Protocol I6T-MC-AMAP
A Phase 3, Multicenter, Open-Label Extension Study to Evaluate the Long-Term Efficacy and Safety of Mirikizumab in Patients with Moderately to Severely Active Ulcerative Colitis
LUCENT 3

EUDRA CTA: 2017-004092-31

Confidential Information

Mirikizumab (LY3074828)

Eli Lilly and Company
Indianapolis, Indiana USA 46285

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

Approval Date: 15-Mar-2018 GMT

Table of Contents

Section **Page**

List of Tables

Table **Page**

List of Figures

Figure **Page**

List of Appendices

1. Synopsis

Title of Study:
A Phase 3, Multicenter, Open-Label Extension Study to Evaluate the Long-Term Efficacy and Safety of Mirikizumab in Patients with Moderately to Severely Active Ulcerative Colitis

Rationale:
Mirkizumab (LY3074828) is a humanized immunoglobulin G4 (IgG4) monoclonal antibody that binds to the p19 subunit of interleukin-23 (IL-23), a cytokine that has been implicated in mucosal inflammation in ulcerative colitis (UC). Study I6T-MC-AMAP (AMAP) is a Phase 3 open-label clinical study designed to evaluate the long-term efficacy and safety of mirikizumab in treating patients from the Phase 2 study, I6T-MC-AMAC (AMAC) and the Phase 3 maintenance study I6T-MC-AMBG (AMBG) who meet all of the AMAP inclusion criteria and none of the exclusion criteria.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary objective To evaluate the long-term efficacy of mirikizumab in the following cohort: Cohort 1: Patients from AMBG who completed Week 40 visit on blinded SC mirikizumab	The proportion of patients in clinical remission at Week 52
Efficacy To evaluate the long-term efficacy of mirikizumab in the following cohort: Cohort 1: Patients from AMBG who completed Week 40 visit on blinded SC mirikizumab	• The proportion of patients in clinical remission at Week 100 or Week 160 • The proportion of patients in endoscopic remission at Week 52, Week 100 or Week 160 • The proportion of patients with endoscopic subscore = 0 (ES=0) at Week 52, Week 100 or Week 160 • Stool frequency and rectal bleeding subscores over time • The proportion of patients in corticosteroid-free remission at Week 52, Week 100 or Week 160 • Among patients entering the AMAP study not on corticosteroids, the time to first use of corticosteroids for UC • Dose of corticosteroid used at Week 52, Week 100 or Week 160
Efficacy To evaluate the long-term efficacy of mirikizumab in the following groups of patients: Cohort 2: Cohort 1 **and** AMAC patients who completed the Maintenance Period Week 52 visit on SC mirikizumab Cohort 3: The remaining patients (those not in Cohort 2)	• The proportion of patients in clinical remission at Week 52, Week 100 or Week 160 • The proportion of patients in endoscopic remission at Week 52, Week 100 or Week 160 • The proportion of patients with ES = 0 at Week 52, Week 100 or Week 160 • Stool frequency and rectal bleeding subscores over time • Among the patients who enter the AMAP study on corticosteroids, the proportion in corticosteroid-free remission at Week 52, Week 100 or Week 160

To evaluate the effect of long term mirikizumab therapy on histologic remission (mucosal healing) in the following cohorts: Cohort 1: Patients from AMBG who completed Week 40 visit on blinded SC mirikizumab Cohort 2: Cohort 1 **and** AMAC patients who completed the maintenance period Week 52 visit on SC mirikizumab	• The proportion of patients in histologic remission at Week 52, Week 100 or Week 160, as defined in the histopathology charter
Health Outcomes To evaluate the long-term effect of mirikizumab on health outcomes in the following cohort: Cohort 1: Patients from AMBG who completed Week 40 visit on blinded SC mirikizumab	• IBDQ scores over time • The proportion of patients who are hospitalized due to UC over time • The proportion of patients who undergo UC surgeries including colectomy over time

Abbreviations: AMAC = Study I6T-MC-AMAC; AMBG = Study I6T-MC-AMBG; ES = endoscopic subscore; IBDQ = Inflammatory Bowel Disease Questionnaire; SC = subcutaneous; UC = ulcerative colitis.

Note: Clinical remission is defined as SF subscore = 0 or SF = 1 with a ≥1-point decrease from induction baseline, and RB subscore = 0, and ES = 0 or 1 (excluding friability). Endoscopic remission is defined as ES = 0 or 1 (excluding friability). For those entering Study AMAP on concomitant corticosteroids, corticosteroid-free remission is defined as clinical remission, and no corticosteroid use for at least 12 weeks prior to Week 52, Week 100, or Week 160.

Summary of Study Design:

Study AMAP is a single-arm, outpatient, open-label, Phase 3, multicenter, long-term extension study evaluating the efficacy and safety of mirikizumab in patients with moderately to severely active UC who have participated in an originator mirikizumab UC study, including, but not limited to, the Phase 2 Study AMAC and the Phase 3 Study AMBG. Patients will receive open-label mirikizumab subcutaneously for an extended period of time (up to 3 years) and then enter a 12-week post-treatment follow-up period.

Patients who meet all of the inclusion criteria and none of the exclusion criteria, and who, in the opinion of the investigator, would receive benefit from open-label treatment with mirikizumab are eligible for enrollment into Study AMAP. It is possible that some patients enrolling from Study AMBG or Study AMAC may have received placebo only in the originating study. These patients will receive mirikizumab for the first time in Study AMAP.

Eligible patients should enter at the time of their last visit of the originating study (unless an endoscopy is performed on that day) or within approximately 4 weeks of the last visit of the originator study. Patients requiring a longer duration for study entry will be discussed on an individual patient basis with the Sponsor.

Treatment Arms and Duration: All patients participating in Study AMAP will receive 200 mg mirikizumab subcutaneously every 4 weeks beginning with a dose at Week 0 of Study AMAP.

Duration of Treatment: The planned maximum duration of treatment for each patient is 3 years, until the patient discontinues from the study, or until mirikizumab is commercially available in the country in which the patient resides, whichever occurs first.

Lead-in or Washout Period: There is no lead-in or washout period. Patients from Study AMBG will be eligible to enroll into StudyAMAP after completing the Week 40 visit or early termination visit for those receiving intravenous (IV) rescue for loss of response (LOR). Patients should not begin AMAP on the same day of endoscopy from their originator study. Patients from Study AMAC will be eligible to enroll in Study AMAP any time after completing the AMAC maintenance period Week 52 or extension period maintenance Week 40 efficacy assessments, including endoscopy.

Treatment Period: 3 years maximum for each patient.

Post-treatment Follow-up Period: All patients, whether they discontinue the study early for any reason or they complete mirikizumab treatment in Study AMAP, will enter the 12-week Post-treatment Follow-up Period.

Number of Patients:

The final sample size of Study AMAP will be determined by the number of patients who enroll in Study AMAP from the preceding studies. From Study AMAC and Study AMBG, it is anticipated that approximately 50% to 70% of the eligible patients will enroll leading to approximately 600 to 840 patients from these 2 studies in Study AMAP.

Statistical Analysis:

For all safety, efficacy and health outcomes analyses, the modified intent-to-treat (mITT) population will be used unless otherwise stated. The mITT population includes all enrolled patients who receive at least one dose of study medication in Study AMAP. Sensitivity analysis will be conducted on intent-to-treat (ITT) and per protocol (PP) populations for the primary efficacy endpoint.

Study AMAP will include the following 3 patient cohorts; additional cohorts may be defined in the SAP:

1. Cohort 1: Patients from AMBG who completed Week 40 visit on blinded subcutaneous (SC) mirikizumab treatment
2. Cohort 2: Cohort 1 **and** patients from Study AMAC who completed the Maintenance Period Week 52 visit on SC mirikizumab treatment
3. Cohort 3: All remaining patients, that is:
    - Patients from Study AMAC who:
        a. completed the Maintenance Period Week 52 visit on SC placebo treatment **or**

b. completed the Week 40 visit of the unblinded Extension Period Maintenance dosing on SC mirikizumab treatment

AND

- Patients from AMBG who:

  a. Completed Week 40 visit on blinded SC placebo treatment **or**
  b. Lost response between Weeks 12 and 28, were rescued with 3 blinded IV rescue doses and were then considered to have clinical benefit, **or**
  c. Received extended induction treatment and completed Week 40 visit on open-label SC mirikizumab

All efficacy analyses including health outcome endpoints will be conducted separately in patients of cohorts (1), (2), and (3). All safety analyses will be conducted on all patients in Study AMAP.

Unless otherwise specified, all references to baseline for efficacy and health outcomes-related endpoints in this study protocol refer to baseline values of the originating induction study (that is, the study in which the patient received their first dose for this program). All references to baseline for safety, vital sign and laboratory-related endpoints refer to the baseline of Study AMAP.

This is an open label extension study with only one treatment arm; therefore, the analyses and summaries will be focused on point estimates and confidence intervals. There is no multiplicity adjustment planned for any analysis in this trial.

For assessment of categorical efficacy and health outcome endpoints, the single proportion will be summarized. The 95% confidence intervals may also be reported using the Wilson Score method (Wilson 1927, Newcombe 1998) and the normal approximation to the binomial distribution (Wald and Walfowitz 1939) as supportive to the Wilson Score method. Categorical repeated measure analyses such as generalized linear model will be explored for selected endpoints. Missing data will be imputed using an NRI method, which means that patients will be considered a nonresponder if they do not meet the categorical response criteria, have missing clinical response data at a time point of interest, or take rescue medication prior to the time point of interest.

For continuous efficacy and health outcome variables with multiple post-baseline measurements, the mean response over time will be estimated using mixed-effects model for repeated measures (MMRM). The model includes induction baseline value, visit, parent study ID (if multiple parent studies involved), and geographic region (North America, Europe or Other). If data has one single postbaseline measurement, the MMRM will reduce to analysis of covariance (ANCOVA) with the same covariates in the MMRM model except for visit in the model. There will be no missing data imputation in the MMRM/ANCOVA model.

Additional sensitivity analyses, including additional methods of handling missing data, which may be required to satisfy regulatory needs will be specified in the SAP or performed as post-hoc analyses.

Safety data, including treatment-emergent adverse events (TEAEs), AESIs, SAEs, laboratory analytes (chemistry, hematology, etc.), and vital signs will be descriptively summarized. Continuous safety data including vital sign and laboratory values for the change from baseline to last observation value will be analyzed by an ANCOVA model with baseline as a covariate, unless otherwise specified. Also, laboratory analytes will be presented as mean changes from baseline and as incidence of shift between normal and abnormal states.

2. Schedule of Activities

Table AMAP.2.1. Schedule of Activities

Protocol I6T-MC-AMAP, First Year

Procedure	Year 1															Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**		
Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**		
O = Office, P = Phone (Visit)	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**P**	**O**	
Day and/or Visit Interval Tolerance	**1**+28	**29** ±7	**57** ±7	**85** ±7	**113** ±7	**141** ±7	**169** ±7	**197** ±7	**225** ±7	**253** ±7	**281** ±7	**309** ±7	**337** ±7	**360** ±7	**365** ±7	
Informed consent	X															See Appendix 3.
Inclusion/exclusion criteria	X															May begin at originator study last visit; reassess prior to dosing. See Section 6.
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X		X	When Visit 1 occurs on the same day as last visit of the originating study, this procedure is not repeated.
Review AEs	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Tobacco/nicotine use	X														X	
Provide 7-day diary													X			Patient should record SF, RB, AP and urgency data for 7 days prior to bowel prep
Remind patient to fill in diary and when to take bowel prep														X		
IP Administration																
Open-label SC dosing	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Physical Examination																
Vital signs (T, BP, PR)	X	X	X	X			X				X				X	When Visit 1 occurs on the same day as last visit of the originating study, this procedure is not repeated.
Weight	X			X											X	
Physical examination	X			X											X	
Evaluate for EIMs	X			X			X								X	

Procedure	Year 1															Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**		
Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**		
O = Office, P = Phone (Visit)	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**P**	**O**	
Day and/or Visit Interval Tolerance	**1**+28	**29** ±7	**57** ±7	**85** ±7	**113** ±7	**141** ±7	**169** ±7	**197** ±7	**225** ±7	**253** ±7	**281** ±7	**309** ±7	**337** ±7	**360** ±7	**365** ±7	
12-Lead ECG	X															
TB Evaluation	X															
Laboratory Investigations																
Urine pregnancy test	X	X	X	X	X	X	X	X	X	X	X	X	X		X	Only in women of childbearing potential. Done locally and prior to dosing.
HBV DNA[a]	X			X			X				X				X	For patients who were previously anti-HBc+. See Section 9.4.5.3.
Hematology	X			X			X				X				X	If interval between last visit in originator study and Week 0 visit is more than 2 weeks, a new sample must be obtained at Week 0.
Chemistry	X			X			X				X				X	
FSH (optional)[b]	X														X	Optional, to confirm post-menopausal status in women ≥50 with amenorrhea for >1 year.

Procedure	Year 1															Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**		
Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**		
O = Office, P = Phone (Visit)	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**P**	**O**	
Day and/or Visit Interval Tolerance	**1**+28	**29** ±7	**57** ±7	**85** ±7	**113** ±7	**141** ±7	**169** ±7	**197** ±7	**225** ±7	**253** ±7	**281** ±7	**309** ±7	**337** ±7	**360** ±7	**365** ±7	
PK assessment	X			X			X								X	Serum for PK assessment and mirikizumab assay development. Patients with potential hypersensitivity event should have sample taken as soon as possible after event occurs, and 4 and 12-16 weeks after the event. If interval between originator study last visit and Week 0 visit is more than 2 weeks, a new sample must be obtained at Week 0. See Section 9.5
ADA assessment	X			X			X								X	Patients with potential hypersensitivity event should have sample taken as soon as possible after event occurs, and 4 and 12-16 weeks after the event. If interval between originator study last visit and Week 0 visit is more than 2 weeks, a new sample must be obtained at Week 0. See Section 9.4.4

Procedure	Year 1															Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**		
Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**		
O = Office, P = Phone (Visit)	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**P**	**O**	
Day and/or Visit Interval Tolerance	**1**+28	**29** ±7	**57** ±7	**85** ±7	**113** ±7	**141** ±7	**169** ±7	**197** ±7	**225** ±7	**253** ±7	**281** ±7	**309** ±7	**337** ±7	**360** ±7	**365** ±7	
Additional Patient-Reported Tests																
C-SSRS, Self-Harm Supplement Form, and Self-Harm "Follow-Up" Form	X															
QIDS-SR16	X			X			X								X	
Stool Samples																
PRN *C. difficile* testing	Xa															May be performed at any visit at investigator's discretion to assess disease exacerbation. Additional local stool testing (eg, ova and parasites) is allowed at the investigator's discretion.
Endoscopic Procedure																
Endoscopy with biopsies	X														X	May be either flexible sigmoidoscopy or colonoscopy if needed for evaluation of ulcerative colitis activity and/or colorectal cancer surveillance (Section 9.1.3).
PRN Endoscopy	Xa															May be performed at any visit at the investigator's discretion to assess disease exacerbation.

Procedure	Year 1															Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**		
Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**		
O = Office, P = Phone (Visit)	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**P**	**O**	
Day and/or Visit Interval Tolerance	**1**+28	**29** ±7	**57** ±7	**85** ±7	**113** ±7	**141** ±7	**169** ±7	**197** ±7	**225** ±7	**253** ±7	**281** ±7	**309** ±7	**337** ±7	**360** ±7	**365** ±7	
UC Activity Assessments																
Collect SF, RB, urgency and AP Data	X	X	X	X	X	X	X	X	X	X	X	X	X		X	When Visit 1 occurs on the same day as last visit of the originating study, this procedure is not repeated.
PGA	X						X								X	
Calculate and review Modified Mayo Score															X	Use endoscopic subscore provided by central reader.
Health Outcome Assessment																
IBDQ	X						X								X	Can use AMAC or AMBG study data so long as it is within 4 weeks of AMAP V1.

Abbreviations: ADA = antidrug antibody; AE = adverse event; AP = abdominal pain; BP = blood pressure; C-SSRS = Columbia–Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EIM = extraintestinal manifestation; FSH = follicle stimulating hormone; HBc = hepatitis B core antibody; HBV = hepatitis B virus; IBDQ = Inflammatory Bowel Disease Questionnaire; O = Office visit; P = Phone visit; PGA = Physician's Global Assessment; PK = pharmacokinetic; PR = pulse rate; PRN = as needed; QIDS-SR16 = Quick Inventory of Depressive Symptomatology—Self-Report (16 Items); SC = subcutaneous; RB = rectal bleeding; SF = stool frequency; T = temperature; TB = tuberculosis; UC = ulcerative colitis.

Notes: Study Week 0 procedures may be done at last visit of originating study (ensuring data are entered into the Study AMAP data capture system). If not performed at last visit of originator study then it may be required to be performed at Week 0. See Notes section of applicable row for details. All activities should be completed prior to any study drug administration unless otherwise stated.

[a] Performed on a subset of study patients as described in the Notes column of the applicable row.

[b] Tests will be run from the "chemistry" sample if collected in the same visit, otherwise a separate draw may be necessary.

Protocol I6T-MC-AMAP, Year 2

Procedure			Year 2												Notes
Visit	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**		**27**	
Week	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**		**104**	
O=Office Visit, P=Phone Visit	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**P**	**O**	**O**	
Day and/or Visit Interval Tolerance	**393 ±7**	**421 ±7**	**449 ±7**	**477 ±7**	**505 ±7**	**533 ±7**	**561 ±7**	**589 ±7**	**617 ±7**	**645 ±7**	**673 ±7**	**694 ±7**	**701 ±7**	**729 ±7**	
Review Inclusion/Exclusion Criteria for Continuing Eligibility	X														
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X		X	X	
Review AEs	X	X	X	X	X	X	X	X	X	X	X		X	X	
Tobacco/Nicotine Use													X		
Provide 7-day diary											X				Patient should record SF, RB, AP and urgency data for 7 days prior to bowel prep
Remind patient to fill in diary and when to take bowel prep												X			
IP Administration															
Open-label SC dosing	X	X	X	X	X	X	X	X	X	X	X		X	X	
Physical Examination															
Vital signs (T, BP, PR)			X			X			X				X		
Weight													X		
Physical examination													X		
TB Evaluation	X														
Evaluate for EIMs						X							X		
Laboratory Investigations															
Urine pregnancy test	X	X	X	X	X	X	X	X	X	X	X		X	X	Only in women of childbearing potential. Done locally and prior to dosing.

Procedure			Year 2											Notes
Visit	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	
Week	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	
O=Office Visit, P=Phone Visit	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**P**	**O**	**O**
Day and/or Visit Interval Tolerance	**393 ±7**	**421 ±7**	**449 ±7**	**477 ±7**	**505 ±7**	**533 ±7**	**561 ±7**	**589 ±7**	**617 ±7**	**645 ±7**	**673 ±7**	**694 ±7**	**701 ±7**	**729 ±7**	
HBV DNA[a]			X			X			X				X		For patients who were previously anti-HBc+. See Section 9.4.5.3.
Hematology						X							X		
Chemistry						X							X		
FSH (optional)[b]	X	X	X	X	X	X	X	X	X	X	X		X	X	Optional, to confirm postmenopausal status in women ≥50 with amenorrhea for >1 year.
PK assessment						X							X		Serum for PK assessment and mirikizumab assay development. Patients with potential hypersensitivity event should have sample taken as soon as possible after event occurs, and 4 and 12-16 weeks after the event.
ADA assessment						X							X		Patients with potential hypersensitivity event should have sample taken as soon as possible after event occurs, and 4 and 12-16 weeks after the event.

Procedure			Year 2												Notes
Visit	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**		**27**	
Week	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**		**104**	
O=Office Visit, P=Phone Visit	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**P**	**O**	**O**	
Day and/or Visit Interval Tolerance	**393 ±7**	**421 ±7**	**449 ±7**	**477 ±7**	**505 ±7**	**533 ±7**	**561 ±7**	**589 ±7**	**617 ±7**	**645 ±7**	**673 ±7**	**694 ±7**	**701 ±7**	**729 ±7**	
Additional Patient-Reported Test															
QIDS-SR16						X							X		
Stool Samples															
PRN *C. difficile* testing	Xa														May be performed at any visit at the investigator's discretion to assess disease exacerbation. Additional local stool testing (eg, ova and parasites) is allowed at the investigator's discretion.
Endoscopic Procedure															
Endoscopy with biopsies													X		May be either flexible sigmoidoscopy or colonoscopy if needed for colorectal cancer surveillance (Section 9.1.3).
PRN Endoscopy	Xa														May be performed at any visit at the investigator's discretion to assess disease exacerbation.
UC Activity Assessments															
Collect SF, RB, AP, and urgency Data	X	X	X	X	X	X	X	X	X	X	X		X	X	
PGA						X							X		

Procedure			Year 2												Notes
Visit	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**		**27**	
Week	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**		**104**	
O=Office Visit, P=Phone Visit	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**P**	**O**	**O**	
Day and/or Visit Interval Tolerance	**393 ±7**	**421 ±7**	**449 ±7**	**477 ±7**	**505 ±7**	**533 ±7**	**561 ±7**	**589 ±7**	**617 ±7**	**645 ±7**	**673 ±7**	**694 ±7**	**701 ±7**	**729 ±7**	
Calculate and review Modified Mayo Score													X		Use endoscopic subscore provided by central reader.
Health Outcome Assessment															
IBDQ						X							X		

Abbreviations: ADA = antidrug antibody; AE = adverse event; AP = abdominal pain; DNA = deoxyribonucleic acid; FSH = follicle stimulating hormone; HBc = hepatitis B core antibody; HBV = hepatitis B virus; IBDQ = Inflammatory Bowel Disease Questionnaire; O = Office visit; P = Phone visit; PGA = Physician's Global Assessment; PK = pharmacokinetic; PRN = as needed; QIDS-SR16 = Quick Inventory of Depressive Symptomatology—Self-Report (16 Items); RB = rectal bleeding; SC = subcutaneous; SF = stool frequency; T = temperature; TB = tuberculosis; UC = ulcerative colitis.

Notes: All activities should be completed prior to any study drug administration unless otherwise stated.

[a] Performed on a subset of patients as described in Notes column of applicable row.

[b] Tests will be run from the "chemistry" sample if collected in the same visit, otherwise a separate draw may be necessary.

Protocol I6T-MC-AMAP, Year 3

Procedure	Year 3															ETV / UV		Post-Treatment (Safety) Follow-up		Notes
Visit	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41 LV**		**N/A**	**997**	**801**	**802**	
Week	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**	**160**		**ETV**	**UV[a]**	**LV+4 weeks**	**LV +12 weeks**	
O = Office Visit P = Phone Visit	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**P**	**O**	**O**	**O**	**O**	**O**	
Day and/or Visit Interval Tolerance	**757 ±7**	**785 ±7**	**813 ±7**	**841 ±7**	**869 ±7**	**897 ±7**	**925 ±7**	**953 ±7**	**981 ±7**	**1009 ±7**	**1037 ±7**	**1065 ±7**	**1093 ±7**	**1115 ±7**	**1121 ±7**	**N/A**	**N/A**	**1149 ±7**	**1205 ±7**	
Review Inclusion/ Exclusion Criteria for Continuing Eligibility	X																			
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	
Review AEs	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	
Tobacco/ Nicotine Use															X	X	X			
Provide 7-day paper diary													X							Patient should record SF, RB, AP, and urgency data for 7 days prior to bowel prep

Procedure	Year 3															ETV / UV		Post-Treatment (Safety) Follow-up		Notes
Visit	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41 LV**		**N/A**	**997**	**801**	**802**	
Week	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**	**160**		**ETV**	**UV[a]**	**LV+4 weeks**	**LV +12 weeks**	
O = Office Visit P = Phone Visit	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**P**	**O**	**O**	**O**	**O**	**O**	
Day and/or Visit Interval Tolerance	**757 ±7**	**785 ±7**	**813 ±7**	**841 ±7**	**869 ±7**	**897 ±7**	**925 ±7**	**953 ±7**	**981 ±7**	**1009 ±7**	**1037 ±7**	**1065 ±7**	**1093 ±7**	**1115 ±7**	**1121 ±7**	**N/A**	**N/A**	**1149 ±7**	**1205 ±7**	
Remind patient to fill in diary and when to take bowel prep														X						
IP Administration																				
Open-label SC dosing	X	X	X	X	X	X	X	X	X	X	X	X	X							
Physical Examination																				
Vital signs (T, BP, PR)		X			X			X			X				X	X	X			
Weight															X	X				
Physical examination															X	X				
TB Evaluation	X																			
Evaluate for EIMs					X						X				X	X	X			

Procedure	Year 3															ETV / UV		Post-Treatment (Safety) Follow-up		Notes
Visit	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41 LV**		**N/A**	**997**	**801**	**802**	
Week	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**	**160**		**ETV**	**UV[a]**	**LV+4 weeks**	**LV +12 weeks**	
O = Office Visit P = Phone Visit	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**P**	**O**	**O**	**O**	**O**	**O**	
Day and/or Visit Interval Tolerance	**757 ±7**	**785 ±7**	**813 ±7**	**841 ±7**	**869 ±7**	**897 ±7**	**925 ±7**	**953 ±7**	**981 ±7**	**1009 ±7**	**1037 ±7**	**1065 ±7**	**1093 ±7**	**1115 ±7**	**1121 ±7**	**N/A**	**N/A**	**1149 ±7**	**1205 ±7**	
Laboratory Investigations																				
Urine pregnancy test	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	Only in women of childbearing potential. Done locally and prior to dosing.
HBV DNA[b]		X			X			X			X				X	X			X	For patients who were previously anti-HBc+. See Section 9.4.5.3.
Hematology					X						X				X	X	X			X	
Chemistry					X						X				X	X	X			X	
FSH (optional)[c]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		Optional, to confirm post-menopausal status in women ≥50 with amenorrhea for >1 year.

Procedure	Year 3															ETV / UV		Post-Treatment (Safety) Follow-up		Notes
Visit	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41 LV**		**N/A**	**997**	**801**	**802**	
Week	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**	**160**		**ETV**	**UV[a]**	**LV+4 weeks**	**LV +12 weeks**	
O = Office Visit P = Phone Visit	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**P**	**O**	**O**	**O**	**O**	**O**	
Day and/or Visit Interval Tolerance	**757 ±7**	**785 ±7**	**813 ±7**	**841 ±7**	**869 ±7**	**897 ±7**	**925 ±7**	**953 ±7**	**981 ±7**	**1009 ±7**	**1037 ±7**	**1065 ±7**	**1093 ±7**	**1115 ±7**	**1121 ±7**	**N/A**	**N/A**	**1149 ±7**	**1205 ±7**	**Notes**
PK assessment					X						X				X	X	X		X	Serum for PK assessment and mirikizumab assay development. Patients with potential hypersensitivity event should have sample taken as soon as possible after event occurs, and 4 and 12-16 weeks after the event.

Procedure	Year 3															ETV / UV		Post-Treatment (Safety) Follow-up		Notes
Visit	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41 LV**		**N/A**	**997**	**801**	**802**	
Week	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**	**160**		**ETV**	**UV[a]**	**LV+4 weeks**	**LV +12 weeks**	
O = Office Visit P = Phone Visit	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**P**	**O**	**O**	**O**	**O**	**O**	
Day and/or Visit Interval Tolerance	**757 ±7**	**785 ±7**	**813 ±7**	**841 ±7**	**869 ±7**	**897 ±7**	**925 ±7**	**953 ±7**	**981 ±7**	**1009 ±7**	**1037 ±7**	**1065 ±7**	**1093 ±7**	**1115 ±7**	**1121 ±7**	**N/A**	**N/A**	**1149 ±7**	**1205 ±7**	**Notes**
ADA assessment					X						X				X	X	X		X	Patients with potential hypersensitivity event should have sample taken as soon as possible after event occurs, and 4 and 12-16 weeks after the event.
Additional Patient-Reported Test																				
QIDS-SR16					X			X							X	X				

Procedure	Year 3															ETV / UV		Post-Treatment (Safety) Follow-up		Notes
Visit	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41 LV**		**N/A**	**997**	**801**	**802**	
Week	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**	**160**		**ETV**	**UV[a]**	**LV+4 weeks**	**LV +12 weeks**	
O = Office Visit P = Phone Visit	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**P**	**O**	**O**	**O**	**O**	**O**	
Day and/or Visit Interval Tolerance	**757 ±7**	**785 ±7**	**813 ±7**	**841 ±7**	**869 ±7**	**897 ±7**	**925 ±7**	**953 ±7**	**981 ±7**	**1009 ±7**	**1037 ±7**	**1065 ±7**	**1093 ±7**	**1115 ±7**	**1121 ±7**	**N/A**	**N/A**	**1149 ±7**	**1205 ±7**	**Notes**
Stool Samples																				
PRN *C. difficile* testing	X[b]																			May be performed at any visit at the investigator's discretion to assess disease exacerbation. Additional local stool testing (eg, ova & parasites) is allowed at the investigator's discretion.

Procedure	Year 3															ETV / UV		Post-Treatment (Safety) Follow-up		Notes
Visit	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41 LV**		**N/A**	**997**	**801**	**802**	
Week	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**	**160**		**ETV**	**UV[a]**	**LV+4 weeks**	**LV +12 weeks**	
O = Office Visit P = Phone Visit	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**P**	**O**	**O**	**O**	**O**	**O**	
Day and/or Visit Interval Tolerance	**757 ±7**	**785 ±7**	**813 ±7**	**841 ±7**	**869 ±7**	**897 ±7**	**925 ±7**	**953 ±7**	**981 ±7**	**1009 ±7**	**1037 ±7**	**1065 ±7**	**1093 ±7**	**1115 ±7**	**1121 ±7**	**N/A**	**N/A**	**1149 ±7**	**1205 ±7**	**Notes**
Endoscopic Procedure																				
Endoscopy with biopsies															X	X				May be either flexible sigmoidoscopy or colonoscopy if needed for colorectal cancer surveillance (Section 9.1.3). Pregnant females **will not** undergo an endoscopy at the ETV (see Section 9.1.3)
PRN Endoscopy	X[b]																			May be performed at any visit at the investigator's discretion to assess disease exacerbation.

Procedure	Year 3															ETV / UV		Post-Treatment (Safety) Follow-up		Notes
Visit	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41 LV**		**N/A**	**997**	**801**	**802**	
Week	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**	**160**		**ETV**	**UV[a]**	**LV+4 weeks**	**LV +12 weeks**	
O = Office Visit P = Phone Visit	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**P**	**O**	**O**	**O**	**O**	**O**	
Day and/or Visit Interval Tolerance	**757 ±7**	**785 ±7**	**813 ±7**	**841 ±7**	**869 ±7**	**897 ±7**	**925 ±7**	**953 ±7**	**981 ±7**	**1009 ±7**	**1037 ±7**	**1065 ±7**	**1093 ±7**	**1115 ±7**	**1121 ±7**	**N/A**	**N/A**	**1149 ±7**	**1205 ±7**	
UC Activity Assessments																				
Collect SF, RB, urgency, and AP Data	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X			
PGA					X										X	X	X			
Calculate and review Modified Mayo Score															X					Use endoscopic subscore provided by central reader.
Health Outcome Assessment																				
IBDQ					X										X	X	X			

Abbreviations: ADA = antidrug antibody; AE = adverse event; AP = abdominal pain; DNA = deoxyribonucleic acid; ETV = Early Termination Visit; FSH = follicle stimulating hormone; HBc = hepatitis B core antibody; HBV = hepatitis B virus; IBDQ = Inflammatory Bowel Disease Questionnaire; LV = Last visit; O = Office visit; P = Phone visit; PGA = Physician's Global Assessment; PK = pharmacokinetic; PRN = as needed; QIDS-SR16 = Quick Inventory of Depressive Symptomatology—Self-Report (16 Items); RB = rectal bleeding; SF = stool frequency; T = temperature; TB = tuberculosis; UC = ulcerative colitis; UV = Unscheduled Visit.

Notes: All activities should be completed prior to any study drug administration unless otherwise stated.

[a] Patients who are seen by the investigator or site staff at a time point not required by the protocol (ie, an unscheduled visit) due to disease exacerbation.

[b] Performed in a subset of study patients as described in Notes column of the applicable row.

[c] Tests will be run from the "chemistry" sample if collected in the same visit, otherwise a separate draw may be necessary.

3. Introduction

3.1. Study Rationale

Mirikizumab (LY3074828) is a humanized immunoglobulin G4 (IgG4) monoclonal antibody that binds to the p19 subunit of interleukin-23 (IL-23), a cytokine that has been implicated in mucosal inflammation. Study I6T-MC-AMAP (AMAP) is a Phase 3 open-label clinical study designed to evaluate the long-term efficacy and safety of mirikizumab in patients with moderately to severely active ulcerative colitis (UC). Patients who have completed their participation in the Phase 2 Study I6T-MC-AMAC (AMAC) or the Phase 3 Study I6T-MC-AMBG (AMBG) are eligible for enrollment into Study AMAP. Patients from future mirikizumab UC studies may also be eligible for Study AMAP.

3.2. Background

3.2.1. Disease State and Treatment Goals

Ulcerative colitis is a chronic disease of unknown etiology that is characterized by inflammation of the rectum and colon. Symptoms include diarrhea, rectal bleeding (RB), urgency, and tenesmus (a feeling of incomplete evacuation of the rectum after defecation). Ulcerative colitis has a relapsing–remitting course, meaning that many patients have intermittent disease flares that are interspersed with periods of remission. Treatment goals in UC include induction of remission (typically within a 6 to 12 week time frame) and maintenance of remission in the longer term (assessed over 52 weeks of continuous treatment in clinical studies). In both clinical practice and clinical studies, clinical response and clinical remission are assessed by a combination of endoscopy (improvement in the endoscopic appearance of the mucosa and healing of ulcers) and patient reported outcomes (PROs), including a reduction in stool frequency (SF) and a resolution of RB (Levesque et al. 2015). Control of intestinal inflammation in UC is also associated with a reduction in the risk of hospitalization, colectomy and, in the longer term, UC-associated dysplasia and colorectal cancer.

3.2.2. Currently Available Treatments and Unmet Need

Medications used for the treatment of UC include 5-amino salicylic acid (5-ASA)–containing medications (sulfasalazine, mesalazine, balsalazide, olsalazine), corticosteroids, immunomodulators such as azathioprine (AZA) and 6 mercaptopurine (6 MP), and biologic medications. A significant proportion of patients with moderately to severely active UC may have an inadequate response to medicines such as 5-ASAs or corticosteroids, be unable to maintain a clinical response to 5-ASAs or AZA, or be unable to discontinue corticosteroids without a relapse in disease activity (reviewed in Dignass et al. 2012). Many of these patients require additional treatment with the next line of therapy, which could include medical treatment with a biologic medication or surgical treatment with a colectomy. Biologics, including antitumor necrosis factor (TNF) antibodies (infliximab, adalimumab, golimumab) and vedolizumab, an anti-α4β7 integrin antibody, are indicated for the treatment of UC in patients who fail to respond to, have an inadequate response to, or are intolerant to other medications used in the treatment of UC, and as a first-line treatment for UC in selected patients. However,

in the pivotal ACT1 and ACT2 studies of infliximab therapy in patients with moderately to severely active UC and in the pivotal PURSUIT studies of golimumab in the same patient population, only approximately 50% to 65% of the patients achieved clinical response (as defined by complete Mayo score) at the induction time point (Weeks 6 to 8), with approximately 50% of the patients maintaining clinical response to Week 54 (Rutgeerts et al. 2005; Sandborn et al. 2014a, 2014b). In the pivotal ULTRA studies of adalimumab in the same patient population, 16.5% of patients achieved clinical remission at Week 8 (Sandborn et al. 2012a). Similarly, in the pivotal GEMINI 1 study of vedolizumab in patients with moderately to severely active disease, 47% achieved a clinical response at Week 6 and up to 45% of these patients were in clinical remission at Week 52 (Feagan et al. 2013). These data illustrate the unmet need for new medications in UC.

3.2.3. Interleukin-23 as a Therapeutic Target in Ulcerative Colitis

IL-23 is a member of the IL-12 family of cytokines. It is a heterodimeric protein composed of 2 subunits: the IL-12p40 subunit, which is shared by IL-12, and the IL-23p19 subunit, which is specific to IL-23.

IL-23 is a pro-inflammatory cytokine. It is expressed by activated innate immune cells, including dendritic cells and tissue-resident macrophages. IL-23 stabilizes the differentiation and maturation of pro-inflammatory IL-23 receptor-expressing (IL-23R$^+$) IL-17$^+$ CD4$^+$ T cells (Th17 cells) through multiple mechanisms, including the maintenance of *Rorc* and *Il17* gene expression, the induction of pro-inflammatory cytokine expression (*Il22*, *Csf2*, and *Ifng*) and positive feedback by inducing expression of its own receptor, IL-23R. IL-23 also activates other IL-23R$^+$ immune cells, including γδ T cells, natural killer cells, and group 3 innate lymphoid cells (Gaffen et al. 2014; Teng et al. 2015).

Genetic deletion or pharmacologic inhibition of IL-23p19 in mice ameliorates or prevents inflammation in mouse models of rheumatoid arthritis (collagen-induced arthritis), multiple sclerosis (experimental autoimmune encephalomyelitis), and intestinal inflammation (Kikly et al. 2006).

IL-23 expression is enriched in the intestine of patients with active UC and active Crohn's disease. In addition, recent genome-wide association scans identified common variants (single nucleotide polymorphisms) in molecules in the IL-23 signaling pathway that modify the risk of UC and/or Crohn's disease in humans, including IL-23R, STAT3, and Janus kinase 2 (Jostins et al. 2012). Taken together, these data provide evidence for IL-23 as a therapeutic target in UC.

3.2.4. Preclinical and Clinical Studies of Mirikizumab

Mirikizumab binds the IL-23p19 subunit of human IL-23 and prevents binding of IL-23 to the IL-23R, neutralizing the activity of human IL-23 in vitro. Mirikizumab also neutralizes human IL-23 in vivo, ameliorating the development of psoriasis-like skin inflammation in mice following subcutaneous (SC) injection of human IL-23. Mirikizumab does not prevent IL-12 signaling in vitro.

LSN2479016 is the mouse anti-mouse surrogate antibody for mirikizumab. This was developed to enable preclinical testing in mice, as mirikizumab does not cross-react with mouse IL-23. LSN2479016 inhibits the development of skin inflammation in the imiquimod-induced psoriasis-like mouse model, inhibits the development of colonic inflammation in the $CD45RB^{hi}$ adoptive transfer mouse model of colitis, and reduces the development of curdlan-induced spondyloarthritis and Crohn's disease-like intestinal inflammation in SKG mice. Additional preclinical data are summarized in the Investigator's Brochure (IB).

A number of clinical studies of mirikizumab have been completed or are currently ongoing in patients with psoriasis, UC, and Crohn's disease.

Study I6T-MC-AMAA (AMAA) is a Phase 1, single-dose administration (up to 600 mg), dose-escalation study that included 40 subjects with psoriasis and 5 healthy controls. Efficacy data from this study show improvement of psoriasis at Week 12, as assessed by the Psoriasis Area and Severity Index (PASI), after a single dose of mirikizumab in the higher-dose cohorts.

Study I6T-MC-AMAF (AMAF) is a Phase 2, placebo-controlled, double-blind clinical trial of mirikizumab in patients with psoriasis, for which preliminary primary analysis results are available. In Study AMAF, patients with moderate-to-severe plaque psoriasis received placebo (n = 52) or mirikizumab 30 mg (n = 51), 100 mg (n = 51) or 300 mg (n = 51) SC at Weeks 0 and 8. The primary objective was to evaluate the superiority of mirikizumab over placebo in achieving ≥90% improvement in Psoriasis Area and Severity Index (PASI 90) response at Week 16. The primary efficacy end point at Week 16 was met for each dose group with PASI 90 responses of 0%, 29.4% ($p<.01$), 58.8% ($p<.001$) and 66.7% ($p<.001$), respectively, for patients treated with placebo and mirikizumab 30 mg, 100 mg and 300 mg (Reich et al 2017a).

Study 16T-MC-AMAC (AMAC) is a Phase 2, placebo-controlled, double-blind clinical trial of mirikizumab in patients with moderate-to-severe UC, for which preliminary primary analysis results are available. Patients with moderately to severely active UC received placebo (n=63) or mirikizumab 50 mg (n = 63), 200 mg (n = 62) or 600 mg (n=61) intravenous (IV) at Weeks 0, 4 and 8. Exposure-based dose adjustments were applied in 2 treatment groups. Based on plasma concentrations of mirikizumab, dose levels in subjects in the 50 mg and 200 mg groups could be increased at the Week 4 and Week 8 visits if the projected trough concentrations for those visits fell below prespecified thresholds: 73% of patients in the 50 mg mirikizumab group and 44% of patients in 200 mg mirikizumab group experienced exposure-based dose adjustments before Week 12, resulting in group mean doses of 100 mg and 250 mg, respectively in these groups. The 600-mg dose group remained on a fixed dose throughout the induction period. The primary efficacy endpoint was clinical remission at Week 12. Clinical remission rates at Week 12 were 4.8%, 15.9% ($p = .07$), 22.6% ($p<.01$), and 11.5% ($p = .14$) for patients treated with placebo and mirikizumab 50 mg, 200 mg and 600 mg, respectively. Clinical response rates at Week 12 were 20.6%, 41.3%, 59.7% and 49.2% for patients treated with placebo and mirikizumab 50 mg, 200 mg and 600 mg, respectively. Endoscopic healing rates (ES=0 or 1, excluding friability; termed "endoscopic remission" in this protocol) were numerically higher in the 50-mg mirikizumab group (23.8%) and 200-mg mirikizumab group (30.6%) compared to placebo (6.3%).

Symptomatic remission rates were numerically higher in the 200-mg mirikizumab group (58.1%,) and 600-mg mirikizumab group (45.9%) compared to placebo (20.6%).

Study 16T-MC-AMAG (AMAG) is a Phase 2, placebo-controlled, double-blind clinical trial of mirikizumab in patients with active Crohn's disease. At the time of writing, this study is ongoing.

Additional clinical trial data are summarized in the IB.

3.2.5. Other IL-23 Targeted Therapies in Humans

IL-23-targeted therapy is the mechanism of action for several compounds under development for the treatment of inflammatory diseases, including the human IL-12 and IL-23 antagonist ustekinumab, which is a monoclonal antibody against IL-12p40, and the human IL-23 antagonists guselkumab, risankizumab, tildrakizumab, and brazikumab, which are monoclonal antibodies against IL-23p19.

Ustekinumab binds IL-12p40, the subunit common to both IL-12 and IL-23, targeting both cytokines, rather than IL-23 specifically. Ustekinumab was the first biologic therapy with an anti-IL-23 action to show clinical benefit in psoriasis (Papp et al. 2008, Leonardi et al. 2008), psoriatic arthritis (Gottlieb et al. 2009) and Crohn's disease (Sandborn et al. 2012b, Feagan et al. 2016). Blockade of the IL-12 pathway may prevent type 1 T helper cell (Th1)-induced inhibition of Th17 cell development, thus potentially limiting the clinical activity of IL-12p40-targeting antibodies. Experimental studies suggest that blocking the IL-23/Th17/IL-17 immune axis, without blocking the IL-12/Th1/IFNγ axis, is sufficient to treat autoimmune inflammation (Monteleone et al. 2009).

To date, guselkumab, an IL-23p19 antibody, has been approved for the treatment of psoriasis and other agents specifically targeting the IL-23p19 subunit, including mirikizumab, have demonstrated clinical activity in psoriasis (Sofen et al. 2014; Kopp et al. 2015; Krueger et al. 2015; Papp et al. 2015; Blauvelt et al 2017; Papp et al. 2017; Reich et al 2017b). IL-23p19 inhibition is also under investigation for the treatment of inflammatory bowel disease and several anti-IL-23p19 antibodies have shown efficacy in the treatment of Crohn's disease (Deepak et al. 2017; Feagan et al. 2017; Sands et al. 2017).

3.3. Benefit/Risk Assessment

Ulcerative colitis remains an important public health challenge. The data for currently available treatments demonstrate the unmet need for new medications for UC (Section 3.2.2) and published literature supports the concept of IL-23 as a therapeutic target for UC therapies (Section 3.2.3). Based on data from the Phase 2 study of mirikizumab in patients with UC (Study AMAC, Section 3.2.4), potential benefits to patients who may receive mirikizumab while participating in Study AMAP may be reasonably anticipated.

At the time of this benefit/risk assessment, evaluation of unblinded safety data from the completed or ongoing clinical studies, including the unblinded period of the Study AMAC, which tests mirikizumab doses up to 600 mg IV Q4W, have not revealed any dose-related safety

or tolerability concerns. In addition, evaluation of blinded safety data in ongoing studies in psoriasis, UC, and Crohn's disease with doses up to 200/300 mg SC Q4W administered up to 92 weeks, and up to 1000 mg IV Q4W for up to 52 weeks have not revealed safety or tolerability concerns. Across ongoing studies, immediate hypersensitivity reactions, including serious nonfatal anaphylaxis, have been reported at the onset or during IV infusion of mirikizumab. As noted in the IB, such reactions are considered by the sponsor to be related to mirikizumab and hence have been identified as adverse drug reactions (ADRs). Consult the most current IB for information regarding ADRs and potential risks with mirikizumab.

Adverse events of special interest (AESIs)—which are not necessarily ADRs, but are of special interest based on standard drug registration topics, safety findings from previous studies in development program, potential risks associated with biologic immunomodulators as noted in product labels and published literature, and comorbidities and risk factors prevalent in the studied populations—are noted in Section 9.2.2 of this protocol. For all AESIs, including hypersensitivity events, the protocol and IB provide monitoring or management guidance to the investigator. In addition, an independent, external data monitoring committee (DMC) will review clinical trial data at prespecified, regular intervals during the study (Section 10.3.8). This independent assessment of clinical trial data will contribute to the overall ongoing evaluation and management of potential risks associated with mirikizumab administration.

The dose levels and regimens to be used in Study AMAP were chosen based on nonclinical safety data and on analyses of safety, efficacy, and pharmacokinetic (PK) data from the primary analysis of Study AMAC (Section 5.5).

In summary, the efficacy and safety data from the Phase 2 UC study support the continued clinical development of mirikizumab as a treatment for patients with UC.

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated AEs of mirikizumab are to be found in the IB.

4. Objectives and Endpoints

Table AMAP.4.1 shows the objectives and endpoints of the study. For definitions of outcomes mentioned in Table AMAP.4.1, please see Table AMAP.9.1.

Table AMAP.4.1. Objectives and Endpoints

Objectives	Endpoints
Primary objective To evaluate the long-term efficacy of mirikizumab in the following cohort: Cohort 1: Patients from AMBG who completed Week 40 visit on blinded SC mirikizumab	The proportion of patients in clinical remission at Week 52
Efficacy To evaluate the long-term efficacy of mirikizumab in the following cohort: Cohort 1: Patients from AMBG who completed Week 40 visit on blinded SC mirikizumab	• The proportion of patients in clinical remission at Week 100 or Week 160 • The proportion of patients in endoscopic remission at Week 52, Week 100, or Week 160 • The proportion of patients with endoscopic subscore = 0 (ES=0) at Week 52, Week 100, or Week 160 • Stool frequency and rectal bleeding subscores over time • The proportion of patients in corticosteroid-free remission at Week 52, Week 100, or Week 160 • Among patients entering the AMAP study not on corticosteroids, the time to first use of corticosteroids for UC • Dose of corticosteroid used at Week 52, Week 100, or Week 160
Efficacy To evaluate the long-term efficacy of mirikizumab in the following groups of patients: Cohort 2: Cohort 1 **and** AMAC patients who completed the Maintenance Period Week 52 visit on SC mirikizumab Cohort 3: The remaining patients (those not in Cohort 2)	• The proportion of patients in clinical remission at Week 52, Week 100, or Week 160 • The proportion of patients in endoscopic remission at Week 52, Week 100, or Week 160 • The proportion of patients with ES = 0 at Week 52, Week 100, or Week 160 • Stool frequency and rectal bleeding subscores over time • Among the patients who enter the AMAP study on corticosteroids, the proportion in corticosteroid-free remission at Week 52, Week 100, or Week 160
To evaluate the effect of long term mirikizumab therapy on histologic remission (mucosal healing) in the following cohorts: Cohort 1: Patients from AMBG who completed Week 40 visit on blinded SC mirikizumab Cohort 2: Cohort 1 **and** AMAC patients who completed the maintenance period Week 52 visit on SC mirikizumab	• The proportion of patients in histologic remission at Week 52, Week 100, or Week 160, as defined in the histopathology charter

Health Outcomes To evaluate the long-term effect of mirikizumab on health outcomes in the following cohort: Cohort 1: Patients from AMBG who completed Week 40 visit on blinded SC mirikizumab	• IBDQ scores over time • The proportion of patients who are hospitalized due to UC over time • The proportion of patients who undergo UC surgeries including colectomy over time

Abbreviations: AMAC = Study I6T-MC-AMAC; AMBG = Study I6T-MC-AMBG; ES = endoscopic subscore; IBDQ = Inflammatory Bowel Disease Questionnaire; SC = subcutaneous; UC = ulcerative colitis.

5. Study Design

5.1. Overall Design

Study AMAP is a single-arm, outpatient, open-label, Phase 3, multicenter, long-term extension study evaluating the efficacy and safety of mirikizumab in patients with moderately to severely active UC who have participated in an originator mirikizumab UC study, including, but not limited to, the Phase 2 Study AMAC and the Phase 3 Study AMBG.

The planned maximum duration of treatment for each patient is approximately 3 years, or until mirikizumab is commercially available in the country in which the patient resides, whichever occurs first. Patients may remain in Study AMAP as long as study drug treatment is tolerated with no safety concerns and, in the opinion of the investigator, the patient is deriving benefit from study drug.

All patients, whether they discontinue study drug early for any reason or complete mirikizumab treatment in Study AMAP, will enter a 12-week posttreatment follow-up period after the last dose of mirikizumab.

Patients from Study AMAC and Study AMBG are eligible for enrollment into Study AMAP (Appendix 5).

Study AMAC

Study AMAC is a Phase 2, randomized, double-blind, placebo-controlled study investigating the efficacy and safety of mirikizumab in patients with moderate-to-severe UC (Appendix 5). Study AMAC consists of a 12-week double-blind induction period followed by either a maintenance period (up to 144 weeks) or an extension period (12 weeks extension induction, up to 132 weeks extension maintenance) for up to 156 weeks total. Study AMAC patients eligible for consideration for enrollment into Study AMAP include the following:

- Patients who complete the maintenance period Week 52 endoscopy visit and the assessments at the end of study/early termination visit, or
- Patients who complete the extension period Week 40 endoscopy visit and the assessments at the end of study/early termination visit.

At the time of their last AMAC visit, a patient may be receiving blinded mirikizumab 200 mg SC Q4W, blinded mirikizumab 200 mg SC Q12W, blinded placebo SC Q4W, or unblinded (open label) mirikizumab 200 mg SC Q4W. Patients receiving blinded placebo SC at the time of their last visit in AMAC will receive mirikizumab for the first time in Study AMAP.

Study AMBG

Study AMBG is a Phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of 200 mg mirikizumab administered SC Q4W in maintaining treatment response at Week 40 (Week 52 of continuous therapy) in patients with moderately to severely active UC who completed 12 weeks of induction treatment (Appendix 5). AMBG patients eligible for consideration for enrollment into AMAP include the following:

- Patients who complete Week 40 visit on blinded SC mirikizumab or placebo therapy without experiencing loss of response (LOR) during Study AMBG
- Patients who complete Week 40 visit on open-label SC mirikizumab after responding to re-induction with IV mirikizumab
- Patients who complete AMBG early termination visit after receiving IV rescue for LOR and who, in the opinion of the investigator, had clinical benefit

At the time of their last AMBG visit, a patient may be receiving blinded mirikizumab 200 mg SC Q4W, blinded placebo SC Q4W, open-label (unblinded) mirikizumab 300 mg IV, or open-label mirikizumab 200 mg SC Q4W. Patients receiving blinded placebo SC at the time of their last visit in AMBG will be receiving mirikizumab for the first time in Study AMAP.

A patient from an originator study is eligible for enrollment into Study AMAP if the patient meets all inclusion criteria and does not meet any of the exclusion criterion (See Section 6).

Eligibility for Study AMAP may be assessed during the last visit of the originator study. Patients meeting the eligibility criteria (Section 6) may enter directly into this study at the time of, or approximately 4 weeks after, their last visit of originator mirikizumab study. Patients should not receive treatment on the same day of an endoscopy. Patients requiring a longer duration for study entry will be discussed on an individual patient basis with the sponsor.

Mirikizumab 200 mg will be administered subcutaneously every 4 weeks. Patients will receive open-label mirikizumab in Study AMAP, regardless of whether they were receiving blinded or unblinded (open-label) mirikizumab or blinded placebo when their participation ended in the originating study. No rescue with mirikizumab will be offered during Study AMAP.

Endoscopy will be performed at Week 52 (Year 1), Week 100 (Year 2), and Week 160 (Year 3) of Study AMAP (See Section 2). The last endoscopy performed in the originator study may be used as baseline for Study AMAP. Patients from Study AMAC who have not had endoscopy performed within 8 months of Week 0 of Study AMAP are to have an endoscopy performed at Week 0. Patients with pancolitis of >8 years' duration, left-sided colitis of >12 years' duration, or primary sclerosing cholangitis require colorectal cancer surveillance colonoscopy for UC-associated dysplasia and malignancy. Patients with a family history of colorectal cancer, personal history of increased colorectal cancer risk, age >50 years, or with other known risk factors also require colonoscopy for colorectal cancer surveillance. If these patients do not have documentation of a surveillance colonoscopy (performed according to local standards) within 18 months of Week 0, a colonoscopy is to be performed at Week 0 for eligibility. Colonoscopy is the required endoscopic procedure for these patients at Weeks 52, 100, and 160. A negative colonoscopy report is required for continuing eligibility (Section 9.1.3).

Patients are allowed to receive corticosteroid and noncorticosteroid conventional UC therapies during the study (see See Section 7.7, Appendix 9 and Appendix 10).

Stool frequency and rectal bleeding over the preceding 24 hours will separately be assessed by a single question administered as shown in the Schedule of Activities (Section 2). For visits at

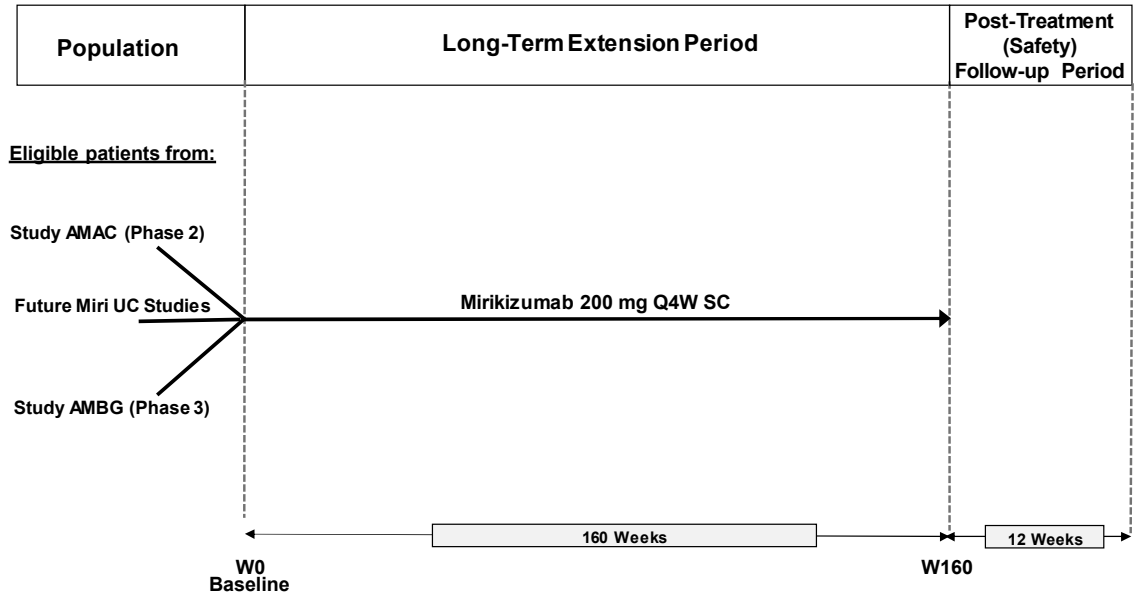
which an endoscopy is scheduled, site personnel are to contact the patient 3 to 4 days prior to the endoscopy visit to collect stool frequency and rectal bleeding data.

Screening: There will be no screening period for Study AMAP. Week 0 visit of Study AMAP may occur at the last visit, or approximately 4 weeks after the last visit, of the originator study. Patients should not begin AMAP on the same day of endoscopy from their originator study. Patients requiring a longer duration for study entry will be discussed on an individual patient basis with the Sponsor.

Long-Term Extension Treatment Period: Patients may remain in Study AMAP as long as study drug treatment is tolerated with no safety concerns and, in the opinion of the investigator, the patient is deriving benefit from study drug.

Post-Treatment Follow-up Period (12 Weeks): All patients, whether they discontinue the study early for any reason or they complete mirikizumab treatment in Study AMAP, will enter a 12-week post-treatment follow-up period after the last dose of mirikizumab.

Study governance considerations are described in detail in Appendix 3.



Abbreviations: Miri = mirikizumab; Q4W = every 4 weeks; SC = subcutaneous; W = week.

Figure AMAP.5.1. Illustration of study design for Clinical Protocol I6T-MC-AMAP.

5.2. Number of Participants

From Study AMAC and Study AMBG, it is anticipated that approximately 50% to 70% of the eligible patients will enroll leading to approximately 600 to 840 patients from these 2 studies in Study AMAP.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

The Phase 3 clinical trial program of mirikizumab in patients with moderate-to-severe UC consists of the following studies:

- Study AMAN: An induction study with a 12-week treatment duration.
- Study AMBG: A maintenance study with a 40-week treatment duration.
- Study AMAP: An open-label, long-term extension study.

Study AMAP is designed to evaluate the long-term efficacy and safety of open-label mirikizumab, in patients who have previously participated in a UC mirikizumab study. The Phase 3 studies are placebo-controlled studies designed to demonstrate the superiority of mirikizumab; Study AMAP does not use a control group as its primary objective is to confirm the long-term clinical benefit of mirikizumab. By enrolling patients who the investigator believes would derive benefit from receiving mirikizumab therapy, Study AMAP represents a population analogous to one that would be treated in clinical practice.

5.5. Justification for Dose

The dose levels and regimens selected for this study were based primarily on analyses of interim PK, safety, and efficacy data from the Phase 2 Study AMAC, safety data from other clinical studies evaluating mirikizumab, and nonclinical safety data.

Safety Considerations

The safety data collected in completed and ongoing clinical studies and in nonclinical toxicology studies support the proposed dose regimen. In particular, there were no dose-related safety or tolerability issues observed in Study AMAC in patients with UC, for a period of up to 92 weeks with doses up to 200 mg SC Q4W.

Single IV doses of up to 600 mg were evaluated in Study AMAA (healthy subjects and psoriasis patients) and up to 1200 mg in Study I6T-JE-AMAD (AMAD) (healthy subjects); no dose-related safety or tolerability issues were observed in either study. Study AMAG is evaluating dose regimens of up to 1000 mg IV Q4W for up to 52 weeks in patients with Crohn's disease, and up to 92 weeks with 300 mg SC Q4W. Evaluation of the unblinded safety data available to date in the ongoing Phase 2 study in patients with psoriasis (Study AMAF) and of the blinded safety data available to date in the ongoing Phase 2 study in patients with Crohn's disease (Study AMAG) has not revealed a safety concern that differs from the safety findings noted for Study AMAC.

The nonclinical safety profile of mirikizumab supports the proposed clinical study on the basis of the no-observed-adverse-effect levels (NOAELs) established in studies in monkeys. The margin of safety (MOS) for the proposed dose of 200 mg Q4W (SC) is 23.

Considerations of Efficacy and Exposure–Response Relationship

The available data from the maintenance period of Study AMAC indicate that the rates for efficacy endpoints at Week 52 were similar between the 200 mg SC Q4W and 200 mg SC Q12W mirikizumab maintenance groups, although there was a trend for higher rates across clinical and symptomatic remission and response endpoints in the Q4W group. Examination of the rectal bleeding time course shows a pattern of loss of response before each dose administration in the 200 mg SC Q12W arm. This suggestion of increased bleeding between doses accompanies a finding that Q12W dosing results in mirikizumab trough concentrations below quantifiable detection limits at time periods between dosing. External experts have interpreted these patterns to suggest that Q12W dosing is inadequate on the basis of inadequately-treated underlying inflammation as well as on the basis of bleeding symptoms between doses. The Q12W regimen produced a more intermittent mirikizumab concentration profile, while the Q4W concentration profile was more consistent, which may correlate with more consistent maintenance of lower (better) rectal bleeding subscores. The Q4W regimen also produced trough concentrations that were similar to the Week-12 trough concentrations produced in the 200-mg induction cohort that achieved the best efficacy. Subjects that achieved clinical response or clinical remission at Week 52 also tended to have higher maintenance exposures.

Therefore, a dose regimen of 200 mg SC Q4W was selected for Study AMAP.

6. Study Population

Study AMAP is a continuation of originator Studies AMAC and AMBG; patients from future mirikizumab UC studies may also be eligible for Study AMAP. Patients may enter into Study AMAP directly from Studies AMAC and AMBG after they sign a study-specific IRB/EC-approved informed consent. A patient is considered enrolled into the study once the patient is randomized and assigned to treatment. There is no screening period for Study AMAP. Data collected during the last visit of originator studies, including laboratory evaluations, endoscopy, and patient-reported data, may be used to review entrance criteria and assess the suitability of a patient for entering this open-label, long-term extension trial. Prior to study entry, patients who do not meet one or more hepatic or hematologic laboratory enrollment criteria may have these blood measures repeated one time at the investigator's discretion to assess patient eligibility.

Patients who terminate from Study AMAN for any reason or who permanently discontinue study drug during Studies AMAC or AMBG are not eligible to enter Study AMAP.

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

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria at enrollment:

Informed Consent

[1.] Have given written informed consent approved by the ethical review board (ERB) governing the site prior to any study-specific procedures being completed.

Type of Patient and Disease Characteristics

[2.] Patients from the Phase 2 Study **AMAC** who:

- completed either the maintenance dosing period Week 52 or extension period maintenance Week 40 assessments including endoscopy, and
- in the opinion of the investigator, would derive benefit from treatment with mirikizumab

Patients should receive first dose of AMAP study within approximately 4 weeks of last dosing visit AMAC. A maximum of 8 weeks will be allowed between last dose in AMAC and first dose in AMAP.

[3.] Patients from the Phase 3 Study **AMBG** who:

- completed the:
  - Week 40 visit on blinded SC therapy without experiencing loss of response during Study AMBG or

  - Week 40 visit on open-label SC mirikizumab after responding to re-induction with IV mirikizumab or
  - AMBG early termination visit after completing IV rescue for LOR

and

- in the opinion of the investigator, would derive benefit from treatment with mirikizumab.

Patients should receive first dose of AMAP study on the day of the AMBG Week 40 visit, or within approximately 4 weeks after Week 40; a maximum of 8 weeks will be allowed between last dose in AMBG and first dose in AMAP.

Patient Characteristics

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

[5.] Contraception

[5a] male patients:

No male contraception required except in compliance with specific local government study requirements

[5b] female patients:

women of **child-bearing potential**:

A. must test negative for pregnancy prior to initiation of treatment as indicated by a negative urine pregnancy test at V1/Week 0 of this study.

B. must agree to either remain abstinent, if complete abstinence is their preferred and usual lifestyle, or remain in same-sex relationships, if part of their preferred and usual lifestyle, without sexual relationships with males. Periodic abstinence (for example, calendar, ovulation, symptothermal, or post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

OR

must use 2 effective methods of contraception for the entirety of the study. Abstinence or contraception must continue following completion of study drug administration for 12 weeks.

i. Two effective methods of contraception (such as male or female condoms with spermicide, diaphragms with spermicide or cervical sponges) will be used. The patient may choose to use a double barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide. It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.

ii. Of note, 1 of the 2 methods of contraception may be a highly effective (<1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine devices).

women **not of child-bearing potential** may participate and include those who are:

A. infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as mullerian agenesis; or

B. postmenopausal – defined as either

i. A woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had either

a. cessation of menses for at least 1 year, or

b. at least 6 months of spontaneous amenorrhea with a follicle stimulating hormone >40 mIU/mL; or

ii. A woman 55 years or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea; or

iii. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

[6.] have documentation of

[6a] a surveillance colonoscopy (performed according to local standard) within 18 months before Week 0 for:

- patients with pancolitis of >8 years' duration, or
- patients with left-sided colitis of >12 years' duration, or
- patients with primary sclerosing cholangitis.

Patients who do not have documentation of a surveillance colonoscopy with negative report within 18 months prior to Week 0 will require a colonoscopy at Week 0 to ensure eligibility.

[6b] in patients for whom inclusion criterion [4a] does not apply, up-to-date screening for colorectal cancer, (performed according to local standard).

6.2. Exclusion Criteria

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

Type of Patient and Disease Characteristics

[7.] Would not, in the opinion of the investigator, derive clinical benefit from open-label treatment with mirikizumab.

[8.] Participated in AMAC and did not complete Maintenance Dosing Period Week 52 or Extension Period Maintenance Week 40 assessments including endoscopy.

[9.] Participated in AMBG and did not benefit, in the opinion of the investigator, from IV rescue for LOR, or did not achieve clinical response following extended IV induction with mirikizumab.

[10.] Had a reported SAE in originator study or developed other condition prior to Week 0 visit that would disqualify them from treatment with mirikizumab according to originator study criteria.

[11.] Had permanently discontinued, or had temporary interruption of, study drug in originator study such that, in the opinion of the investigator or Sponsor, restarting of mirikizumab would pose an unacceptable risk for the patient's participation in Study AMAP.

Medical Conditions

[12.] Presence of significant uncontrolled neuropsychiatric disorder or judged at risk of suicide in the opinion of the investigator;

OR

marked "yes" to Columbia-Suicide Severity Rating Scale (C-SSRS) Question 4 or 5 on ideation prior to dosing at Week 0;

OR

marked "yes" to C-SSRS suicide behaviors questions prior to dosing at Week 0;

AND

the ideation or behavior occurred within the past month.

[13.] Have an unstable or uncontrolled illness, including, but not limited to, cerebro-cardiovascular, respiratory, gastrointestinal (excluding UC), hepatic, renal, endocrine, hematologic or neurological disorders, or abnormal laboratory values that developed during a previous mirikizumab study that, in the opinion of the investigator, would pose an unacceptable risk to the patient if investigational product continues to be administered.

[14.] Are diagnosed with any medical condition (or signs or symptoms thereof) including developing malignancy or suspicion of active malignant disease during the originator study or prior to Week 0, which would have precluded enrollment in a prior mirikizumab study or would have required discontinuation. Patients who require colorectal cancer surveillance colonoscopy to (see IC [6a] and Section 9.1.3) will need a colonoscopy within 18 months of Week 0 or at Week 0 to ensure eligilibity.

[15.] Have been diagnosed with serious infection (including but not limited to hepatitis B, hepatitis C, HIV, and active tuberculosis [TB]) during the originator study or prior to Week 0.

[16.] Have been diagnosed with latent TB during an originator study or prior to Week 0 and is not willing to comply with completing TB treatment as appropriate.

[17.] Have a known hypersensitivity to any component of this investigational product, or has experienced an acute systemic hypersensitivity event with previous study drug administration, that precludes mirikizumab therapy.

[18.] Have any other condition that in the opinion of the investigator, renders the patient unable to understand the nature, scope, and possible consequences of the study or precludes the patient from attending study visits, completing study procedures, or adhering to prohibited concomitant medication requirements (Appendix 9).

General Exclusion Criteria

[19.] Are pregnant, lactating, or planning pregnancy (women only) while enrolled in the study, or within 12 weeks after receiving the last dose of study drug.

[20.] Had surgical intervention for ulcerative colitis after participation in a previous mirikizumab UC study or likely to require surgery for treatment of UC during the study.

[21.] Intend to receive a Bacillus Calmette-Guerin (BCG) vaccination or live attenuated vaccine(s) during the study.

[22.] Have current adenomatous polyps that have not been removed. Patient may be eligible for study after polyps are removed and histopath report received. Patients with dysplasia within a polyp (dysplasia-associated lesion or mass) should have documentation of a follow-up colonoscopy without recurrence.

[23.] Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study

[24.] Are a Lilly employee, employee of third party organizations involved with the study, or investigator site personnel directly affiliated with this study and/or their immediate families, during the originator study.

6.3. Lifestyle Restrictions

In order to participate in the study, patients must agree to the contraception, reproduction and breastfeeding criteria detailed in inclusion criterion [5] and exclusion criterion [19]. Study participants should be instructed not to donate blood or blood products during the study or for 16 weeks following study participation.

7. Treatments

7.1. Treatments Administered

All enrolled patients will receive open label mirikizumab administered subcutaneously as two 1-mL injections administered by authorized site personnel.

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 Labelling

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

Study drug will be supplied as single use solution in a 1 mL pre-filled syringe manufactured to deliver 100 mg of mirikizumab.

Study drug will be provided with study-specific labels. Syringes will be supplied in cartons, with the appropriate quantity specific to the planned dispensing schedule of the investigational product. No concomitant UC therapies will be provided by Lilly or its designee.

7.2. Method of Treatment Assignment

This is an open-label study. All patients enrolled will receive open-label mirikizumab.

7.2.1. Selection and Timing of Doses

All patients will receive a 200 mg dose of mirikizumab every 4 weeks as described in the SOA (Section 2). The actual time of dose administration is to be recorded in the electronic case report form (eCRF). Doses should not be administered during unscheduled visits unless the unscheduled visit occurs during the next scheduled dosing window.

7.3. Blinding

This is an unblinded, open-label study.

7.4. Dosage Modification

Dose adjustments are not permitted in this study.

7.5. Preparation/Handling/Storage/Accountability

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

- Confirming appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Ensuring that only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

Detailed instructions regarding supplies and preparation and handling of mirikizumab will be provided by the sponsor in the Pharmacy Manual.

Investigational products will be supplied by Lilly or its designee, in accordance with current GMP and will be supplied with lot numbers, expiry dates, and certificates of analysis, as applicable.

Mirikizumab should be stored in refrigerated conditions 2° C to 8° C (36° F to 46° F).

7.6. Treatment Compliance

All doses of study medication will be administered by authorized site personnel. Deviations from the prescribed dosage regimen should be recorded in the eCRF.

Every attempt will be made to select patients 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 patient before randomization.

If a patient is noncompliant with study procedures and/or investigational product administration, the investigator should assess the patient to determine the reason for noncompliance and educate and/or manage the patient as appropriate to improve compliance. If, in consultation with Lilly or its designee, the noncompliance is deemed to be significant such that it affects the safety of the patient or the evaluation of the efficacy and safety data in this study, the patient may be discontinued from the study.

7.7. Concomitant Therapy

All concomitant medications taken during the study must be recorded on the Concomitant Medication eCRF. All patients should maintain their usual medication regimens for concomitant conditions or diseases throughout the study unless those medications are specifically excluded (Appendix 9). Stable doses of concomitant medications are encouraged.

Patients taking permitted UC concomitant medications, other than oral corticosteroids, are to keep doses stable unless modifications are needed due to AEs and follow the instructions regarding dose stabilization as detailed in Appendix 10. Patients taking oral corticosteroids are to follow the corticosteroid taper instructions described below. Patients who enter the study not on corticosteroids may begin a course of corticosteroids for disease exacerbation (flare) and should be tapered as soon as clinically appropriate as determined by the investigator. Administration of prohibited UC medications, approved or investigational, constitutes treatment failure. Use of such medications should not be withheld if, in the opinion of the investigator, failure to prescribe them would compromise patient safety. Patients who require a prohibited medication to treat their UC (see Appendix 9) need to be discontinued from study drug and complete an ETV and post-treatment follow-up visits.

If a concomitant medication is needed to treat an AE or for appropriate medical management, the investigator should base decisions on the patient and clinical factors, considering prohibited medication. Local administration of corticosteroids (for example, intranasal, inhaled, intraarticular) are allowed as required for the management of pre-existing conditions and AEs. A patient who initiates a prohibited medication for a non-UC indication may either discontinue the study drug, or discontinue the prohibited medication.

Use of BCG vaccination is prohibited throughout the duration of the study and for 12 months after discontinuation of study drug. Use of nonlive (killed, inactivated, or subunit) vaccinations are allowed for all patients; however, their efficacy with concomitant mirikizumab is unknown. Use of live, attenuated vaccines are prohibited during the study and for 3 months after discontinuation of study drug.

The list of prohibited medications and the list of permitted medications with dose stabilization guidance are provided in Appendix 9 and Appendix 10, respectively.

Corticosteroid Taper

Patients who enter the study on corticosteroids should begin taper as soon as clinically appropriate as determined by the investigator with the goal of becoming corticosteroid-free as soon as clinically feasible and appropriate. During the course of the study, corticosteroid doses may be adjusted up or down according to standards of care and patient response, as long as corticosteroid taper is initiated as clinically appropriate as determined by the investigator.

7.8. Treatment after the End of the Study

No further study treatment will be available to patients at the end of Study AMAP.

7.8.1. Treatment after Study Completion

Mirikizumab will not be made available to patients after conclusion of the study.

7.8.2. Special Treatment Considerations

7.8.2.1. Management of Hypersensitivity and Injection Site Reactions

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

Hypersensitivity Events

If a patient experiences a systemic hypersensitivity reaction 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 11 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, antihistamine, systemic steroids and/or bronchodilators).
- After patient's stabilization, an ADA and PK sample should be collected; additional samples should be obtained 4 and 12 to 16 weeks after the event.
- The patient should be monitored until resolution or stabilization of the symptoms, as clinically appropriate.
- Study drug should be permanently discontinued after a systemic drug administration reaction. The patient should undergo post-treatment follow-up procedures after study drug discontinuation.
- The medical monitor should be notified as soon as feasible.

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

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

Study treatment may be permanently discontinued during the study. If a patient's study treatment is discontinued before the end of the study, the patient should complete the ETV and should return for post-treatment follow-up visits at 4 and 12 weeks after the end of treatment visit (Visits 801 and 802). The investigator will also complete any AE reporting and follow-up that may be required (if applicable, see Section 9.2).

Possible reasons leading to permanent discontinuation of investigational product include (list is not exhaustive):

Patient Decision

- The patient requests to discontinue investigational product.

Discontinuation due to a hepatic event or liver test abnormality.

- Patients who are discontinued from investigational product due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via the hepatic eCRF packet.

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

  - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8x upper limit of normal (ULN)
  - ALT or AST >5xULN for more than 2 weeks
  - ALT or AST >3xULN and total bilirubin level (TBL) >2xULN or international normalized ratio >1.5
  - ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
  - Alkaline phosphatase (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%)

Safety Criteria for Study Drug Discontinuation

- The patient requires a prohibited medication to treat their UC (Appendix 9). A patient who initiates a prohibited medication for a non-UC indication may either discontinue the study drug, or discontinue the prohibited medication.

- The patient requires a colectomy during the study.
- A diagnosis of cancer, other than squamous cell or basal cell carcinoma of the skin, during the study.
- Dysplasia occurring in flat mucosa or dysplasia-associated mass or lesion (DALM).
- A diagnosis of active TB during the study.
- A diagnosis of HIV/AIDS during the study.
- A diagnosis of hepatitis B during the study or development of detectable HBV DNA during the study (see Section 9.4.5.3).
- A diagnosis of hepatitis C during the study or development of detectable HCV RNA during the study (see Section 9.4.5.4).
- The patient becomes pregnant. Pregnant patients **will not** undergo an endoscopy at the ETV.
- The patient experiences an AE or SAE that would preclude him/her from participating in the trial.
- Systemic hypersensitivity event or anaphylaxis to mirikizumab.

It is recommended that the patient be assessed by an appropriately trained professional to assist in deciding whether the patient is to be discontinued from the study if:

- The patient scores a 3 for Item 12 (Thoughts of Death or Suicide) on the Quick Inventory of Depressive Symptomatology-Self-Report (16 Items) (QIDS-SR16) at any time in the study, or
- The patient reports suicidal ideation or suicide-related behaviors during the study

Other Reasons for Study Drug Discontinuation

- Inadvertent enrollment (see Section 8.1.3)

Patients discontinuing from the investigational product prematurely for any reason should complete adverse event and other follow-up procedures per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.1.2. Temporary Interruption (Withholding) from Study Treatment

Some possible reasons for temporarily withholding the investigational product include (but are not limited to):

- Patient develops a clinically important intestinal or extraintestinal infection, including latent TB infection (LTBI), during the study.
- Patient requires major surgery (resume administration of the investigational product only after adequate wound healing).

- Patient develops a confirmed absolute neutrophil count <$1x10^9$/L (<$1x10^3$/µL or <1 GI/L) (2 assessments below this threshold).
- Patient develops absolute lymphocyte count <500 cells/µL(<$0.5x10^3$/µL or <0.50 GI/L). Azathioprine, 6-mercaptopurine or methotrexate must be discontinued, if applicable, for a confirmed absolute lymphocyte count <$0.5x10^3$/µL (2 assessments below this threshold). The hematology must be repeated in 2 weeks. If the absolute lymphocyte count remains <$0.5x10^3$/µL, the hematology will be repeated again in 2 weeks (ie, prior to the next dose of study drug). If the absolute lymphocyte count remains <$0.5x10^3$/µL, the next dose of study drug will not be administered. The hematology will be repeated again in 2 weeks. If the absolute lymphocyte count remains <$0.5x10^3$/µL, study drug will be permanently discontinued. White blood cell and lymphocyte counts will be followed for these patients until they return to an acceptable level.

Cases that may merit temporary withholding of the study treatment will be discussed with the medical monitor. The medical monitor, in consultation with the investigator, will determine when it is appropriate to resume study treatment.

8.1.3. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identify a patient who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the patient to continue on study treatment. If the investigator and the sponsor agree it is medically appropriate to continue on study treatment, the investigator must obtain documented approval from the sponsor to allow the inadvertently enrolled patient to continue in the study. Patients who are discontinued from study treatment should have safety follow-up is as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of the protocol.

8.2. Discontinuation from the Study

Patients will be discontinued in the following circumstances:

- Enrollment in any other clinical study 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 patient should be discontinued from the study
    - If the patient, 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

- Patient decision
  - The patient requests to be withdrawn from the study

Patients discontinuing from the study prematurely for any reason should complete AE and other safety follow-up per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.3. Lost to Follow-Up

A patient 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 patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, 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

Table AMAP.9.1. Endpoint Definitions in Study AMAP

Endpoint	Definition
Clinical remission	• Stool frequency (SF) subscore = 0, or SF = 1 with a ≥1-point decrease from induction baseline, and • Rectal bleeding (RB) subscore = 0; and • Endoscopic subscore (ES) = 0 or 1 (excluding friability)
Clinical remission (using a more stringent ES)	• SF subscore = 0, or SF = 1 with a ≥1-point decrease from induction baseline, and • RB subscore = 0; and • ES = 0
Clinical response	• A decrease in the modified Mayo score (MMS) of ≥2 points and ≥30% decrease from induction baseline, and • A decrease of ≥1 point in the RB subscore from induction baseline or a RB score of 0 or 1
Endoscopic remission	• ES = 0 or 1 (excluding friability)
Corticosteroid-free remission	For those entering AMAP on concomitant corticosteroids, • Clinical remission and • No corticosteroid use for at least 12 weeks prior to Week 52, Week 100, or Week 160
Histologic remission (mucosal healing)	Mucosal healing is defined in the Histopathology Image Review Charter

Abbreviations: ES = endoscopic subscore; MMS = modified Mayo score; RB = rectal bleeding; SF = stool frequency.

Note: The term "mucosal healing" may be used in study reports to describe histologic remission or to describe a Mayo ES of 0-1, and the definition will be clarified in the study report.

9.1.1. Primary Endpoint

The primary endpoints is the proportion of patients from Cohort 1 (patients originating from AMBG who completed Week 40 visit of that study on blinded SC mirikizumab) in clinical remission at Week 52 (Table AMAP.4.1). Clinical remission is based on the modified Mayo Score and is defined in Table AMAP.9.1.

9.1.2. Mayo Score

This study utilizes components of the Mayo score (Schroeder et al. 1987) to assess UC disease activity for the efficacy endpoints (see Appendix 8). Adequate bowel preparation and an endoscopy with adequate visualization of the mucosa will enable calculation of the Mayo endoscopic subscore (ES).

The Mayo score is a composite instrument comprised of the following 4 subscores:

Stool Frequency: The SF subscore is a patient-reported measure. This item reports the number of stools in a 24-hour period, or in some cases over a 7-day period, relative to the normal number of stools for that patient in the same period, on a 4-point scale (see Appendix 8). **A stool is defined as a trip to the toilet when the patient has either a bowel movement, or passes blood alone, blood and mucus, or mucus only**. The reference "normal" SF for each patient is based on the reported SF when the patient was in remission or reported SF before initial onset of signs and symptoms of UC and is recorded at the screening visit prior to mirikizumab induction. At most office visits the patient will be asked a single question to provide the absolute number of stools passed in the 24-hour period immediately preceding the office visit. For office visits which include endoscopy, patients will be recording SF on a 7-day paper diary in the week prior to the bowel prep and provide the completed diaries at the endoscopy office visit. The site staff will record the patient-reported SF in the source documents. Further details on the analysis of the collected SF data are contained in the statistical analysis plan (SAP).

Rectal Bleeding (RB): The RB subscore is a patient-reported measure. This item reports the most severe amount of blood passed with stool for a given day, on a 4-point scale (see Appendix 8). At each office visit, the patient will be asked a single question to provide the most severe amount of blood passed with stool in the 24-hour period immediately preceding the office visit, or in some cases over a 7-day period (see Appendix 8). For office visits which include endoscopy, patients will be recording RB on a 7-day paper diary in the week prior to the bowel prep and provide the completed diaries at the endoscopy office visit. The site staff will record the patient-reported RB subscore in the source documents. Further details on the analysis of the collected RB data are contained in the SAP.

Endoscopic Subscore: The ES is a physician-reported measure that reports the worst appearance of the mucosa on flexible sigmoidoscopy or colonoscopy, on a 4-point scale (see Appendix 8). Determination of the ES is further detailed in Section 9.1.3. Consistent with current clinical practice and regulatory advice, this study excludes friability from the definition of an ES of 1.

Physician's Global Assessment (PGA): The PGA is a physician-reported measure that summarizes the investigator's assessment of the patient's UC disease activity on a 4-point scale (see Appendix 8). The investigator will record the PGA in the source documents at appropriate study visits. Consistent with regulatory guidance, the PGA will not be used for efficacy assessment in this study.

Each subscore is scored on a 4-point scale, ranging from 0 to 3. The modified Mayo score is a 9-point score, calculated by combining the SF, RB, and ES sub-scores. The PGA is collected in this study to facilitate historical comparisons of study data.

9.1.3. Endoscopy

Endoscopy will be used to determine the Mayo ES at the time points described in the Schedule of Activities (Section 2).

Flexible sigmoidoscopy is the standard endoscopic procedure for assessment of endoscopic disease activity in this study. However, colonoscopy can be performed instead of flexible sigmoidoscopy within this study in order to surveille for dysplasia, screen for colorectal cancer (see inclusion criterion [6]), or for other clinically indicated reasons, in the judgement of the investigator.

Patients who do not have a documented colorectal cancer surveillance colonoscopy with a negative pathology report within 18 months of Week 0, are to have a surveillance colonoscopy performed at Week 0 to be eligible. Colonoscopy is the required endoscopic procedure for these patients at Weeks 52, 100, and 160 and a negative colonoscopy report is required for continuing eligibility.

Patients with a family history of colorectal cancer, personal history of increased colorectal cancer risk, age >50 years, or with other known risk factor must be up to date with their colorectal cancer surveillance according to local standards to enroll. If not up to date, then a surveillance colonoscopy is to be performed at Week 0. Colonoscopy may be the endoscopic procedure for these patients at Weeks 52, 100, and 160 if needed to meet local standards. A negative colonoscopy report is required for continuing eligibility. A surveillance colonoscopy should be performed according to local guidelines and include random and targeted biopsies which are to be sent to the local histopathology laboratory. Chromoendoscopy may be an acceptable method of targeting biopsies, if allowed according to local guidelines.

Endoscopic response will be assessed during endoscopy (colonoscopy/flexible sigmoidoscopy) performed in the originator study. The last endoscopy performed in the originating study may serve as Study AMAP baseline endoscopy. If the last endoscopy from the originating study was performed more than 8 months prior to Week 0 of AMAP, an endoscopy will need to be performed at Week 0 of Study AMAP to serve as AMAP baseline.

If a patient becomes pregnant during the study, no additional endoscopies will be performed.

The endoscopy report and histopathology report (if biopsies sent to the local histopathology laboratory) must be available in the source documents.

The endoscopist will be a licensed physician, who is qualified by education, training, and experience to perform endoscopy. Investigators may delegate endoscopy to other members of the study team. However, all study staff performing endoscopy must receive training from the sponsor or designee in the determination and calculation of the Mayo ES. The site endoscopist will determine the Mayo ES at each endoscopy and it will be recorded in the eCRF.

All endoscopic procedures will be video recorded using a storage medium provided by the sponsor or designee. The video images will be sent for independent central reading. A detailed image review charter from the central reading laboratory will outline the standard study procedures used to capture and transmit video recordings of endoscopic procedures throughout the study, and the qualifications required of the central reader. The central reader will determine the Mayo ES at each colonoscopy in a blinded manner, as detailed in the image review charter.

Disagreement between the site and the central reader in Mayo ES scoring will be adjudicated by an additional blinded central reader, as detailed in the image review charter. The ES to be used for assessment of the MMS will be provided to the sites from the central reader vendor.

9.1.4. Endoscopic Biopsies

Biopsies will be obtained at each endoscopy to support assessment of the histopathology endpoint in this study. These will be sent to the central study laboratory for processing and will be stored for up to 15 years, where permitted by local regulation. Histopathologic scoring of these biopsies will be performed by a blinded central reader. A detailed histopathology charter will outline the procedures to be used for secure specimen transfer, processing, slide preparation and digitization of slides for histopathologic scoring. Centrally read histopathology results will not be made available to study sites. The biopsy samples may also be used in future exploratory biomarker analyses, where permitted by local regulation and ERBs.

9.1.5. Extraintestinal Manifestations

Review of extraintestinal manifestations (EIMs) will be performed at the time points described in the Schedule of Activities (Section 2). Extraintestinal manifestations that are present prior to V1 (Week 0) are to be recorded as ongoing adverse events. New events, or ongoing events that change in severity, are to be recorded as adverse events. Extraintestinal manifestations include, but are not limited to: uveitis, episcleritis, peripheral arthritis, dactylitis, enthesitis, sacroileitis, ankylosing spondylitis, erythema nodosum, pyoderma gangrenosum, primary sclerosing cholangitis, and oral aphthous ulcers.

9.1.6. Patient Reported Outcome Instrument Used to Assess Endpoints

Inflammatory Bowel Disease Questionnaire (IBDQ). The IBDQ is a 32-item patient-completed questionnaire that measures 4 aspects of patients' lives: symptoms directly related to the primary bowel disturbance, systemic symptoms, emotional function, and social function (Guyatt 1989; Irvine et al. 1994; Irvine et al. 1996). 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. Patients will record their responses to the IBDQ in source documents at visits indicated in the SOA (Section 2).

Urgency Numeric Rating Scale (NRS): A single item that measures the severity of the urgency (sudden or immediate need) to have a bowel movement in the past 24 hours, using an 11-point NRS ranging from 0 (no urgency) to 10 (worst possible urgency). Patients will record their

responses pertaining to their severity of urgency in source documents at visits indicated in the SOA (Section 2).

Abdominal Pain NRS: A single item that measures the "worst abdominal pain in the past 24 hours" using an 11-point NRS ranging from 0 (no pain) to 10 (pain as bad as can imagine). Patients will record their responses pertaining to their worst abdominal pain experience in source documents at visits indicated in the SOA (Section 2).

9.1.7. Histopathology Assessment

Biopsy samples will be collected at each endoscopy for histopathology assessment, as described in the histopathology charter. The histopathology instruments that will be used for the evaluation of microscopic inflammation and histopathologic disease activity will be specified in the histopathology charter.

9.1.8. Appropriateness of Assessments

The clinical safety parameters in this study are routine elements of clinical health assessment and Phase 3 drug development. The disease activity measurements are used in clinical practice and UC clinical trials.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of patients 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 patient.

The investigator is responsible for the appropriate medical care of patients 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 patient to discontinue the investigational product before completing the study. The patient 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 informed consent form (ICF) is signed, study site personnel will record via e-CRF the occurrence and nature of each patient'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), including exacerbation of UC, and any new conditions as AEs.

Investigators should record their assessment of the potential relatedness of each AE to 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 patient'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.

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in any 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.

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the patient has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines (see Section 9.2) 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. Patients with a serious hepatic AE should have additional data collected using the hepatic eCRF packet.

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 patients once they have discontinued and/or completed the study (the patient disposition eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a patient 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.

9.2.1.1. 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 identification, recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Adverse Events of Special Interest

Adverse events of special interest (AESIs) are AEs which the Sponsor specifies as being of special interest based on standard drug registration topics, safety findings from previous studies in development program, potential risks associated with biologic immunomodulators as noted in product labels and published literature, and comorbidities and risk factors prevalent in the studied populations. The AESIs for this study are defined in the statistical analysis plan, and may include but not be limited to:

- Opportunistic infections
- Hypersensitivity events, including anaphylaxis
- Injection site events
- Cerebro-cardiovascular events
- Malignancies
- Depression, or suicidal ideation and behavior
- Hepatic AEs

For some AESIs, sites should provide additional information regarding the event, as instructed on the eCRF.

Opportunistic Infections

Infections will be categorized by Lilly as opportunistic according to *Opportunistic Infections and Biologic Therapies in Immune-Mediated Inflammatory Diseases: Consensus Recommendations for Infection Reporting during Clinical Trials and Postmarketing Surveillance* by Winthrop et al. (2015).

Hypersensitivity Events

Site personnel should educate patients and/or caregivers about the symptoms and signs of hypersensitivity events and provide instructions on dealing with these events. For recommendations on the management and follow-up of hypersensitivity events (See Section 7.8.2.1).

Cerebro-Cardiovascular Event Adjudication

Data collected regarding a potential or actual cerebro-cardiovascular AE will be provided to, and adjudicated by, an independent, external adjudication committee. The role of the committee is to adjudicate the reported cardiovascular AEs in a blinded, consistent, and unbiased manner throughout the course of the study, thereby ensuring that all such reported events are evaluated uniformly.

9.2.3. 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.

Patients 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.

9.3. 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 mirikizumab.

9.4. Safety

When multiple safety assessments are scheduled for the same time point, the preferred order of completion is as follows: vital signs, ECG, and then blood sampling.

9.4.1. Vital Signs

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

Sitting blood pressure and pulse rate should be measured after the patient has been sitting for at least 5 minutes. Any clinically significant findings from vital signs measurement that result in a diagnosis and that occur after the patient receives the first dose of study treatment should be reported to Lilly or its designee as an AE via eCRF.

Vital signs and body temperature collected at the last visit of the originator study may be used for the Week 0 assessment. If a vital signs or body temperature are not collected at the last visit of the originator study, they are to be collected at the Week 0 visit. If the interval between the last visit of the originator study and Week 0 is more than 4 weeks, vital signs and body temperature are to be collected at Week 0.

9.4.2. Electrocardiograms

For each patient, electrocardiograms (ECGs) should be collected according to the Schedule of Activities (Section 2).

ECGs should be completed prior to any blood draw. Patients should be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. ECGs will be read locally. Any clinically significant findings from ECGs that result in a diagnosis and that occur after the patient receives the first dose of the investigational treatment should be reported to Lilly or its designee as an AE via eCRF.

The ECG collected at the last visit of the originator study may be used for the Week 0 assessment. If an ECG is not collected at the last visit of the originator study, it is to be collected at the Week 0 visit.

9.4.3. Laboratory Tests

For each patient, laboratory tests detailed in (Appendix 2) should be conducted according to the Schedule of Activities (Section 2). Results of laboratory tests conducted at the last visit of the originator study may be used for Week 0 if the interval between the two visits is 2 weeks or less. If the interval is more than 2 weeks, retesting should occur.

With the exception of laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial. The investigator or designee is expected to review laboratory reports in a timely manner throughout the study.

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

9.4.3.1. Pregnancy Testing

Pregnancy testing is to be performed on all females ≤60 years old, unless they meet the criteria describing women not of child-bearing potential, outlined in inclusion criteria [5b].

Urine pregnancy testing will be performed locally during designated scheduled visits, as described in the Schedule of Activities (Section 2). The urine pregnancy test must be "negative" within 24 hours prior to administration of investigational product.

Urine pregnancy testing may be performed at additional time points during the treatment period and/or follow-up period, at the discretion of the investigator or if this is required by local regulations.

If a urine pregnancy test is not available, a serum pregnancy test is an acceptable alternative.

Assessment of follicle-stimulating hormone (FSH) levels can assist in determining if a woman meets the definition of "postmenopausal," as outlined in inclusion criterion [5b]. FSH can also be optionally obtained at any visit during the study, as indicated in the Schedule of Activities

(Section 2), to determine if a woman meets the definition of "postmenopausal," as outlined in inclusion criterion [5b].

9.4.4. Immunogenicity Assessments

Venous blood samples will be collected to determine antibody production against mirikizumab at the visits and times specified in the Schedule of Activities (Section 2). To aid interpretation of these results, a blood sample for PK analysis is to be collected at the same time points. Samples for ADA and accompanying PK analysis should be taken prior to dosing.

The samples collected at the last visit of originator study may be used for the Week 0 collection if the interval between the 2 visits is 2 weeks or less. If the interval is greater than 2 weeks, new samples are to be collected.

In the event of a drug hypersensitivity event (immediate or nonimmediate), additional samples for ADA and PK will be collected as close to the onset of the event as possible and at 4 and 12 to 16 weeks after the event. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and ERBs allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to mirikizumab. Any samples remaining after 15 years will be destroyed.

9.4.5. Other Tests

9.4.5.1. Physical Examination

Physical examination will be performed as specified in the Schedule of Activities (Section 2). Physical examination should include a symptom-directed evaluation as well as examination of heart, lungs, abdomen, and visual examination of the skin, and exclude pelvic, rectal, and breast examinations. Physical examination can also be performed at the discretion of the investigator at any additional time points, for example, to assist in the evaluation of a new symptom during the study. Any clinically significant findings from physical examination that result in a diagnosis and that occur after the patient receives the first dose of investigational product should be reported to Lilly or its designee as an AE via eCRF.

9.4.5.2. Tuberculosis Evaluation

Evaluation for TB reactivation or new TB is to be performed as specified in Schedule of Activities (Section 2). Patients should be evaluated for signs and symptoms of active TB as well as possible TB exposure or close contact with person with active TB. Evaluation will consist primarily of medical history and physical examination; additional tests (such as chest x-ray or immune response tests) are only required if clinically indicated. Details of these tests are provided in Appendix 6. If the evaluation suggests possible TB reactivation or new TB infection, study drug should be withheld and the patient immediately referred for further evaluation,

including, where possible, consultation with physician specializing in TB, and an adverse event form completed.

9.4.5.3. Hepatitis B

Patients who are HBsAg- anti-HBc+ will be allowed to enter Study AMAP if the following criteria are fulfilled:

- HBV DNA is not detected at the final visit of the originator study *and*
- If HBV DNA was tested at other times in the originator study, HBV DNA was not detected *and*
- The other inclusion/exclusion criteria of Study AMAP are met.

Such patients will undergo HBV DNA testing:

- Approximately every 12 weeks (plus ETV) per the Schedule of Activities (Section 2), **and**
- If an elevated ALT or AST level >3xULN is detected. In this circumstance, if HBV DNA is not detected, the investigator should consult with the Lilly-designated medical monitor regarding further management of the patient.

If HBV DNA is detected during study AMAP, the study drug will be discontinued, an early termination visit will take place and the patient will then enter the post-treatment follow-up period. The sponsor recommends that a hepatologist (or a physician with a specialist interest in viral hepatology) is consulted and that it is determined whether it is appropriate to start antiviral therapy prior to discontinuation of any immunosuppressant or immunomodulatory therapy, or the study drug. Such patients should also receive appropriate follow-up medical care

If HBV DNA is detected during the study, the investigator should consider using one of the following terms to report the adverse event:

- "Detectable HBV DNA," if HBV DNA is detected without an increase in aminotransferase levels.
- "Reactivation of hepatitis B," if HBV DNA is detected with an increase in aminotransferase levels.

Anyone with a new diagnosis of hepatitis B made during this study will be discontinued from study treatment, undergo an early termination visit and post-treatment follow-up, and receive appropriate follow-up medical care.

9.4.5.4. Hepatitis C

Patients who test positive for HCV RNA during Studies AMAN, AMBG or AMAC will be excluded.

Any patient with a history of HCV infection who develops elevated ALT >3xULN will be tested for HCV RNA (see Section 9.4.6.1).

Patients diagnosed with hepatitis C infection or who test positive for HCV RNA during the study will be discontinued from study treatment and should receive appropriate follow-up medical care.

9.4.5.5. Depression and Suicidality

Suicide-related events (behavior and/or ideations) will be assessed and evaluated at Week 0 with the administration of the C-SSRS, the Self-Harm Supplement Form, and the Self-Harm "Follow-Up" Form (if applicable). Depressive symptomology will be assessed with the QIDS-SR16, as specified in Schedule of Activities (Section 2). These assessments are described below, and further information is provided in Appendix 12.

Columbia-Suicide Severity Rating Scale: The C-SSRS (Columbia University Medical Center [WWW]) is a scale that captures the occurrence, severity, and frequency of suicide-related ideations and behaviors during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine if suicidal ideation and/or behavior occurred. The C-SSRS is administered by an appropriately trained health care professional with at least 1 year of patient care/clinical experience. Patient data for the C-SSRS will be documented in the source files.

Self-Harm Supplement Form: The Self-Harm Supplement Form is a single question to enter the number of suicidal behavior events, possible suicide behaviors, or nonsuicidal self-injurious behaviors the patient has experienced since the last assessment. For each unique event identified, a questionnaire (Self-Harm Follow-Up Form) that collects supplemental information on the self-injurious behavior is to be completed. This information will be documented in the source files.

Quick Inventory of Depressive Symtomatology—Self-Report (16 Items): 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, 5th Edition (DSM-V) (APA 2013). Patients will record their responses to the QIDS-SR16 in a source document at the visits indicated in the SOA.

Spontaneous AE collection should occur prior to the collection of the C-SSRS or QIDS. If a suicide related event is discovered during the C-SSRS but was not captured during the spontaneous AE collection at Week 0, sites should not change the AE form. If an event is serious or leads to discontinuation, this is an exception where the SAE and/or AE leading to discontinuation should be included on the AE form and the process for reporting SAEs should be followed.

9.4.6. Safety Monitoring

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

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 to Interim Analyses section [Section 10.3.8]) can conduct additional analyses of the safety data.

9.4.6.1. Hepatic Safety Monitoring

If a study patient experiences elevated ALT ≥3xULN, ALP ≥2xULN, or elevated TBL ≥2xULN, liver testing (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical, and laboratory monitoring should be initiated by the investigator and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Hepatic Safety Data Collection

Additional safety data should be collected via the hepatic eCRF packet if 1 or more of the following conditions occur:

- Elevation of serum ALT to ≥5xULN on 2 or more consecutive blood tests
- Elevated serum TBL to ≥2xULN (except for cases of known Gilbert's syndrome)
- Elevation of serum ALP to ≥2xULN on 2 or more consecutive blood tests
- Patient discontinued from treatment due to a hepatic event or abnormality of liver tests
- Hepatic event considered to be a SAE
- Patient with a history of HCV infection develops elevated ALT >3xULN. Patient will be tested for HCV RNA
- Patient experiences an ALT or AST >3xULN and TBL >2xULN or international normalized ratio >1.5. The study medical monitor should be consulted as soon as possible for further guidance

9.5. Pharmacokinetics

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

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor. Serum concentrations of mirikizumab will be determined using a validated enzyme-linked immunosorbent assay. Additional samples may be collected and used for exploratory analyses such as bioanalytical method development or validation exercises.

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

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

An aliquot of the PK sample may be used for mirikizumab assay development and validation. These samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs/investigational review boards impose shorter time limits.

9.6. Pharmacodynamics

Not applicable.

9.7. Pharmacogenomics

9.7.1. Whole Blood Sample for Pharmacogenetic Research

Collection of a blood sample for pharmacogenetic analysis will not be performed in this study. All patients in this study will have participated in a previous study (eg, AMAC, AMAN) for which collection of a blood sample for pharmacogenetic analysis has been performed.

9.8. Biomarkers

Not applicable.

9.9. Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

10. Statistical Considerations

10.1. Sample Size Determination

The final sample size of Study AMAP will be determined by the number of patients who enroll in Study AMAP from the preceding studies. From Study AMAC and Study AMBG, it is anticipated that approximately 50 to 70% of the eligible patients will enroll leading to approximately 600 to 840 patients from these 2 studies in Study AMAP.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Intent-to-Treat (ITT) Population	All enrolled patients.
Modified Intent-to-Treat (mITT) Population	All enrolled patients who receive at least 1 dose of study treatment during this trial (regardless if the patient does not receive the correct treatment, or otherwise does not follow the protocol). Patients will be analyzed according to the treatment to which they were assigned
Safety Population	Same as mITT Popuation
Per-Protocol (PP) Population	All mITT patients who are not deemed noncompliant with treatment, who do not have significant protocol deviations (defined in the SAP), and whose investigator site does not have significant GCP deviations that require a report to regulatory agencies (regardless of study period).

Abbreviations: GCP = good clinical practice; SAP = statistical analysis plan.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

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

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, such as the analysis method for the primary objective. 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.

All safety, efficacy, and healthy outcomes analyses will be conducted on the modified ITT (mITT) population, unless otherwise stated.

10.3.1.1. Cohort Definition

Study AMAP will include the following 3 patient cohorts; additional cohorts may be defined in the SAP:

1. Cohort 1: Patients from AMBG who completed Week 40 visit on blinded SC mirikizumab treatment
2. Cohort 2: Cohort 1 **and** patients from AMAC who completed the Maintenance Period Week 52 visit on SC mirikizumab treatment

3. Cohort 3: All remaining patients, that is:

    - Patients from Study AMAC who:

        a. completed the Maintenance Period Week 52 visit on SC placebo treatment **or**
        b. completed the Week 40 visit of the unblinded Extension Period Maintenance dosing on SC mirikizumab treatment

        AND

    - Patients from AMBG who:

        a. Completed Week 40 visit on blinded SC placebo treatment **or**
        b. Lost response between Weeks 12 and 28, were rescued with 3 blinded IV rescue doses and were then considered to have clinical benefit, **or**
        c. Received extended induction treatment and completed Week 40 visit on open-label SC mirikizumab

Figure AMAP.12.1 and Figure AMAP.12.2 (AMAC), and Figure AMAP.12.3 (AMBG) provide a pictorial representation of the AMAP patient cohort assignments.

All efficacy analyses including health outcome endpoints will be conducted separately in patients of cohort (1), (2), and (3). All safety analyses will be conducted on all patients in Study AMAP.

10.3.1.2. Baseline Definition

Unless otherwise specified, all references to baseline for efficacy and health outcomes related endpoints in this study protocol refer to baseline values of the originating induction study (that is, the study in which the patient received their first dose for this program). All references to baseline for safety, vital sign and laboratory-related endpoints refer to the baseline of AMAP. Further details about baseline definitions along with any supportive analysis will be described in the SAP.

10.3.1.3. Analyses

Continuous data will be summarized in terms of mean, standard deviation, median, and minimum and maximum values; categorical data will summarized as frequency counts and percentages. This is an open label extension study with only one treatment arm; therefore, the analyses and summaries will be focused on point estimates and confidence intervals.

For assessment of categorical efficacy and health outcome endpoints, the single proportion will be summarized. The 95% confidence intervals may also be reported using the Wilson Score method (Wilson 1927, Newcombe 1998) and the normal approximation to the binomial distribution (Wald and Walfowitz 1939) as supportive to the Wilson Score method. Categorical repeated measure analyses such as generalized linear model will be explored for selected endpoints.

For continuous efficacy and health outcome variables with multiple post-baseline measurements, the mean response over time will be estimated using mixed-effects model for repeated measures (MMRM). The model includes induction baseline value, visit, parent study ID (if multiple parent studies involved), and geographic region (North America, Europe, or Other). 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. Least squares means (LS means) will be reported along with the 95% confidence interval.

For continuous efficacy and health outcome variables with a single post-baseline time point, the mean response will be estimated using analysis of covariance (ANCOVA) including induction baseline value, parent study ID (if multiple parent studies involved) and geographic region in the model. Least squares means (LS means) will be reported along with the 95% confidence intervals. Missing data imputation method for the ANCOVA model will be specified in the SAP.

Continuous safety data including vital sign and laboratory values will be analyzed by an ANCOVA with baseline value as a covariate. Also, laboratory analytes will be presented as mean changes from baseline and as incidence of shift between normal and abnormal states.

The change from baseline of the continuous variables will be assessed by using a paired t-test of the LS means along with 95% CI.

Utilizing visualization tools will also be used to summarize the data as deemed appropriate.

10.3.1.4. Missing Data Imputation

While every effort will be made to reduce missing data, the missing data imputation methods described below will be used to assess the efficacy endpoints when patients are permanently discontinued from study drug or otherwise have missing data.

- Nonresponder imputation (NRI): For analysis of categorical efficacy and health outcomes variables, missing data will be imputed using an NRI method. Patients will be considered a nonresponder for the NRI analysis if they do not meet the categorical response criteria, have missing clinical response data at a time point of interest, or take rescue medication prior to the time point of interest.
- Mixed model for repeated measures: For continuous variables, the primary analysis will be MMRM with the missing at random assumption for handling missing data. This analysis takes into account both missingness of data and the correlation of the repeated measurements. No additional imputation methods will be applied to the MMRM analysis.

Additional missing data imputation methodologies, for example, modified baseline observation carried forward (mBOCF) may be considered as sensitivity analyses and will be fully detailed in the SAP. By using mBOCF, for patients discontinuing investigational product due to an AE or lack of efficacy, the baseline observation will be carried forward to the corresponding primary endpoint for evaluation. For patients discontinuing investigational product for any other reason, the last nonmissing postbaseline observation before discontinuation will be carried forward to the corresponding primary endpoint for evaluation. Those sensitivity analyses and other additional methods to handle missing data or analyzing data that may be required to address regulatory needs will be specified in the SAP or performed as post-hoc analyses as deemed appopriate.

10.3.1.5. Multiple Comparisons/Multiplicity

This is an open label extension study with 1 treatment arm. No multiplicity adjustment is planned for in this trial.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

Reasons for discontinuing the study drug/study will be summarized for each cohort defined in Section 10.3.1. Frequency counts and percentages of completing the study or discontinue the study drug/study early will be presented.

10.3.2.2. Patient Characteristics

Year of birth, sex, weight, height, smoking habits, previous treatment failure (CS only, immunomodulator failure without biologic failure, biologic failure), baseline corticosteroid use and other demographic and disease characteristics will be recorded. Age and body mass index will be calculated. Demographic and baseline disease characteristics will be summarized by cohorts defined in Section 10.3.1.

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 drug dictionary. The current concomitant therapy (will be presented separately in frequency tables by drug name and by cohorts defined in Section 10.3.1.

10.3.2.4. Treatment Compliance

Treatment compliance will be summarized by cohorts. The details of noncompliance will be defined in the SAP. A contingency table of numbers of noncompliant patients by cohorts will be provided.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary endpoint is proportion of patients having clinical remission at Week 52 among patients in cohort 1. The primary analysis will be conducted on mITT population. Sensitivity analysis will be conducted on ITT population and PP population.

For study visits that include endoscopy as a study procedure, the SF and RB subscores of the Mayo score will be calculated from daily diary data by averaging the most recent 3 valid days (possibly nonconsecutive) in the 7 days prior to commencing bowel preparation for endoscopy. If fewer than 3 valid days are available, the subscores will be considered missing. The 3 days of patient diary data used for SF and RB calculation will exclude data from the following days: (i) days when patients receive bowel preparation, (ii) the day of an endoscopy, and (iii) the day after an endoscopy. At other study visits, where endoscopy is not performed, SF and RB data will be collected in the preceding 24-hour period of the visit.

To calculate the SF subscore, the reference stool frequency from the induction baseline will be subtracted from the SF stool frequency. The subtracted stool frequency value will then be rounded to the nearest integer and then mapped to obtain Mayo SF subscore. Rectal bleeding

subscore will be rounded to the nearest integer value of the 3-day averaged RB for visits including endoscopy.

The proportion of patients reaching clinical remission at Week 52 will be summarized, and the 95% confidence interval will be provided by using Wilson Score method and the normal approximation to the binomial distribution as supportive to the Wilson Score method. NRI approach defined in Section 10.3.1.1 will be applied to handle missing data. Other sensitivity analyses for handling missing data will be defined in SAP.

10.3.3.2. Secondary Analyses

The secondary efficacy and health outcome endpoints of the trial are presented in Table AMAP.4.1. Details of the analysis methods that will be utilized are provided in Section 10.3.1. Additional analyses of the secondary efficacy and health outcome endpoints may be considered and will be detailed in the SAP.

10.3.4. Safety Analyses

Safety data, including treatment-emergent adverse events (TEAEs), AESIs, SAEs, laboratory analytes (chemistry, hematology, etc), and vital signs will be descriptively summarized as indicated in Section 10.3.1.

Treatment-emergent adverse events are defined as AEs that first occurred or worsened in severity on or after the date of the first dose of study treatment in Study AMAP. The number of TEAEs and the number and percentage of patients who experience at least 1 TEAE will be summarized using *Medical Dictionary for Regulatory Activities* (MedDRA) for each system organ class (or a body system) and each preferred term by cohort and treatment group (step-down). Exposure-adjusted incidence rates will be provided. Serious adverse events and AEs that lead to investigational product discontinuation will also be summarized.

All clinical laboratory results will be descriptively summarized. Individual results that are outside of normal reference ranges will be flagged in data listings. Quantitative clinical hematology, chemistry, and urinalysis variables will be summarized as changes from baseline. Categorical variables, including the incidence of abnormal values and incidence of AESIs, will be summarized by frequency and percentage of patients in corresponding categories. Shift tables will be presented for selected measures.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Analyses of pharmacokinetic data will be limited to graphical or tabular summaries of mirikizumab concentrations. No model-based analyses of the data are planned unless deemed necessary based on unanswered questions raised in preceding studies. Exploratory evaluations of the relationships between mirikizumab exposure and efficacy and safety may be performed.

10.3.6. Evaluation of Immunogenicity

The frequency and percentage of patients with preexisting (baseline) ADA, ADA at any time post baseline, and with treatment-emergent (TE) ADA to mirikizumab will be tabulated. If no ADAs are detected at baseline, TE ADA are defined as those with a titer 2-fold (1 dilution)

greater than the minimum required dilution of the assay. For samples with ADA detected at baseline TE ADA are defined as those with a 4-fold (2 dilutions) increase in titer compared to baseline. For patients who have TE ADA the distribution of maximum titers will be described. The frequency of neutralizing antibodies will also be tabulated.

The relationship between the presence of antibodies and the PK parameters and PD response including safety and efficacy to mirikizumab will be assessed.

10.3.7. Other Analyses

10.3.7.1. Health Economics

Not applicable.

10.3.7.2. Subgroup Analyses

Additional subgroup analyses will be conducted for select safety and efficacy endpoints. Subgroups to be evaluated may include the original biologic status (biologic failed or conventional failed), original corticosteroid use (yes or no), gender, age group, race, region, patients requiring hospitalization for UC, and patients requiring surgery related to UC. Additional subgroups will be defined in the SAP.

10.3.8. Interim Analyses

One DMC consisting of members external to Lilly will be established for periodic monitoring of clinical trial data across all Phase 3 trials for UC adult program. This committee will consist of a minimum of 3 members, including a physician with expertise in gastroenterology and a statistician. No member of the DMC may have contact with study sites. A statistical analysis Center (SAC) will prepare and provide unblinded data to the DMC. The SAC members may be Lilly employees or from third-party organizations designated by Lilly. However, they will be external to the study team and will have no contact with sites and no privileges to influence changes to the ongoing studies. The timing and frequency of the periodic clinical trial data review by the DMC will the detailed in the DMC charter.

In addition to the periodic clinical trial data reviews conducted by the DMC, an interim analysis conducted by the sponsor may be performed to support a potential regulatory submission when Study AMBG patients have completed 40 weeks treatment (continuous treatment of 52 weeks) or have discontinued early. Subsequent to that, additional yearly interim analysis may be performed along with the 4-month safety update to support regulatory submissions.

11. References

American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-V). 5th ed. Washington DC: APA; 2013.

[APA] American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-V). 5th ed. Washington DC: APA; 2013.

Blauvelt A, Papp KA, Griffiths CE, Randazzo B, Wasfi Y, Shen YK, Li S, Kimball AB. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *J Am Acad Dermatol*. 2017;76(3):405-417.

Columbia University Medical Center. Columbia–Suicide Severity Rating Scale (C-SSRS) Web site. 2016. Available at: http://www.cssrs.columbia.edu. Accessed June 20, 2017.

Deepak P, Sandborn WJ. Ustekinumab and anti-Interleukin-23 agents in Crohn's disease. Gastroenterol Clin North Am. 2017;46(3):603-626.

Dignass A, Lindsay JO, Sturm A, Windsor A, Colombel JF, Allez M, D'Haens G, D'Hoore A, Mantzaris G, Novacek G, Oresland T, Reinisch W, Sans M, Stange E, Vermeire S, Travis S, van Assche G. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. *J Crohns Colitis*. 2012;6(10):991-1030.

Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, Van Assche G, Axler J, Kim HJ, Danese S, Fox I, Milch C, Sankoh S, Wyant T, Xu J, Parikh A; GEMINI 1 Study Group. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2013;369(8):699-710.

Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, Blank MA, Johanns J, Gao L-L, Miao Y, Adedokun OJ, Sands BE, Hanauer SB, Vermeire S, Targan S, Ghosh S, de Villiers WJ, Colombel J-F, Tulassay Z, Seidler U, Salzberg BA, Desreumaux P, Lee SD, Loftus EVJ, Dieleman LA, Katz S , Rutgeerts P. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. *N Engl J Med*. 2016;375(20):1946-1960.

Feagan BG, Sandborn WJ, D'Haens G, Panés J, Kaser A, Ferrante M, Louis E, Franchimont D, Dewit O, Seidler U, Kim K-J, Neurath MF, Schreiber S, Scholl P, Pamulapati C, Lalovic B, Visvanathan S, Padula SJ, Herichova I, Soaita A, Hall DB , Böcher WO. Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomised, double-blind, placebo-controlled phase 2 study. *The Lancet*. 2017;389(10080):1699-1709.

Gaffen SL, Jain R, Garg AV, Cua DJ. The IL-23-IL-17 immune axis: from mechanisms to therapeutic testing. *Nat Rev Immunol*. 2014;14(9):585-600.

Gottlieb A, Menter A, Mendelsohn A, Shen YK, Li S, Guzzo C, Fretzin S, Kunynetz R, Kavanaugh A. Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. *Lancet*. 2009;373(9664):633-640. Erratum in: *Lancet*. 2010;376(9752):1542.

Guyatt G, Mitchell A, Irvine EJ, Singer J, Williams N, Goodacre R, Tompkins C. A new measure of health status for clinical trials in inflammatory bowel disease. *Gastroenterology*. 1989;96(3):804-810.

Horsburgh CR Jr, Rubin EJ. Latent Tuberculosis Infection in the United States. *N Engl J Med*. 2011;364(15):1441-1448.

Irvine EJ, Feagan B, Rochon J, Archambault A, Fedorak RN, Groll A, Kinnear D, Saibil F, McDonald JW. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's Relapse Prevention Trial Study Group. *Gastroenterology*. 1994;106(2):287-296.

Irvine EJ, Zhou Q, Thompson AK. The short inflammatory bowel disease questionnaire: a quality of life instrument for community physicians managing inflammatory bowel disease. CCRPT investigators. Canadian Crohn's Relapse Prevention Trial. *Am J Gastroenterol*. 1996;91(8):1571–8.

Jostins L, Ripke S, Weersma RK, Duerr RH, McGovern DP, Hui KY, Lee JC, Schumm LP, Sharma Y, Anderson CA, Essers J, Mitrovic M, Ning K, Cleynen I, Theatre E, Spain SL, Raychaudhuri S, Goyette P, Wei Z, Abraham C, Achkar JP, Ahmad T, Amininejad L, Ananthakrishnan AN, Andersen V, Andrews JM, Baidoo L, Balschun T, Bampton PA, Bitton A, Boucher G, Brand S, Büning C, Cohain A, Cichon S, D'Amato M, De Jong D, Devaney KL, Dubinsky M, Edwards C, Ellinghaus D, Ferguson LR, Franchimont D, Fransen K, Gearry R, Georges M, Gieger C, Glas J, Haritunians T, Hart A, Hawkey C, Hedl M, Hu X, Karlsen TH, Kupcinskas L, Kugathasan S, Latiano A, Laukens D, Lawrance IC, Lees CW, Louis E, Mahy G, Mansfield J, Morgan AR, Mowat C, Newman W, Palmieri O, Ponsioen CY, Potocnik U, Prescott NJ, Regueiro M, Rotter JI, Russell RK, Sanderson JD, Sans M, Satsangi J, Schreiber S, Simms LA, Sventoraityte J, Targan SR, Taylor KD, Tremelling M, Verspaget HW, De Vos M, Wijmenga C, Wilson DC, Winkelmann J, Xavier RJ, Zeissig S, Zhang B, Zhang CK, Zhao H; International IBD Genetics Consortium (IIBDGC), Silverberg MS, Annese V, Hakonarson H, Brant SR, Radford-Smith G, Mathew CG, Rioux JD, Schadt EE, Daly MJ, Franke A, Parkes M, Vermeire S, Barrett JC, Cho JH. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature*. 2012;491(7422):119-124.

Kikly K, Liu L, Na S, Sedgwick JD. The IL-23/Th(17) axis: therapeutic targets for autoimmune inflammation. *Curr Opin Immunol*. 2006;18(6):670-675.

Kopp T, Riedl E, Bangert C, Bowman EP, Greisenegger E, Horowitz A, Kittler H, Blumenschein WM, McClanahan TK, Marbury T, Zachariae C, Xu D, Hou XS, Mehta A, Zandvliet AS, Montgomery D, van Aarle F, Khalilieh S. 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, Lalovic B, Aslanyan S, Wang EE, Hall D, Solinger A, Padula S, Scholl P. 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.

Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, Li S, Dooley LT, Gordon KB; PHOENIX 1 study investigators. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet*. 2008;371(9625):1665-1674. Erratum in: *Lancet*. 2008;371(9627):1838.

Levesque BG, Sandborn WJ, Ruel J, Feagan BG, Sands BE, Colombel JF. Converging goals of treatment of inflammatory bowel disease from clinical trials and practice. *Gastroenterology*. 2015;148(1):37–51. e1.

Lewinsohn DM, Leonard MK, LoBue PA, Cohn DL, Daley CL, Desmond E, Keane J, Lewinsohn DA, Loeffler AM, Mazurek GH, O'Brien RJ, Pai M, Richeldi L, Salfinger M, Shinnick TM, Sterling TR, Warshauer DM , Woods GL. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: diagnosis of tuberculosis in adults and children. *Clin Infect Dis*. 2017;64(2):111-115.

Monteleone I, Pallone F, Monteleone G. Interleukin-23 and Th17 cells in the control of gut inflammation. *Mediators Inflamm*. 2009;2009:297645.

Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. *Stat Med*. 1998 17(8):857-72.

Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, Guzzo C, Hsu MC, Wang Y, Li S, Dooley LT, Reich K; PHOENIX 2 study investigators. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet*. 2008;371(9625):1675-1684.

Papp K, Thaçi D, Reich K, Riedl E, Langley RG, Krueger JG, Gottlieb AB, Nakagawa H, Bowman EP, Mehta A, Li Q, Zhou Y, Shames R. Tildrakizumab (MK-3222), an anti-interleukin-23p19 monoclonal antibody, improves psoriasis in a phase IIb randomized placebo-controlled trial. *Br J Dermatol*. 2015;173(4):930-939.

Papp KA, Blauvelt A, Bukhalo M, Gooderham M, Krueger JG, Lacour JP, Menter A, Philipp S, Sofen H, Tyring S, Berner BR, Visvanathan S, Pamulapati C, Bennett N, Flack M, Scholl P, Padula SJ. Risankizumab versus Ustekinumab for Moderate-to-Severe Plaque Psoriasis. *N Engl J Med*. 2017;376(16):1551-1560.

Reich K, Bissonnette R, Menter A, Klekotka P, Patel D, Li J, Tuttle J, Papp K. Efficacy and safety of mirikizumab (LY3074828) in the treatment of moderate-to-severe plaque psoriasis: results from a phase II study. Psoriasis Gene to Clinic, 8th International Congress. The Queen Elizabeth II Conference Centre, London, U.K., 30th November – 2nd December 2017. *Br J Dermatol*. 2017a;177:e249. doi:10.1111/bjd.16059

Reich K, Armstrong AW, Foley P, Song M, Wasfi Y, Randazzo B, Li S, Shen YK, Gordon KB. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. *J Am Acad Dermatol*. 2017b;76(3):418-431.

Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* 2005;353(23):2462-2476.

Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, Adedokun OJ, Guzzo C, Colombel JF, Reinisch W, Gibson PR, Collins J, Järnerot G, Hibi T, Rutgeerts P; PURSUIT-SC Study Group. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2014a;146(1):85-95; quiz e14-15.

Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, Adedokun OJ, Guzzo C, Colombel JF, Reinisch W, Gibson PR, Collins J, Järnerot G, Rutgeerts P; PURSUIT-Maintenance Study Group. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2014b;146(1):96-109. e1.

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

Sandborn WJ, van Assche G, Reinisch W, Colombel JF, D'Haens G, Wolf DC, Kron M, Tighe MB, Lazar A, Thakkar RB. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology.* 2012a;142(2):257-265.e1-e3.

Sands BE, Chen J, Feagan BG, Penney M, Rees WA, Danese S, Higgins PDR, Newbold P, Faggioni R, Patra K, Li J, Klekotka P, Morehouse C, Pulkstenis E, Drappa J, van der Merwe R, asser RA. Efficacy and safety of MEDI2070, an antibody against interleukin 23, in patients with moderate to severe Crohn's disease: A phase 2a study. *Gastroenterology*. 2017;153(1):77-86. e76.

Scherl EJ, Pruitt R, Gordon GL, Lamet M, Shaw A, Huang S, Mareya S, Forbes WP. Safety and efficacy of a new 3.3 g b.i.d. tablet formulation in patients with mild-to-moderately-active ulcerative colitis: a multicenter, randomized, double-blind, placebo-controlled study. *Am J Gastroenterol*. 2009;104:1452-1459.

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

Sofen H, Smith S, Matheson RT, Leonardi CL, Calderon C, Brodmerkel C, Li K, Campbell K, Marciniak SJ Jr, Wasfi Y, Wang Y, Szapary P, Krueger JG. 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.

Teng MW, Bowman EP, McElwee JJ, Smyth MJ, Casanova JL, Cooper AM, Cua DJ. IL-12 and IL-23 cytokines: from discovery to targeted therapies for immune-mediated inflammatory diseases. *Nat Med*. 2015;21(7):719-729.

Wald A. and Wolfowitz J. Confidence limits for continuous distribution functions. *Ann Math Stat*. 1939;10:105-118.

Wilson EB. Probable inference, the law of succession, and statistical inference, *J Am Stat Assoc.* 1927;22:209-212.

[WHOa] World Health Organization. WHO guidelines on tuberculosis. Available at: http://www.who.int/publications/guidelines/tuberculosis/en. Accessed November 21, 2017.

[WHOb] World Health Organization. Use of high burden country lists for TB by WHO in the post-2015 era. Available at: http://www.who.int/tb/publications/global_report/high_tb_burdencountrylists2016-2020.pdf. Accessed September 5, 2017.

Winthrop KL, Novosad SA, Baddley JW, Calabrese L, Chiller T, Polgreen P, Bartalesi F, Lipman M, Mariette X, Lortholary O, Weinblatt ME, Saag M , Smolen J. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. *Ann Rheum Dis*. 2015;74:2107-2116.

12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	Anti-drug antibody
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation patient 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.
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
anti-HBc	anti-hepatitis B core antibody
ASA	aminosalicylic acid
AST	aspartate aminotransferase
AZA	azathioprine
BCG	Bacillus Calmette-Guerin
blinding	A double-blind study is one in which neither the patient nor the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received.
clinical research physician	Individual responsible for the medical conduct of the study. Responsibilities of the clinical research physician may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
complaint	Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice, and applicable regulatory requirements.
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	electronic case report form

enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
ES	endoscopic subscore(s)
ETV	early termination visit
EUDRA	European Union Drug Regulatory Authorities
FSH	follicle-stimulating hormone
GEMINI 1	Phase 3, Randomized, Placebo-Controlled, Blinded, Multicenter Study of the Induction and Maintenance of Clinical Response and Remission by Vedolizumab (MLN0002) in Patients with Moderate to Severe Ulcerative Colitis (GEMINI 1)
GMP	Good Manufacturing Practices
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	informed consent form
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IL	interleukin
IV	intravenous
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study after having been informed of all aspects of the study that are relevant to the patient decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
interim analysis	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	intent-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 patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients 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.
LOR	loss of response
modified ITT	modified intent-to-treat: All randomized/enrolled patients who received at least 1 dose of study treatment, do not receive the correct treatment, or otherwise do not follow the protocol. Patients will be analyzed according to the treatment to which they were assigned
MMRM	mixed-effects model for repeated measures
MP	mercaptopurine
NRI	nonresponder imputation
PD	pharmacodynamic(s)
PGA	Physician's Global Assessment
PK	pharmacokinetic(s)
PROs	patient-reported outcomes
Q4W	every 4 weeks
QIDS-SR16	Quick Inventory of Depressive Symptomatology (self-report)
RB	rectal bleeding
SAE	serious adverse event
SAP	statistical analysis plan
SF	stool frequency
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.
SOA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis

TBL	total bilirubin level
TE ADA	treatment-emergent antidrug antibody
TEAE	treatment-emergent adverse event
UC	ulcerative colitis
ULN	upper limit of normal

Appendix 2. Clinical Laboratory Tests

Hematology[a,b]	**Clinical Chemistry**[a,b]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Chloride
Mean cell volume	Bicarbonate
Mean cell hemoglobin	Potassium
Mean cell hemoglobin concentration	Total bilirubin
Leukocytes (WBC)	Total protein
Cell morphology	Direct bilirubin
Neutrophils, segmented	Alkaline phosphatase
Lymphocytes	Alanine aminotransferase (ALT)
Monocytes	Aspartate aminotransferase (AST)
Eosinophils	Gamma-Glutamyl Transferase (GGT)
Basophils	Blood urea nitrogen (BUN)
Platelets	Creatinine
	Uric acid
	Calcium
	Glucose, nonfasting
	Albumin
	Cholesterol (total)
	Triglycerides
	Creatine kinase (CK)
	Other Tests[a]
	Hepatitis B DNA PCR (if indicated)[b,c]
	Pregnancy test (urine[d])
	FSH[b,d]
	Anti-mirikizumab antibodies (immunogenicity)
	QuantiFERON-TB Gold test or T-SPOT or TST
	Serum mirikizumab concentration (PK)
	Clostridium difficile[e] and Stool Culture[e]

Abbreviations: DNA = deoxyribonucleic acid; FSH = follicle-stimulating hormone; PCR = polymerase chain reaction; PK = pharmacokinetic; RBC = red blood cell; WBC = white blood cell.

[a] Assayed by Lilly-designated laboratory.

[b] Results will be confirmed by the Central Laboratory/other at the time of initial testing.

[c] Hepatitis B DNA PCR testing will be performed on patients from Studies AMAN or AMAC, known to be anti-HBc+.

[d] Urine pregnancy test will be evaluated locally. If a urine pregnancy test is not available, a serum pregnancy test is an acceptable alternative. FSH test can be performed to confirm that women ≥50 years of age with spontaneous amenorrhea for at least 6 months lack childbearing potential, see Inclusion Criteria [5b].

[e] Can be done locally by investigator as needed.

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 patient/patient's legal representative understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- Ensuring that informed consent is given by each patient 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.
- Enswering any questions the patient/patient's legal representative may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's/patient's legal representative willingness to continue his or her participation in the study.
- Ensuring that a copy of the ICF is provided to the participant or the participant's legal representative and is kept on file.
- Ensuring that the medical record includes a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Appendix 3.1.2. Recruitment

Eli Lilly and Company (Lilly) is responsible for the central recruitment strategy for patients. Individual investigators may have additional local requirements or processes.

Appendix 3.1.3. Ethical Review

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

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERB(s), 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 protocol and related amendments and addenda, current Investigator Brochure (IB), and updates during the course of the study
- ICF

- other relevant documents (for example, curricula vitae, advertisements)

Appendix 3.1.4. Regulatory Considerations

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

- 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 3.1.5. Investigator Information

Physicians with a specialty in gastroenterology will participate as investigators in this clinical trial. Site-specific contact information may be provided in a separate document.

Appendix 3.1.6. 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 3.1.7. Final Report Signature

The CSR coordinating investigator 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.

The investigator with the most enrolled patients will serve as the CSR coordinating investigator. 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 eCRFs, and study procedures.

- Make periodic visits to the study site
- Be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- Review and evaluate eCRF data and 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 patient 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

Case report form data will be encoded and stored in a clinical trial database.

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

Data managed by a central vendor, such as laboratory test data or endoscopic 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.

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

Appendix 3.3.2. Discontinuation of the Study

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

Appendix 3.4. Publication Policy

The publication policy for Study I6T-MC-AMAP is described in the letters of agreement between the sponsor and the investigators and institutions.

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 patients in consultation with the Lilly, or its designee, clinical research physician. These tests will be performed at a Lilly-designated laboratory.

Hepatic Monitoring Tests

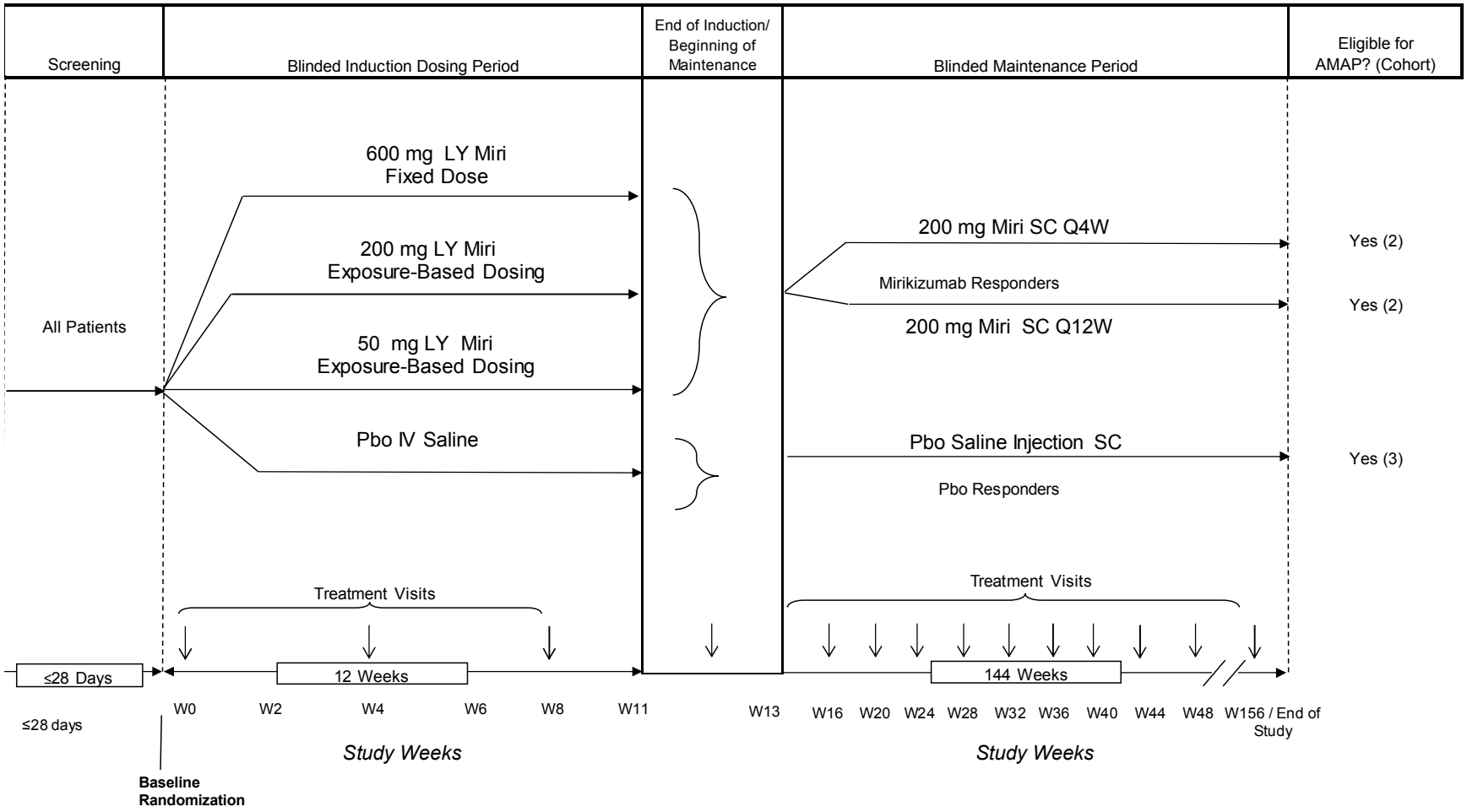
Hepatic Hematology[a]	**Haptoglobin**
Hemoglobin	
Hematocrit	**Hepatic Coagulation**
RBCs	Prothrombin Time
WBCs	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody**
AST	
GGT	**Alkaline phosphatase isoenzymes**
CPK	
	Anti-smooth muscle antibody (or anti-actin antibody)

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

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

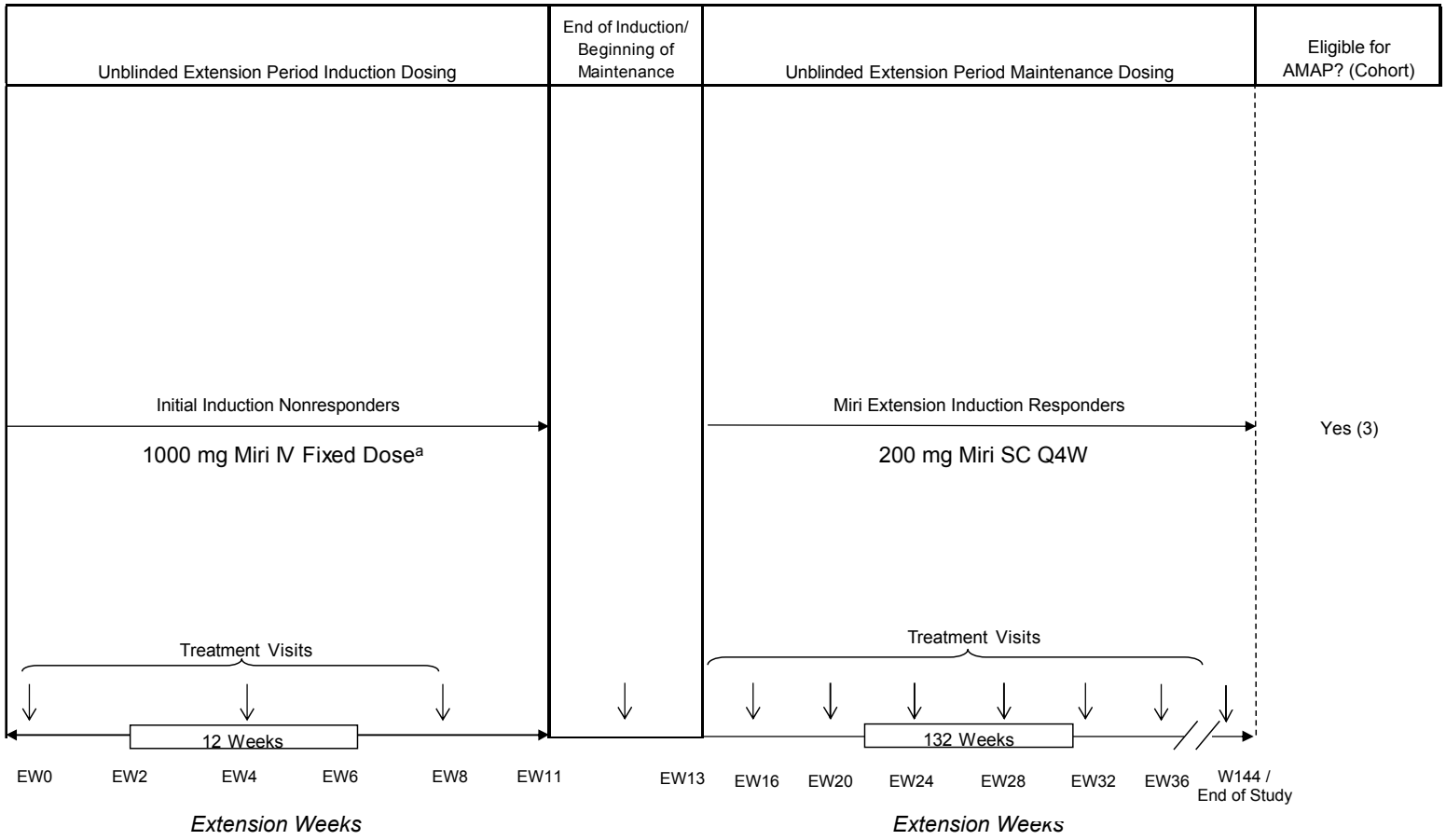
Appendix 5. Study AMAC and AMBG Study Design Figures

I6T-MC-AMAC Study Diagram



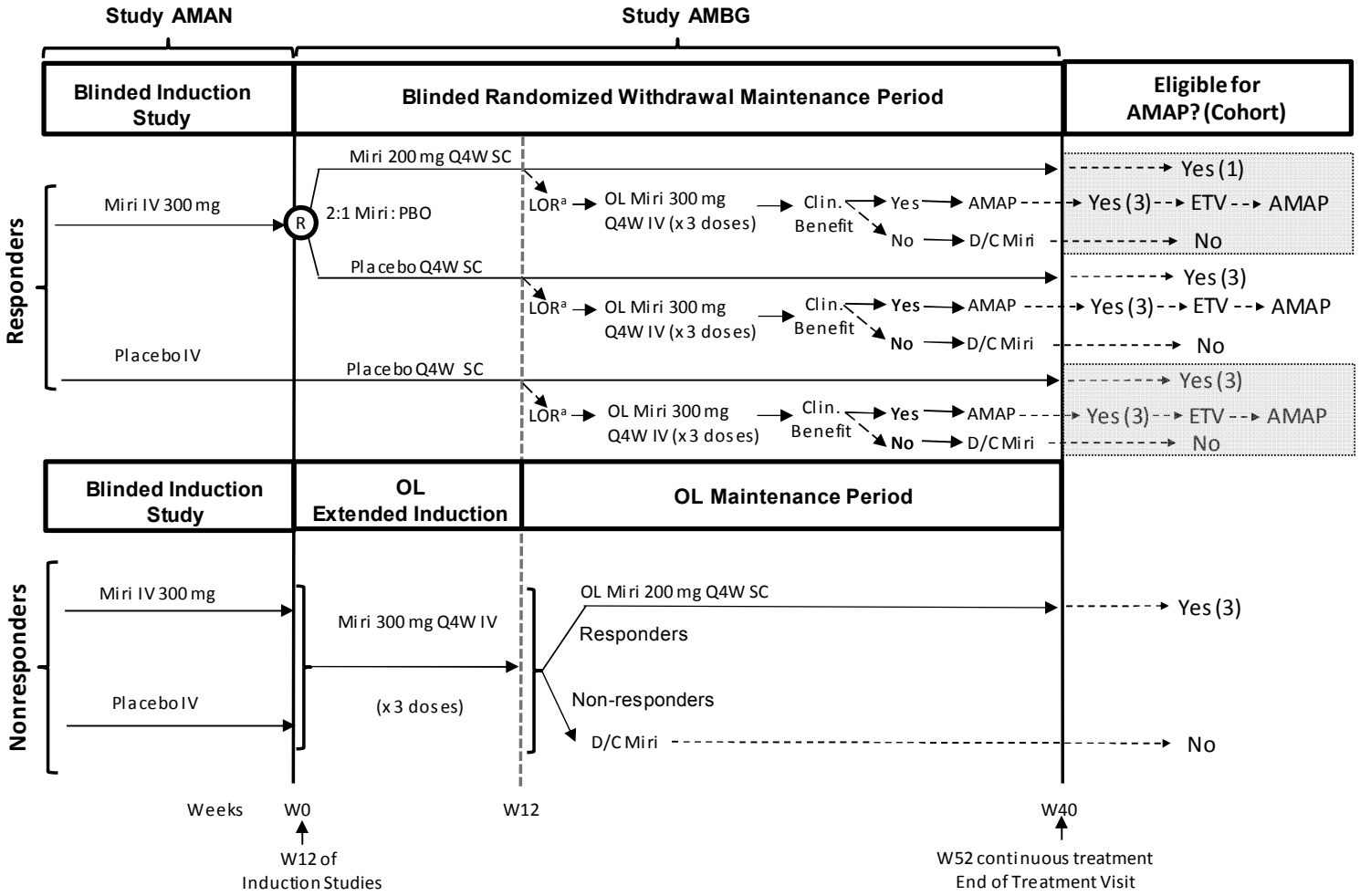
Abbreviations: IV = intravenous; Miri = mirikizumab; SC = subcutaneous; W = week.
Note: Patients eligible for Study AMAP must meet all of the inclusion criteria and none of EC to enroll.

Figure AMAP.12.1 Illustration of study design for Study AMAC.



Abbreviations: EW = extension week; IV = intravenous; Miri = mirikizumab; SC = subcutaneous.
Note: Patients eligible for Study AMAP must meet all of the inclusion criteria and none of EC to enroll.
a Dose was originally 600 mg. This was increased to 1000 mg with a protocol amendment.

Figure AMAP.12.2 Illustration of study design for Study AMAC, extension study.



Abbreviations: D/C = discontinue; IV = intravenous; LOR = loss of response; Miri = mirikizumab; OL = open-label; PBO = placebo; R = randomization; SC = subcutaneous; W = week.
Note: Patients eligible for AMAP must meet all of the inclusion criteria and none of EC to enroll.
a Loss of response at or after Week 12.

Figure AMAP.12.3 Illustration of study design for Study AMBG, maintenance study.

Appendix 6. Tuberculosis Evaluation

All patients will be evaluated annually for active and latent TB infection (LTBI). Evaluations may incorporate:

- Medical history, and physical examination as described in Section 9.4.5.1,
- Chest x-ray (CXR), and
- A test to assess immune response to mycobacterial antigens:
    - Interferon-γ release assay (IGRA, eg, QuantiFERON-TB Gold or T-SPOT.TB), or
    - Tuberculin skin test (TST, also called a purified protein derivative [PPD] or Mantoux test).

Tests for Immune Response to Mycobacterial Antigens

In people aged 5 years and over, IGRA is the preferred test for LTBI, and should be performed in this study in preference to TST. IGRA is also the preferred screening test for LTBI in patients who have received a BCG vaccination. In countries where the TST is available and is preferred (in the judgment of the investigator) as an alternative screening test for LTBI, that test may be used instead of an IGRA for appropriate patients.

Interpretation of Tests for LTBI

The QuantiFERON-TB Gold assay will be reported as negative, indeterminate, or positive. The T-SPOT.TB assay will be reported as negative, borderline, or positive.

The TST should be read 48 to 72 hours after test application. Skin induration ≥5mm in diameter is interpreted as positive for the purpose of this study, regardless of BCG vaccination history.

Retesting and Confirmatory Testing

One retest is allowed for patients with an "indeterminate" QuantiFERON-TB Gold assay or "borderline" T-SPOT assay. Patients with 2 indeterminate QuantiFERON-TB Gold assays or 2 borderline T-SPOT assays will be excluded.

Confirmatory testing with an IGRA is allowed for selected patients who have a positive QuantiFERON-TB Gold assay, positive T-SPOT.TB assay, or positive TST who meet all of the following criteria, and are assessed by the investigator as likely having a false-positive test result: no risk factors for LTBI, no risk factors for increased likelihood of progressing from LTBI to active TB, and have never resided in a high-burden country (detailed in Appendix 7).

Patients with a negative TST or IGRA can be re-tested with an IGRA where, in the judgement of the investigator, the initial test result may be a false negative, for example, due to a technical difficulty in administering the TST or due to concomitant immunosuppressant therapy.

Diagnosis of LTBI during Study

Patients diagnosed with LTBI during the study must have study drug interrupted. If treatment for LTBI is considered to be appropriate, the patient must complete at least 4 weeks of appropriate therapy for LTBI, based on national or international guidelines (for example, United States Centers for Disease Control and Prevention (CDC [WWW]); or the World Health Organization (WHOa [WWW]), and have no evidence of hepatotoxicity (ALT and AST levels

must remain ≤2xULN) upon retesting of serum ALT and AST levels after at least 4 weeks of LTBI treatment. Such patients may then resume study drug treatment and must continue with and complete a full course of treatment for LTBI in order to continue on study drug. Noncompliance with LTBI treatment during the study is a reason for permanent discontinuation from study drug.

Household Contact

Patients who have had household contact with a person with active TB must be evaluated for TB infection.

Active TB

If a patient is diagnosed with active TB during the study, the study drug will be discontinued, the patient will undergo an ETV and then enter the post-treatment follow-up period. The patient should also be referred by the investigator for appropriate TB treatment and follow-up.

Appendix 7. Risk Factors for Latent Tuberculosis Infection

Risk Factors for Latent Tuberculosis Infection
Household contact or recent exposure to an active case
Birth or residency in a high burden country (>20/100,000)
Residents and employees of high risk congregate settings, for example, prisons, homelessness, intravenous drug use

Source: Adapted from Horsburgh and Rubin 2011 and Lewinsohn et al. 2017.

Risk Factors for Increased Likelihood of Progression from LTBI to Active TB
Household contact or close contact with an active case
HIV
Radiographic evidence of old, healed TB that was not treated
Silicosis
Treatment with ≥15 mg prednisone (or equivalent) per day
Children <5 years of age
Chronic renal failure
Treatment with an anti-TNF antibody
Poorly controlled diabetes
Intravenous drug use
Weight ≥10% below normal
Smoking

Abbreviations: HIV = human immunodeficiency virus; LTBI = latent tuberculosis infection; TB = tuberculosis; TNF = tumor necrosis factor.

Source: Adapted from Horsburgh and Rubin 2011.

WHO List of High Burden Countries (as at 28 Oct 2015, includes but may not be limited to)		
Angola	India	Peru
Azerbaijan	Indonesia	Philippines
Bangladesh	Kenya	Russian Federation
Belarus	Kazakhstan	Sierra Leone
Botswana	Democratic People's Republic of Korea	Somalia
Brazil	Kyrgyzstan	South Africa
Cambodia	Lesotho	Swaziland
Cameroon	Liberia	Tajikistan
Central African Republic	Malawi	United Republic of Tanzania
Chad	Republic of Moldova	Thailand
China	Mozambique	Uganda
Congo	Myanmar	Ukraine
Democratic Republic of the Congo	Namibia	Uzbekistan
Ethiopia	Nigeria	Vietnam
Ghana	Pakistan	Zambia
Guinea-Bissau	Papua New Guinea	Zimbabwe

Source: WHOb [WWW].

Appendix 8. Mayo Scoring System for the Assessment of Ulcerative Colitis Activity

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

Note: The Mayo score ranges from 0 to 12, with higher scores indicating more severe disease. Modified Mayo score excludes PGA and ranges from 0 to 9. Composite SF and RB score ranges from 0 to 6. The original description of the Mayo score included friability in the definition of an endoscopic subscore of 1. Consistent with current clinical practice and regulatory guidance, this study excludes friability from the definition of an endoscopic subscore of 1.

Source: Adapted from Schroeder et al. (1987), Scherl et al. (2009)

Appendix 9. Prohibited Medications

This section outlines medications that are prohibited during the treatment phase of the study, if applicable. Use of the medications listed in this appendix is allowed at the discretion of the investigator after a patient discontinues study drug and completes the early termination visit.

Drug Class	**Comments**
Anti-TNF antibodies (for example, infliximab, adalimumab or golimumab)	Prohibited throughout treatment period
Anti-integrin antibodies (for example, vedolizumab)	Prohibited throughout treatment period
Agents depleting B or T cells (for example, rituximab, alemtuzumab, or visilizumab)	Prohibited throughout treatment period
Immunomodulatory medications, including oral cyclosporine, IV cyclosporine, tacrolimus, mycophenolate mofetil, thalidomide or JAK inhibitors (for example, tofacitinib)	Prohibited throughout treatment period
Rectally administered 5-ASAs (enemas or suppositories)	Prohibited throughout treatment period
Rectally administered corticosteroids (enemas or suppositories)	Prohibited throughout treatment period
Intravenous corticosteroids	A course of IV corticosteroids is prohibited
Systemic corticosteroids for non-UC indications (oral or IV)	Patients requiring systemic corticosteroids for non-UC conditions (except corticosteroids to treat adrenal insufficiency) are excluded. Locally administered corticosteroids (eg, inhaled, intranasal, intra-articular, topical) are allowed.
Oral budesonide standard formulation (that is, *not* the oral budesonide extended release tablet formulation [budesonide MMX])	Prohibited throughout treatment period.
Any investigational therapy (biologic or nonbiologic)	Prohibited throughout treatment period
Interferon therapy	Prohibited throughout treatment period
Leukocyte apheresis (leukopheresis, for example, Adacolumn)	Prohibited throughout treatment period
Anti-IL12p40 antibodies (for example, ustekinumab [Stelara®]) or anti-IL-23p19 antibodies (for example, risankizumab [BI-655066], brazikumab [MEDI-2070], guselkumab [CNTO1959], tildrakizumab [MK-3222]) for any indication, including investigational use	Prohibited throughout treatment period
Bacillus Calmette-Guerin (BCG) vaccine	BCG vaccination prohibited throughout the duration of the study and for 12 months after discontinuation of study drug.
Live attenduated vaccines	Live attenuated vaccines are prohibited throughout the duration of the study and for 3 months after discontinuation of study drug.

Abbreviations: 5-ASA = 5-aminosalicyclic; IV = intravenous; JAK = Janus Kinase; TNF = tumor necrosis factor.

Appendix 10. Permitted Medications with Dose Stabilization

Drug Class	Comments
Oral 5-ASAs (for example, mesalamine, balsalazide, olsalazide)	May continue during study with stable doses encouraged
Oral corticosteroids (prednisone ≤20 mg/day or equivalent, or budesonide MMX 9 mg/day)	May use during study with stable doses encouraged. Pulse dosing up to prednisone 40 mg/day or equivalent is permitted with tapering to begin as soon as clinically feasible with a goal of returning to the previous stable dose or discontinuing the corticosteroid within 3 months. Patients who require increasing corticosteroid doses, repeated pulse dosing, or are intolerant to tapering should be considered for study drug discontinuation and early termination.
Immunomodulators (for example AZA, 6-MP, or methotrexate)	Stable doses encouraged throughout study unless medication is discontinued due to a toxicity related to the medication.
Antidiarrheals (for example, loperamide, diphenoxylate with atropine)	May continue during study with stable doses encouraged
Low-dose or baby aspirin (75 mg to 162.5 mg)	Daily use for cardiovascular prophylaxis permitted
Non-live (killed, inactivated or subunit) vaccines	Allowed during the study. The efficacy of non-live vaccinations with concomitant mirikizumab treatment is unknown.

Abbreviations: 5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; AZA = azathioprine; IV = intravenous.

Appendix 11. Additional Information on Systemic Drug Administration Reactions

A systemic drug administration reaction is defined if any of the following symptoms is present, in the absence of other plausible and more likely etiology, per investigator judgment:

- 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
- Collapse
- Vomiting
- Abdominal pain
- Diarrhea
- Bladder/bowel incontinence

Appendix 12. Additional Information on the Columbia Suicide Severity Rating Scale, and Quick Inventory of Depressive Symptomatology (Self-Report)

Columbia Suicide Severity Rating Scale

The Columbia Suicide Severity Rating Scale (C-SSRS) was developed by the National Institute of Mental Health Treatment of Adolescent Suicide Attempters trial group for the purpose of being a counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events. For this study, the scale has been adapted (with permission from the scale authors) to include only the portion of the scale that captures the occurrence of the 11 preferred ideation and behavior categories.

Quick Inventory of Depressive Symptomatology—Self-Report (16 Items)

For the Quick Inventory of Depressive Symptomatology—Self-Report (16 Items) (QIDS-SR16), a patient 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. Patients will record their responses to the QIDS-SR16 electronically as source data in the tablet device at appropriate visits.

Leo Document ID = d5db863b-2b46-4355-975c-1a753ff56077

Approver: Vipin K Arora (AM\RM89774)
Approval Date & Time: 15-Mar-2018 22:14:37 GMT
Signature meaning: Approved

Approver: Catherine Milch (AM\C242386)
Approval Date & Time: 15-Mar-2018 22:14:37 GMT
Signature meaning: Approved