found at the University of Pittsburgh IDS/QIDS internet page [www.http://www.ids-qids.org/].

9.3. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

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

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

After the ICF is signed, study site personnel will record via electronic case report form (eCRF) the occurrence and nature of each subject's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure, investigational product, via eCRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, study device and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a subject's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

9.3.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Although all AEs occurring after signing the ICF are recorded in the eCRF, SAE reporting begins after the subject has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, it needs to be reported ONLY if it is considered reasonably possibly related to study procedure.

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.

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

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.

9.3.1.1. 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.

9.3.2. Complaint Handling

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

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.

9.4. Treatment of Overdose

In case of suspected overdose, hematology, chemistry, vital signs, and oxygen saturation should be monitored and supportive care provided as necessary. There is no known antidote for LY3074828.

9.5. Safety

9.5.1. Electrocardiograms

For each subject, ECGs should be collected according to the Schedule of Activities (Section 2). Electrocardiograms should be recorded according to the study-specific recommendations included in the Schedule of Activities.

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the subject receives the first dose of the investigational treatment should be reported to Lilly or its designee as an AE via eCRF.

9.5.2. Vital Signs

For each subject, vital signs measurements should be conducted according to the Schedule of Activities (Section 2).

Any clinically significant findings from vital signs measurement that result in a diagnosis and that occur after the subject receives the first dose of study treatment should be reported to Lilly or its designee as an AE via eCRF.

9.5.3. Laboratory Tests

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

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the subject receives the first dose of investigational product should be reported to Lilly or its designee as an AE via eCRF.

9.5.4. Other Tests

9.5.4.1. Chest Radiography and Tuberculosis Testing

Posterior-anterior view chest radiography (CXR) will be obtained at screening (Visit 1) (unless local standards dictate posterior–anterior and lateral views), 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 Schedule of Activities 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 48 to 72 hours after test application (regardless of Bacillus Calmette-Guerin vaccination history). In countries where the QuantiFERON-TB Gold test (or equivalent, for example, T-SPOT) 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. Retesting following a positive test is allowed in patients, who in the opinion of the investigator, are unlikely to be infected with *Mycobacterium tuberculosis*. In this circumstance, 2 positive tests is considered evidence of active or latent TB infection. Patients in whom retesting has been performed must be discussed with the medical monitor prior to inclusion in the study.

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 QuantiFERON-TB Gold test 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 ≤2xULN) 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 re-exposure 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.

9.5.5. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

If a study patient/subject experiences elevated ALT ≥3xULN, ALP ≥2xULN, or elevated TBL ≥2xULN, 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 patient/subject safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP regarding collection of specific recommended clinical information and follow-up laboratory tests (see Appendix 4).

Any enrolled subject who is HBcAb+ will undergo periodic monitoring of HBV deoxyribonucleic acid (DNA) per the Schedule of Activities.

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 >3xULN 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.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the data monitoring board (an advisory group for this study

formed to protect the integrity of data; refer Section 10.3.7, Interim Analyses) can conduct additional analyses of the safety data.

9.6. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine the serum concentrations of LY3074828.

A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and 24-hour clock time of each sampling will be recorded.

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 following last subject visit for the study.

9.7. Pharmacodynamics

Not applicable.

CCI


CCI

10. Statistical Considerations

10.1. Sample Size Determination

Approximately 180 participants will be randomized with a 2:1:1:2 allocation across 4 treatment arms (1000, 600, 200 mg LY3074828, and placebo).

The primary endpoint is Week 12 endoscopic response rate (as defined as a 50% reduction in SES-CD). Based on 60 patients per comparison treatment arm and the assumed LY3074828 and placebo endoscopic response rates of 35% and 15%, respectively, the test of the superiority versus placebo will have 81% power when performed via a chi-squared test at a 2-sided 0.1 significance level.

Subjects will be stratified by prior biologic Crohn's disease therapy use (yes/no). The exact number enrolled in either group will be dependent upon the enrollment rate of the patient populations described below:

- A minimum of approximately 30% of subjects will be naive to biologic Crohn's disease therapy (including experimental biologic Crohn's disease therapy).
- At least 50% of the subjects will be prior biologic Crohn's disease therapy-experienced (including experience with experimental biologic Crohn's disease therapy).

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Intent-to-Treat (ITT)	The ITT population is defined as all randomized patients, even if the subject does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Subjects will be analyzed according to the treatment to which they were randomized.
Safety	All randomized participants who take at least 1 dose of double-blind study treatment. Participants will be included in the treatment group to which they were randomized.

Additional subpopulations may be identified. Full details would be provided in the study statistical analysis plan (SAP).

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. A detailed SAP describing the statistical methodologies will be developed by the sponsor or its designee. SAS (Version 9.2 or higher, SAS Institute, Cary, NC, USA) will be used for the statistical analysis.

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 (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

Continuous data will be summarized in terms of the mean, standard deviation, minimum, maximum, median, and number of observations. Categorical data will be summarized as frequency counts and percentages. Unless otherwise specified, statistical tests of treatment effects will be conducted using 2-sided tests at an alpha level of 0.1. This will include the tests for continuous variables and categorical variables.

Treatment comparisons of categorical efficacy variables will be conducted using a logistic regression analysis with treatment, geographic region and prior biologic Crohn's disease therapy use (yes/no) in the model. The proportions and 90% confidence intervals (CI) will be reported.

Treatment comparisons of continuous efficacy and health outcome variables will be made using mixed effects for repeated measures (MMRM) analysis. When the MMRM model is used, the model includes treatment, geographic region, prior biologic Crohn's disease therapy use, baseline value, visit, and the interactions of treatment-by-visit and baseline-by-visit as fixed factors. The covariance structure to model the within-patient errors will be unstructured. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure will be used. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III sums of squares for the least-squares (LS) means will be used for the statistical comparison; the 90% CI will also be reported.

When necessary, additional analyses of categorical efficacy variables may be conducted to address sparse data or small sample sizes. Additional sensitivity analyses of continuous efficacy and health outcomes variables will be conducted using an analysis of covariance (ANCOVA).

Full details of these analyses including missing imputation methods and covariates will be provided in the SAP.

10.3.1.1. Analysis of Populations

Unless otherwise specified, efficacy and health outcomes analyses will be conducted on the intent-to-treat population (ITT), as defined in Section 10.2.

Unless otherwise specified, safety analyses will be conducted on the safety population, as defined in Section 10.2.

Additional subpopulations may be identified. Full details would be provided in the SAP.

10.3.1.2. Missing Data Imputation

Analysis of categorical efficacy and health outcome variables will be assessed using a non-responder imputation (NRI) method. Subjects will be considered a non-responder for the analysis if they do not meet the response criteria or have missing response data at the analysis

time point. Randomized subjects without at least 1 postbaseline observation will also be defined as non-responders for the NRI analysis.

Full details of the NRI methodology will be provided in the SAP. Additional missing data imputation methodologies may be considered and will be fully detailed in the SAP.

10.3.1.3. Adjustment for Multiple Comparisons

Unless otherwise specified, no multiplicity adjustment will be applied for planned analyses.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

The number of randomized patients will be summarized by treatment period. Frequency counts and percentages of all patients who are randomized and completing the study or discontinue the study drug/study early will be presented for each treatment period. Reasons for discontinuing the study drug/study will be summarized by treatment period.

A detailed description of patient disposition will be provided at the end of the study.

10.3.2.2. Patient Characteristics

Year of birth, sex, weight, height, smoking habits, prior biologic Crohn's disease therapy, and other demographic characteristics will be recorded and summarized for all patients. 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.

10.3.2.3. Concomitant Therapy

Concomitant therapy will be collected at each visit, and the reported term will be classified by the World Health Organization (WHO) 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.

Concomitant therapy may be summarized for the prior biologic Crohn's disease therapy patient populations separately.

The number and percentage of patients taking concomitant Crohn's disease therapies (overall and by therapy type) and corticosteroid products (overall and by steroid type) will be summarized by treatment group and study period if appropriate.

Full details of the analysis of concomitant medication will be described in the SAP.

10.3.2.4. Treatment Compliance

Subjects who are noncompliant according to the definition in Section 7.6 will be listed by treatment. A contingency table of numbers of noncompliant subjects by treatment will be provided.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Efficacy Analyses

Rates of endoscopic response at Week 12, as defined in Section 10.1, will be analyzed. Subjects who do not achieve endoscopic response by Week 12 or who do not reach the Week 12 assessment will be considered to be non-responders at Week 12. Details of the NRI are provided in Section 10.3.1.2.

The primary endpoint analysis will utilize the statistical methodology described in Section 10.3.

Additional analyses of the primary endpoint may be considered and will be fully detailed in the SAP.

10.3.3.2. Secondary Efficacy Analyses

The secondary efficacy endpoints of the trial are:

- To evaluate the efficacy of treatment with LY3074828 on endoscopic response at Week 52 (defined as 50% reduction from baseline in SES-CD Score).
- To evaluate the efficacy of treatment with LY3074828 on endoscopic remission at Weeks 12 and 52 (defined as a SES-CD score of <4 ileal-colonic disease or <2 for isolated ileal disease, and no subscore >1).
- To evaluate the efficacy of treatment with LY3074828 on PRO remission at Weeks 12 and 52 (defined as SF ≤2.5 and AP ≤1).

For endoscopic remission and PRO remission, subjects who do not achieve remission or who do not reach the assessment time point (Week 12 or 52) will be considered to be non-remitters for that particular endpoint at that time point and later time points if applicable.

Details of the NRI are provided in Section 10.3.1.2.

Details of the analysis methods that will be utilized are provided in Section 10.3.1.

Additional analyses of the secondary efficacy endpoints may be considered and will be fully detailed in the SAP.

10.3.3.3. Health Outcomes/Quality-of-Life Analyses

There are 10 additional self-administered questionnaires used to evaluate the effect of LY3074828 on health outcomes/quality-of-life measures in this trial: PGRS, PGRC, IBDQ, SF-36, FACIT-Fatigue, CCI BMC, QIDS-SR16, CCI and CCI .

Where appropriate, the total scores and sub-totals for individual dimensions collected will be summarized with means and 90% CI by time point and by treatment group. The summary table will also include the change from baseline scores wherever applicable.

The intent-to-treat (ITT) population will be used for all health outcome analyses.

10.3.3.4. Exploratory Efficacy Analyses

There are a number of exploratory efficacy endpoints defined:

- To evaluate durability of endoscopic response and remission at Week 52
- To evaluate PRO2 response (defined as a decrease in PRO2 of at least 5 points) at Weeks 12 and 52
- To evaluate PRO2 remission at Weeks 12 and 52 (defined as PRO2 <8)
- To evaluate durability of PRO2 response and remission at Week 52
- To evaluate composite endoscopic remission and PRO remission at Weeks 12 and 52
- To evaluate durability of composite endoscopic remission and PRO remission at Week 52
- CCI
- To evaluate the effect of LY3074828 on BMC
- To explore the development of any anti-LY3074828 antibodies that are formed and their effect on safety, PK, and pharmacodynamics (PD) of LY3074828
- To evaluate changes in CDAI from baseline
- To evaluate the effect of LY3074828 on QIDS-SR16 at Weeks 12 and 52.
- To assess the psychometric properties (including reliability, validity, and responsiveness) of the CCI , BMC, CCI .

Details of the analysis of exploratory endpoints will be fully detailed in the SAP.

10.3.4. Safety Analyses

The evaluation of safety and tolerability of treatment with LY3074828 is a secondary endpoint of this trial.

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 during the treatment periods will be calculated for each subject and summarized by treatment group. AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC), preferred term (PT), severity, and relationship to investigational product.

A TEAE is defined as an event that first occurred or worsened in severity after baseline. The MedDRA Lowest Level Term (LLT) will be used in the treatment-emergent computation. 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 may be presented.

An overall summary of AEs will be provided for the study. This includes the number and percentage of subjects who experienced TEAE, TEAE by maximum severity, death, SAE, TEAE related to study drug, discontinuations from the treatment due to an AE. Treatment-emergent adverse events (all, by maximum severity, and TEAEs possibly related to study drug by the investigator), SAEs including deaths, AEs that lead to treatment discontinuation will be

summarized and analyzed by MedDRA SOC and PT or by PT alone. Study periods may also be summarized separately for key safety displays.

Additional safety parameters include laboratory test results, ECGs (when reported, see Section 9.5.1), and vital sign measurements. The parameters will be listed and summarized with standard descriptive statistics. Change from baseline will also be summarized by randomized treatment where appropriate.

Assessment of immunogenicity with respect to safety will include comparison of subjects who experience TEAEs of systemic allergy/hypersensitivity and of injection-site reactions and who also develop treatment-emergent anti-LY3074828 antibody positivity with subjects who experience the same types of TEAEs but who remain treatment-emergent anti-LY3074828 antibody negative. Anti-LY3074828 antibody titers will also be evaluated in anti-LY3074828 antibody positive subjects who experience these events.

Other safety parameters, including body weight, will be descriptively summarized by treatment groups. Further analyses may be performed comparing the treatment groups.

All safety analyses will be fully detailed in the SAP.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Analyses of data will be performed using a nonlinear mixed-effect modeling (NONMEM) 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 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. These analyses will include model-based and graphical evaluations of the data. Estimates of PK model parameters and covariate effects and corresponding 90% CI will be reported.

Analyses of exposure-response relationships will be conducted using both exploratory graphical approaches and model based approaches. Exploratory graphical analysis approaches for SES-CD may consist of graphs showing the percentage of subjects who achieve a 50% reduction at different percentiles (for example, quartiles) of exposure of LY3074828 at Weeks 12 and 52. Measures of exposure may include population PK estimated average concentrations ($C_{ss,avg}$) or observed trough concentrations. Model based analyses of SES-CD will utilize population exposure-response models, where maximum effect (E_{max}) or other model structures may be used to relate exposure to either the change in SES-CD score and/or the probability of achieving a 50% reduction in SES-CD score. These models may be used to evaluate subject factors that may impact the relationship between exposure and response. Longitudinal exposure-response models for CDAI scores or subcomponents of the CDAI score (PRO2, SF, AP) may be developed, which relate the time course and magnitude of LY3074828 exposure to the time course and magnitude of response.

Additional analyses may be conducted if they are deemed appropriate. Further details on PK and PK/PD analyses will be provided in the PK/PD analysis plan.

10.3.6. Other Analyses

10.3.7. Interim Analyses

Planned interim analyses that may occur before the primary efficacy data lock include:

- when efficacy data from approximately 50% of subjects through Week 12 are available
- when efficacy data from approximately 50% of subjects through Week 52 are available.

The purpose of all interim analyses will be to support further development planning. The study will not be stopped for futility or efficacy and, as such, will not require an alpha penalty.

Changes to the timing and number of interim analyses may occur. Any changes to the planned analyses which occur prior to the primary endpoint analysis (100% of subjects through Week 12) will be fully captured in the SAP. Additional analyses and snapshots of study data occurring after the primary endpoint data lock may be performed after an adequate number of subjects have completed 52 weeks of treatment. To minimize any bias being introduced into the analysis of the study, the SAP and PK/PD analysis plan will be approved before the efficacy interim analysis is initiated.

A limited number of pre-identified individuals may gain access to the limited unblinded data, as specified in the unblinding plan, prior to the interim or final database lock, in order to initiate the final population PK/PD model development processes for interim or final analyses. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded.

Unblinding details are specified in the unblinding plan section of the SAP.

Interim assessments will be conducted by a sponsor Assessment Committee comprised of a limited number of preidentified team members who do not have direct site contact or data entry/validation responsibilities.

Ongoing monitoring of safety data (including AEs, SAEs, and selected laboratory measurements) will be continued throughout the study using blinded data. Details of the trial level safety review (TLSR) are specified in the TLSR plan or a separate document.

11. References

Adedokun OJ, Xu Z, Gasink C, Friedman J, Szapary P, Lang Y, et al. OP028 Pharmacokinetics and exposure-response relationships of intravenously administered ustekinumab during induction treatment in patients with Crohn's disease: results from the UNITI-1 and UNITI-2 studies [oral presentation]. At: 11th Congress of European Crohn's and Colitis Organisation (ECCO): Inflammatory Bowel Diseases; Mar 16-19 2016; Amsterdam, The Netherlands. Oral presentation (OP) 028.

[APA] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. (DSM-IV). Washington, DC: APA; 1994.

D'Haens GR, Geboes K, Peeters M, Baert F, Penninckx F, Rutgeerts P. Early lesions of recurrent Crohn's disease caused by infusion of intestinal contents in excluded ileum. *Gastroenterology*. 1998;114(2):262-267.

Daperno M, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc*. 2004;60(4):505-512.

El-Bassat, AboAli L, El Yamany S, Al Shenawy H, Al Din RA, Taha A. Interleukin-23p19 expression in patients with ulcerative colitis and its relation to disease severity. *AIDM*. 2015; In press. Available at: http://dx.doi.org/10.1016/j.aidm.2015.04.002. Accessed 12 July 2016.

Feagan BG, Sandborn W, Panés J, Ferrante M, Edouard L, Geert R, et al. 812a Efficacy and safety of induction therapy with the selective IL-23 inhibitor BI 655066, in patients with moderate-to-severe Crohn's disease: results of a randomized, double-blind, placebo-controlled Phase II study. *Gastroenterology*. 2016;150(4) suppl 1:S1266. Abstract 812a.

Gheita TA, El Gazzar II, El-Fishawy HS, Aboul-Ezz MA, Kenawy SA. Involvement of IL-23 in enteropathic arthritis patients with inflammatory bowel disease: preliminary results. *Clin Rheumatol*. 2014;33(5):713-717.

Globig AM, Hennecke N, Martin B, Seidl M, Ruf G, Hasselblatt P, Thimme R, Bengsch B. Comprehensive intestinal T helper cell profiling reveals specific accumulation of IFN-γ+IL-17+coproducing CD4+ T Cells in active inflammatory bowel disease. *Inflamm Bowel Dis.* 2014;20(12):2321-2329.

Gordon JP, McEwan PC, Maguire A, Sugrue DM, Puelles J. Characterizing unmet medical need and the potential role of new biologic treatment options in patients with ulcerative colitis and Crohn's disease: a systematic review and clinician surveys. *Eur J Gastroenterol Hepatol.* 2015;27(7);804-812.

Kopp T, Riedl E, Bangert C, Bowman EP, Greisenegger E, Horowitz A, et al. Clinical improvement in psoriasis with specific targeting of interleukin-23. *Nature.* 2015;521(7551):222-226.

Krueger JG, Ferris LK, Menter A, Wagner F, White A, Visvanathan S, et al. Anti–IL-23A mAb BI 655066 for treatment of moderate-to-severe psoriasis: safety, efficacy, pharmacokinetics, and biomarker results of a single-rising-dose, randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol.* 2015;136(1):116-124.e7.

Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol.* 1997;32(9):920-924.

Mosli MH, Feagan BG, Zou G, Sandborn WJ, D'Haens G, Khanna R, Shackelton LM, Walker CW, Nelson S, Vandervoort MK, Frisbie V, Samaan MA, Jairath V, Driman DK, Geboes K, Valasek MA, Pai RK, Lauwers GY, Riddell R, Stitt LW, Levesque BG. Development and validation of a histological index for UC. *Gut*. 2017;66(1):50-58.

Monteleone I, Pallone F, Monteleone G. Interleukin-23 and Th17 cells in the control of gut inflammation. *Mediators Inflamm.* doi: 10.1155/2009/297645. Epub 2009 May 27.

Rutgeerts P, Van Assche G, Vermeire S. Optimizing anti-TNF treatment in inflammatory bowel disease. *Gastroenterology*. 2004;126(6):1593-1610.

Sandborn WJ, Gasink C, Gao LL, Blank MA, Johanns J, Guzzo C, Sands BE, Hanauer SB, Targan S, Rutgeerts P, Ghosh S, de Villiers WJ, Panaccione R, Greenberg G, Schreiber S, Lichtiger S, Feagan BG; CERTIFI Study Group. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *N Engl J Med.* 2012;367(16):1519-1528.

Sands BE, Chen J, Penney M, Newbold P, Faggioni R, van der Merwe R, et al. 830 Initial evaluation of MEDI2070 (specific anti-IL-23 antibody) in patients with active Crohn's disease who have failed anti-TNF antibody therapy: a randomized, double-blind placebo-controlled Phase 2A induction study. *Gastroenterology.* 2015;148(4) suppl 1:S163-S164. Abstract 830.

Sofen H, Smith S, Matheson RT, Leonardi CL, Calderon C, Brodmerkel C, et al. Guselkumab (an IL-23–specific mAb) demonstrates clinical and molecular response in patients with moderate-to-severe psoriasis. *J Allergy Clin Immunol*. 2014;133(4):1032-1040.

Stelara [prescribing information]. Horsham, PA: Janssen Biotech, Inc.; 2014. Available at: *www.stelarainfo.com/pdf/PrescribingInformation.pdf. Accessed 13 July 2016.*

Vuitton L, Marteau P, Sandborn WJ, Levesque BG, Feagan B, Vermeire S, et al. IOIBD technical review on endoscopic indices for Crohn's disease clinical trials. *Gut*. 2015. doi: 10.1136/gutjnl-2015-309903. [Epub ahead of print].

12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
6-MP	6-mercaptopurine
ADA	anti-drug antibodies
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An 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.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AP	abdominal pain
ASA	aminosalicylic
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
AZA	azathioprine
blinding/masking	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.
BMC	bowel movement count
CDAI	Crohn's Disease Activity Index
CCI [redacted]	
CI	confidence interval
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.
CRF/eCRF	case report form/electronic case report form

CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CSR	clinical study report
ECG	electrocardiogram
eCOA	electronic clinical outcome assessments
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
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy–Fatigue
FCP	fecal calprotectin
GCP	good clinical practice
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	informed consent form
ICH	International Council for Harmonisation
IgG	immunoglobulin G
IL	interleukin
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.
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.

IV	intravenous
IVRS/IWRS	interactive voice-response system/interactive web-response system
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
NOAEL	no-observed-adverse-effect level
NSAIDS	nonsteroidal anti-inflammatory drugs
NRI	non-responder imputation
CCI	
PCR	polymerase chain reaction
PD	pharmacodynamics
PGRC	Patient's Global Rating of Change (Crohn's disease)
PGRS	Patient's Global Rating of Severity (Crohn's disease)
PK	pharmacokinetics
PPD	purified protein derivative
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
PRO2	Patient Reported Outcome2: a 2-item index comprised of the SF and AP items from the CDAI
PT	preferred term
Q4W	every 4 weeks
QIDS-SR16	Quick Inventory of Depressive Symptomatology–Self Report (16 Items)
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.
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF	stool frequency
SF-36	Medical Outcomes Study 36-Item Short Form Health Survey

SOC	system organ class
SUSARs	suspected unexpected serious adverse reactions
TB	tuberculosis
TBL	total bilirubin level
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, which and does not necessarily have to have a causal relationship with this treatment.
TNF	tumor necrosis factor
UC	ulcerative colitis
ULN	upper limit of normal

Appendix 2. Clinical 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 (ALP)
Monocytes	Alanine aminotransferase (ALT)
Eosinophils	Aspartate aminotransferase (AST)
Basophils	Gamma-glutamyl transferase (GGT)
Platelets	Blood urea nitrogen
Cell morphology	Creatinine
Urinalysis[a]:	Uric acid
Specific gravity	Calcium
pH	Glucose (random)
Protein	Albumin
Glucose	Total protein
Ketones	Total cholesterol
Blood	Creatine phosphokinase (CPK)
Urine leukocyte esterase	
Nitrite	

Other Tests:	
QuantiFERON-TB Gold[b] or PPD	Biopsy material
high sensitivity C-reactive protein (hsCRP)	LY3074828 concentration (PK)
Pregnancy[c]	[redacted]
Follicle-stimulating hormone (FSH)	
Human immunodeficiency virus antibody[d]	Fecal calprotectin (FCP)
Hepatitis B surface antigen[d]	Exploratory storage samples (whole blood, serum, plasma, colonic tissue, stool, RNA and DNA)
Hepatitis B surface antibody[d]	Anti-LY3074828 antibodies (immunogenicity)
Hepatitis B core antibody[d]	Clostridium difficile (C diff) [d]
Hepatitis B DNA PCR (if indicated)[e]	Hepatitis C antibody[d]
	Hepatitis C RNA PCR (if indicated)
	Hypersensitivity Markers[f]

Abbreviations: PCR = polymerase chain reaction; PK = pharmacokinetics; PPD = purified protein derivative.

[a] Unscheduled blood chemistry, hematology, & urinalysis panels may be performed at discretion of investigator as needed.

[b] Can be performed centrally or locally.

[c] Serum pregnancy test.

[d] Test required only at screening (Visit 1) to determine eligibility of subject for the study.

[e] Hepatitis B PCR testing will be performed in subjects (i) who test positive for HBsAb, HBsAg, or Hepatitis B core antibody at baseline, and (ii) at protocol-specified intervals in patients with the following HBV serology status at baseline: HBsAg-, HBcAb+, with no detectable HBV DNA at baseline.

[f] See Section 7.8.2.2

Appendix 3. Study Governance Considerations

Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 3.1.1. Informed Consent

The investigator is responsible for ensuring:

- that the subject understands the potential risks and benefits of participating in the study
- that informed consent is given by each subject or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject's willingness to continue his or her participation in the trial.

Appendix 3.1.2. Ethical Review

The investigator must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Conference on Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF and Assent Form must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on Good Clinical Practice (GCP).

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

- the current Investigator Brochure (IB) and updates during the course of the study
- informed consent form
- relevant curricula vitae

Appendix 3.1.3. Regulatory Considerations

This study will be conducted in accordance with:

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

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

Appendix 3.1.4. Investigator Information

Physicians with a specialty in gastroenterology will participate as investigators in this clinical trial.

Appendix 3.1.5. 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.

Appendix 3.1.6. Final Report Signature

The CSR coordinating investigator, selected by the sponsor, will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

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

Appendix 3.2. 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 or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Appendix 3.2.1. Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Electronic Clinical Outcome Assessments (eCOA) (for example, a rating scale) or other data reported directly by the subject (for example, event diary), or clinician (for example, tablet) are entered into an eCOA instrument (for example, personal digital assistant [PDA], tablet, or by means of IWRS) at the time that the information is obtained. In these instances where there is no prior written or electronic source data at the site, the eCOA instrument record will serve as the source.

If eCOA records are stored at a third party site, investigator sites will have continuous access to the source documents during the study and will receive an archival copy at the end of the study for retention.

Any data for which the eCOA instrument record will serve to collect source data will be identified and documented by each site in that site's study file.

Case report form data collected by a third-party will be encoded by the third-party and stored electronically in the third-party's database system. Validated data will subsequently be transferred to the sponsor's data warehouse, using standard Lilly file transfer processes.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

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.

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

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

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

Appendix 3.3.2. Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
MCV	Prothrombin Time, INR
MCHC	
WBC	**Hepatic Serologies[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
RBC morphology	Hepatitis E antibody, IgG
	Hepatitis E antibody, IgM
Hepatic Chemistry[a]	
Total bilirubin	**Anti-nuclear antibody[a]**
Direct bilirubin	
ALP	**ALP isoenzymes[a]**
ALT	
AST	**Anti-smooth muscle antibody (or anti-actin antibody)[a]**
GGT	
CPK	

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

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

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

Appendix 5. Histologic Grading Indices

RHI Score[a]

Histologic Finding	Range/Weight	Scores Allowed for Histologic Remission in CD
Chronic inflammatory infiltrate	(0-3)x1	0-3
Lamina propria neutrophils	(0-3)x2	0
Neutrophils in epithelium	(0-3)x3	0
Erosion or ulceration	(0-3)x5	0
		Max RHI = 3 as long as LP neutrophils, neutrophils in epithelium, and erosion or ulceration are 0.

Abbreviations: CD = Crohn's disease; RHI = Robarts Histologic Index.

[a] Mosli MH, Feagan BG, Zou G, Sandborn WJ, D'Haens G, Khanna R, Shackelton LM, Walker CW, Nelson S, Vandervoort MK, Frisbie V, Samaan MA, Jairath V, Driman DK, Geboes K, Valasek MA, Pai RK, Lauwers GY, Riddell R, Stitt LW, Levesque BG. Development and validation of a histological index for UC. *Gut*. 2017;66(1):50-58.

GHAS Score[a]

Histologic Finding	Range	Scores allowed for histologic remission
Epithelial damage	0-2	0
Architectural damage	0-2	0-2
Infiltration of mononuclear cells in the lamina propria	0-2	0-2
Infiltration of polymorphonuclear cells in lamina propria	0-2	0
Polymorphonuclear cells in epithelium	0-3	0
Presence of erosions and/or ulcers	0-1	0
Presence of granuloma	0-1	0-1
No. of biopsy specimens affected	0-3	0-3
		MAX GHAS = 8 as long as epithelial damage, infiltration of polymorphonuclear cells in lamina propria, polymorphonuclear cells in epithelium, and erosions/ulcers are all 0.

Abbreviation: GHAS = Global Histologic Disease Activity Score.

[a] D'Haens GR, Geboes K, Peeters M, Baert F, Penninckx F, Rutgeerts P. Early lesions of recurrent Crohn's disease caused by infusion of intestinal contents in excluded ileum. *Gastroenterology*. 1998;114(2):262-267.

Note: Minor changes to the indices above may be made without protocol amendment by including detailed description of the changes in the clinical study report.

Appendix 6. Additional Information on Systemic Drug Administration Reactions

Per investigator's judgement, in the absence of other plausible and more likely etiology, a systemic drug administration reaction is defined as the presence of any of the following symptoms (list is not exhaustive):

- Generalized urticaria or pruritus
- Angioedema at a location other than the injection site
- Throat tightness
- Difficulty swallowing/talking
- Stridor
- Chest tightness/dyspnea
- Wheeze/bronchospasm
- Hypoxemia
- Sense of impending doom
- Hypotension (systolic blood pressure change >20 mmHg from baseline)
- Syncope
- Cardiovascular collapse
- Vomiting
- Abdominal pain
- Diarrhea
- Bladder/bowel incontinence

Appendix 7. Protocol Amendment I6T MC AMAG(b) Summary: A Phase 2, Multicenter, Randomized, Parallel-Arm, Placebo-Controlled Study of LY3074828 in Subjects with Active Crohn's Disease (SERENITY)

Overview

Protocol I6T-MC-AMAG (A Phase 2, Multicenter, Randomized, Parallel-Arm, Placebo-Controlled Study of LY3074828 in Subjects with Active Crohn's Disease [SERENITY]) has been amended. The new protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

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

- Increased duration of all IV study drug administration to 2 hours. The 2-hour duration provides a rate (at the highest dose in Study AMAG) that approximates the rate being used across other mirikizumab studies.
- Addition of a 1-hour post infusion observation period to allow adequate evaluation of potential hypersensitivity or infusion related reactions.
- Added text on how to manage hypersensitivity events, including guidance on the collection of additional immunogenicity, PK, and hypersensitivity markers samples following a possible infusion related hypersensitivity event. Samples will be used to evaluate for possible etiologies of hypersensitivity reactions.
- Clarification added that patients who experience serious adverse reactions (anaphylaxis, systemic hypersensitivity event) related to an infusion are to have their investigational product discontinued.
- Clarification comments added to Schedule of Activities that additional immunogenicity, PK, and hypersensitivity markers samples may be collected in order to understand etiology of infusion related events
- Correction in Schedule of Activities that V8 is to include Days 86-92, instead of Days 85-92
- Clarification comment added to Schedule of Activities that colonoscopy/SES-CD is performed only at the early termination visit if the visit occurs 16 weeks after the last colonoscopy. Additionally, for patients who discontinue treatment but continue in the study the colonoscopy is to be performed within 4 weeks of last dose of study drug. The colonoscopy/SES-CD is not to be performed at Period 1, Period 3 or Visit 804.
- Replaced eligibility criteria of patients to proceed to Period 3 with clinical benefit as determined by the investigator. Allowing patients with a clinical benefit as determined by the investigator to proceed to Period 3 allows assessment of long-term efficacy of mirikizumab in a broad population felt to be receiving benefit.
- Clarification added that the intent of the treatment regimens is to keep the dosing within the visit windows and as close to every 4 weeks as possible.

- Appendix 6 added that provides additional information on systemic drug administration reactions.
- Appendix 2 removed Treg/TH17 from list of tests because it is not being performed in the study and added hypersensitivity markers.

Revised Protocol Sections

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

Synopsis

- Period 3 (Weeks 52 to 104): All subjects having clinical benefit per investigator and continuing on study treatment may proceed to Period 3 and receive 300 mg SC LY3074828 Q4W open-label starting at Week 52 through Week 104. ~~Clinical benefit is defined as having an endoscopic response (50% reduction from baseline in SES-CD score), or a 25% reduction from baseline in SES-CD score, combined with a 40% reduction from baseline in stool frequency (SF) or abdominal pain (AP) score.~~ Patients not receiving clinical benefit at Week 52 will discontinue treatment and will enter the Follow-Up period.

2. Schedule of Activities

Screening and Period 1 [V1–V7] Schedule of Activities								
Visit Number:	**V1** Screening	**V2** Baseline/ Randomization	**V3**	**V4**	**V5**	**V6**	**V7**	**Comments**
Week Relative to Study Drug Start	**-4**	**0**	**2**	**4**	**6**	**8**	**11-12**	All activities should be completed prior to any study drug administration unless otherwise stated below.
Visit Tolerance Interval (days)	**≤28 from V2**	**1± 3**	**15± 3**	**29 ± 3**	**43 ± 3**	**57 ± 3**	**78-85**	Visit 1 procedures may be conducted over more than 1 day as long as all tasks are completed within the allowable visit tolerance (at least 3 days should be allowed for receipt of laboratory test results).
LY3074828 PK Samples		Pre-dose and end of infusion	X	Pre-dose & end of infusion	X	Pre-dose & end of infusion	X	Additional immunogenicity, PK, and hypersensitivity markers samples may be collected. See Section 7.8.2.2.
Immunogenicity Samples		X	X	X		X	X	Additional immunogenicity, PK, and hypersensitivity markers samples may be collected. See Section 7.8.2.2.

Period 2 [V8–V18] Schedule of Activities												
Visit Number:	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**Comments**
Week Relative to Study Drug Start	**12-13**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	All activities should be completed prior to any study dose administration unless otherwise stated below.
Day with Visit Tolerance Interval	**~~85~~86-92**	**113 ± 5**	**141± 5**	**169 ± 5**	**197 ± 5**	**225 ± 5**	**253 ± 5**	**281 ± 5**	**309 ± 5**	**337 ± 5**	**365 ± 5**	
LY3074828 PK Samples	X	X	X	X	X		X		X		X	Additional immunogenicity, PK, and hypersensitivity markers samples may be collected. See Section 7.8.2.2.
Immunogenicity Samples	X	X		X			X				X	Additional immunogenicity, PK, and hypersensitivity markers samples may be collected. See Section 7.8.2.2.

Period 3 [V19–V31] Schedule of Activities														
Visit Number:	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**V30**	**V31**	**Comments**
Week Relative to Study Drug Start	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	All activities should be completed prior to any study drug administration unless otherwise stated below.
Day with Visit Tolerance Interval	**393 ± 5**	**421 ± 5**	**449 ± 5**	**477 ± 5**	**505 ± 5**	**533 ± 5**	**561 ± 5**	**589 ± 5**	**617 ± 5**	**645 ± 5**	**673 ± 5**	**701 ± 5**	**729 ± 5**	
LY3074828 PK Samples		X		X		X		X		X			X	Additional immunogenicity, PK, and hypersensitivity markers samples may be collected. See Section 7.8.2.2.
Immunogenicity Samples		X		X		X		X		X			X	Additional immunogenicity, PK, and hypersensitivity markers samples may be collected. See Section 7.8.2.2.

Unscheduled Visit / Follow-Up Period						
Visit Number:	**UV[c]**	**V801**	**V802**	**V803**	**V804/ET[a]**	**Comments**
Week Relative to Study Drug Start	**N/A**	**108**	**112**	**116**	**120**	
Visit Tolerance Interval (days)	**N/A**	**757 ± 5**	**785 ± 5**	**813 ± 5**	**841 ± 5**	
Colonoscopy/ SES-CD					X[a]	Performed only at early termination visit if the visit occurs 16 weeks after last colonoscopy. For patients who discontinue treatment but continue in the study perform colonoscopy within 4 weeks of last dose of study drug. Colonoscopy/SES-CD is not to be performed at Period 1, Period 3 or ~~not at~~ Visit 804.
LY3074828 PK Samples		X	X	X	X	Additional immunogenicity, PK, and hypersensitivity markers samples may be collected. See Section 7.8.2.2.
Immunogenicity Samples		X	X	X	X	Additional immunogenicity, PK, and hypersensitivity markers samples may be collected. See Section 7.8.2.2.

5.1 Overall design

- Period 3 (Weeks 52 to 104): All subjects ~~with~~having clinical benefit per investigator and continuing on study treatment may proceed to Period 3 and receive ~~SC~~ 300 mg SC LY3074828 Q4W open-label starting at Week 52 through Week 104. ~~Clinical benefit is defined as having an endoscopic response (50% reduction from baseline in SES-CD score), or a 25% reduction from baseline in SES-CD score, combined with a 40% reduction from baseline in stool frequency (SF) or abdominal pain (AP) score.~~ Patients not receiving clinical benefit at Week 52 will discontinue treatment and will enter the Follow-Up period.

5.4 Scientific Rationale for Study Design

Period 3 is intended to provide extension therapy for subjects considered to be demonstrating~~receiving~~ clinical benefit and will provide longer term evaluation of safety and durability of clinical benefit.

7.1 Treatments Administered

Intravenous infusion of mirikizumab or placebo will occur over at least 2 hours. All patients receiving IV infusion should be monitored for 1 hour or longer (per investigator discretion or local standard of care) after IV dosing is complete. Sites must have resuscitation equipment, emergency medications, and appropriately trained staff available during the infusion and monitoring period. Detailed instructions for investigational product administration will be provided separately by the sponsor.

Subcutaneous administration of mirikizumab or placebo will be given in 3 injections. Detailed instructions regarding supplies and preparation and handling of LY3074828 will be provided by the sponsor.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the investigational agent(s) to the site personnel
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection
- at the end of the study, returning all unused medication to Lilly, or its designee, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law.

7.8.2.2 Management of Hypersensitivity Events, Fever Associated Reactions, and Infusion/Injection Site Reactions

During and after study drug administration, patients should be closely monitored for signs or symptoms of AEs, including hypersensitivity events, other fever associated reactions and infusion or injection site reactions.

Systemic Hypersensitivity Events

If a patient experiences a systemic hypersensitivity event involving the skin or mucous membranes, respiratory, cardiovascular, gastrointestinal, or urinary systems, during or up to

6 hours after an infusion of study drug, the following guidance should be followed (see Appendix 6 for additional information):

- Study drug infusion should be stopped immediately and appropriate supportive care provided according to local standard practice (for example, administration of epinephrine, anti-histamine, systemic steroids, and/or bronchodilators).
- After the patient's stabilization, additional immunogenicity, PK, and hypersensitivity markers samples should be collected as follows:
    - As soon as possible after the event occurs
    - 4 weeks after the event
    - 12 weeks after the event
- The patient should continue to be monitored until resolution or stabilization of the symptoms, as clinically appropriate.
- Permanently discontinue the study drug after a systemic drug administration reaction.
- If the patient discontinues study drug but remains in the study, management should follow as outlined in Section 8.1.1, and immunogenicity, PK, and hypersensitivity markers should be collected at 4 and 12 weeks after the event.
- If the patient discontinues participation in the study, the patient should proceed to early termination procedures. The patient will need to return after early termination procedures for 4 and 12 week immunogenicity, PK, and hypersensitivity markers collections.
- The medical monitor should be notified as soon as feasible.

Fever-Associated Reactions

If a patient experiences a fever-associated reaction consisting of headache, rigors and/or temperature >38°C (in the absence of signs or symptoms of a systemic hypersensitivity event) during or up to 6 hours after an infusion of study drug, the following guidance should be followed:

- Study drug infusion should be interrupted and appropriate medical care should be administered (for example, nonsteroidal anti-inflammatory drugs [NSAIDS], anti-pyretics or antihistamines).
- Additional immunogenicity, PK, and hypersensitivity markers samples should be collected as follows:
    - As soon as possible after the event occurs
    - 4 weeks after the event
    - 12 weeks after the event
- Resumption of study drug infusion after interruption, possibly at a slower rate of administration, can be considered if symptoms resolve and it is deemed to be medically appropriate based on the investigator's discretion, and considering the risk/benefit of readminstration.
- Patient should remain in observation, as is clinically appropriate for the patient's symptoms.
- Premedication prior to subsequent study drug administration may be considered, if judged by the investigator to be appropriate for the individual patient.

- If the patient discontinues study drug but remain in the study, management should follow as outlined in Section 8.1.1, and immunogenicity, PK, and hypersensitivity markers should be collected at 4 and 12 weeks after the event.
- If the patient discontinues from the study early for any reason, they should return to complete 4 and 12 week follow-up immunogenicity, PK, and hypersensitivity markers collections.
- If the patient develops systemic hypersensitivity symptoms or signs, they should be managed as described above for a systemic hypersensitivity event.

Infusion Site Reactions

If a patient experiences an infusion site reaction, including urticaria, pruritus, or angioedema localized to the IV infusion site (in the absence of systemic hypersensitivity signs or symptoms), during or up to 6 hours after an infusion of study drug, the following guidance should be followed:

- Study drug infusion should be interrupted and appropriate medical care should be administered (for example, NSAIDS, anti-pyretics or antihistamines).
- Additional immunogenicity, PK, and hypersensitivity markers samples should be collected as follows:
    - As soon as possible after the event occurs
    - 4 weeks after the event
    - 12 weeks after the event
- Resumption of study drug infusion after interruption, possibly at a slower rate of administration, can be considered if symptoms resolve and it is deemed to be medically appropriate based on the investigator's discretion, and considering the risk/benefit of readminstration.
- Patient should remain in observation, as is clinically appropriate for the patient's symptoms.
- Premedication prior to subsequent study drug administration may be considered, if judged by the investigator to be appropriate for the individual patient.
- If the patient discontinues from the study early for any reason, they should return to complete 4 and 12 week follow-up immunogenicity, PK, and hypersensitivity markers collections.
- If the patient develops systemic hypersensitivity symptoms or signs, they should be managed as described above for a systemic hypersensitivity event.

Injection Site Reactions

If a patient experiences an injection site reaction, including pain, erythema, urticaria, pruritus, or angioedema localized to the SC injection site (in the absence of systemic hypersensitivity signs or symptoms), the following guidance should be followed:

- Patient should be instructed to contact the study site to report any symptoms experienced following a SC injection.

- Premedication prior to subsequent study drug administration may be considered as appropriate for the individual patient.
- If the patient develops systemic hypersensitivity symptoms, they should be managed as described above for a systemic hypersensitivity event.

~~Because of the risk of an infusion reaction with any biological agent, all subjects should be monitored 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:~~
  - ~~supportive care should be employed in accordance with the symptoms or signs~~
  - ~~if slowed or stopped, the infusion may be continued in accordance with signs and symptoms at the investigator's discretion.~~

~~All biological agents carry the risk of an injection site and/or hypersensitivity general reaction. Therefore, all subjects should be closely monitored for signs or symptoms that could result from such reactions. Sites should have appropriately trained medical staff and appropriate medical equipment available when subjects are receiving study drug. If a subject experiences an acute hypersensitivity reaction after an injection of study drug, he or she should receive appropriate supportive care and consideration for any premedication; future injections will be agreed upon between the investigator and sponsor.~~

8.1.1 Permanent Discontinuation from Study Treatment

Subjects may discontinue treatment for any of the reasons noted above, or for other reasons such as the development of a serious adverse event. To better communicate patient flow throughout the study, different study period situations are provided below:

- Subjects who discontinue the investigational product in Period 1 or Period 2 may continue in the study according to the visit schedule (Section 2).
- At Week 52/Visit 18, subjects who have previously discontinued the investigational product will continue to Visit 801 of the Follow-up Period.
- Subjects who discontinue the investigational product in Period 3 may continue in Period 3 and then proceed to Week 104/Visit 801 of the Follow-up Period.

Investigational product is to be discontinued for patients who experience clinically significant systemic hypersensitivity events (such as anaphylaxis) following administration of investigational product.

Appendix 1 Abbreviations and Definitions

NSAIDS	nonsteroidal anti-inflammatory drugs

Appendix 2 Clinical Laboratory Tests

Other Tests:	
~~Treg/Th17~~	Biopsy material
QuantiFERON-TB Gold[b] or PPD	LY3074828 concentration (PK)
high sensitivity C-reactive protein (hsCRP)	CCI
Pregnancy[c]	
CCI	Fecal calprotectin (FCP)
Human immunodeficiency virus antibody[d]	Exploratory storage samples (whole blood, serum, plasma, colonic tissue, stool, RNA and DNA)
Hepatitis B surface antigen[d]	
Hepatitis B surface antibody[d]	Anti-LY3074828 antibodies (immunogenicity)
Hepatitis B core antibody[d]	Clostridium difficile (C diff) [d]
Hepatitis B DNA PCR (if indicated)[e]	Hepatitis C antibody[d]
	Hepatitis C RNA PCR (if indicated)
	Hypersensitivity Markers[f]

Abbreviations: PCR = polymerase chain reaction; PK = pharmacokinetics; PPD = purified protein derivative~~;~~ ~~Treg/Th17 = T-regulatory/T-helper 17 cells~~.

[f] See Section 7.8.2.2.

Appendix 6 Additional Information on Systemic Drug Administration Reactions

Per investigator's judgement, in the absence of other plausible and more likely etiology, a systemic drug administration reaction is defined as the presence of any of the following symptoms (list is not exhaustive):

- Generalized urticaria or pruritus
- Angioedema at a location other than the injection site
- Throat tightness
- Difficulty swallowing/talking
- Stridor
- Chest tightness/dyspnea
- Wheeze/bronchospasm
- Hypoxemia
- Sense of impending doom
- Hypotension (systolic blood pressure change >20 mmHg from baseline)
- Syncope
- Cardiovascular collapse
- Vomiting
- Abdominal pain
- Diarrhea
- Bladder/bowel incontinence

Appendix ~~6~~7 Protocol Amendment I6T-MC-AMAG(~~a~~b) Summary

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