Protocol I6T-MC-AMBG(a)

A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Arm, Placebo-Controlled Maintenance Study of Mirikizumab in Patients with Moderately to Severely Active Ulcerative Colitis.

LUCENT 2

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Confidential Information

Mirikizumab (LY3074828)

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1. Synopsis

Title of Study:
A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Arm, Placebo-Controlled Maintenance Study 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-AMBG (AMBG) is a Phase 3 clinical study that is designed to evaluate the safety and efficacy of mirikizumab in maintaining remission at Week 40 in patients who completed the 12-week induction study I6T-MC-AMAN (AMAN).

Objective(s)/Endpoints:

Objectives	Endpoints
Primary[a]	
• To test the hypothesis that mirikizumab is superior to placebo in achieving clinical remission at Week 40 (Week 52 of continuous therapy) among patients induced into **clinical response** with mirikizumab in Study AMAN	• The proportion of patients in clinical remission at Week 40, defined as: o Stool frequency (SF) subscore = 0, or SF = 1 with a ≥1-point decrease from induction baseline, and o Rectal bleeding (RB) subscore = 0, and o Endoscopic subscore (ES) = 0 or 1 (excluding friability).
Major Secondary[a,b]	
• To evaluate the efficacy of mirikizumab compared to placebo in maintaining clinical remission at Week 40 (Week 52 of continuous therapy) among patients induced into **clinical remission** with mirikizumab	• The proportion of patients who were in clinical remission at Week 40 among patients in clinical remission at Week 12 in Study AMAN (i.e. durable clinical remission). Clinical remission is defined as: o SF subscore = 0 or SF = 1 with a ≥1-point decrease from induction baseline, and o RB subscore = 0, and o ES subscore = 0 or 1 (excluding friability)
• To evaluate the efficacy of mirikizumab compared to placebo on endoscopic remission at Week 40 among patients induced into **clinical response** with mirikizumab	• The proportion of patients in endoscopic remission at Week 40, defined as: o ES = 0 or 1 (excluding friability)
• To evaluate the efficacy of mirikizumab compared to placebo in achieving corticosteroid-free remission without surgery among patients induced into **clinical response** with mirikizumab and receiving corticosteroids at induction baseline	• Corticosteroid-free remission without surgery at Week 40, defined as: o Clinical remission at Week 40, and o Symptomatic remission at Week 28, and o No corticosteroid use for ≥12 weeks prior to Week 40

• To evaluate the efficacy of mirikizumab compared to placebo on histologic remission at Week 40 among patients induced into **clinical response** with mirikizumab	• Proportion of patients in histologic remission at Week 40, as defined in the SAP
• To evaluate the efficacy of mirikizumab compared to placebo on stable maintenance of symptomatic remission among patients who were induced into **clinical response** and **symptomatic remission** with mirikizumab	• The proportion of patients in symptomatic remission defined as being in symptomatic remission for at least 7 out of 9 visits from Week 4 to Week 36 and being in symptomatic remission at Week 40 among patients in symptomatic remission at Week 12 of Study AMAN. • Symptomatic remission is defined as: o SF = 0, or SF = 1 with a ≥1-point decrease from induction baseline and o RB = 0
• To evaluate the efficacy of mirikizumab compared to placebo on bowel movement urgency improvement at Week 40, among patients who: (1) had bowel urgency symptoms at induction baseline and (2) were induced into clinical response with mirikizumab	• The proportion of patients with bowel movement urgency improvement at Week 40 as defined in the study SAP.
Other Secondary	
• To evaluate the efficacy of mirikizumab compared to placebo in achieving clinical remission at Week 40 among patients induced into **clinical response** with mirikizumab, in the subgroup of patients in whom biologic agents have failed or caused intolerance.	• Clinical remission at Week 40 in the subgroup of patients in whom biologic agents have failed or caused intolerance. Clinical remission is defined as: o SF subscore = 0 or SF = 1 with a ≥1-point decrease from induction baseline, and o RB subscore = 0, and o ES = 0 or 1 (excluding friability)
• To evaluate the efficacy of mirikizumab compared to placebo in achieving endoscopic remission at Week 40 among patients induced into **clinical response** with mirikizumab, in the subgroup of patients in whom biologic agents have failed or caused intolerance.	• Endoscopic remission at Week 40 in the subgroup of patients in whom biologic agents have failed or caused intolerance. Endoscopic remission is defined as: ES = 0 or 1 (excluding friability)
• To evaluate the efficacy of mirikizumab as compared to placebo in maintaining clinical remission at Week 40 (Week 52 of continuous therapy) among patients induced into clinical remission with mirikizumab, in the subgroup of patients in whom biologic agents have failed or caused intolerance	• The proportion of patients who were in clinical remission at Week 40 among patients in clinical remission at Week 12 in Study AMAN (i.e. durable clinical remission) in whom biologic agents have failed or caused intolerance. Clinical remission is defined as: o SF subscore = 0 or SF = 1 with a ≥1-point decrease from induction baseline, and o RB subscore = 0, and o ES = 0 or 1 (excluding friability)

• To evaluate the efficacy of mirikizumab compared to placebo in achieving corticosteroid-free remission without surgery among patients induced into **clinical remission** with mirikizumab and receiving corticosteroids at induction baseline	• Corticosteroid-free remission without surgery at Week 40 among induction clinical remitters, defined as: o Clinical remission at Week 40, and o No corticosteroid use for ≥12 weeks prior to Week 40
• To evaluate the efficacy of mirikizumab compared to placebo in achieving clinical remission (using a more stringent ES) at Week 40 among patients induced into **clinical response** with mirikizumab	• The proportion of patients with clinical remission (using a more stringent ES) at Week 40, with clinical remission defined as: o SF subscore = 0, or SF = 1 with a ≥1-point decrease from induction baseline, and o RB subscore = 0; and o ES = 0
• To evaluate the efficacy of mirikizumab compared to placebo on achieving ES of 0 at Week 40 among patients induced into **clinical response** with mirikizumab	• The proportion of patients achieving ES = 0
• To evaluate the efficacy of mirikizumab compared to placebo in achieving an endoscopic response at Week 40 among patients induced into **clinical response** with mirikizumab	• The proportion of patients in endoscopic response at Week 40 defined as: o A decrease in ES of ≥1 point from induction baseline.
• To evaluate the treatment of mirikizumab compared with placebo on achieving the symptomatic components of clinical remission as defined by the modified Mayo score (MMS) at Week 40	• The proportion of patients at Week 40 with SF subscore = 0, or SF = 1 with a ≥1-point decrease from induction baseline • The proportion of patients at Week 40 with RB subscore = 0
• To evaluate the numerical value and change from baseline of the individual MMS subscores and the composite symptom subscore over time during maintenance between mirikizumab and placebo	• The numerical value and change from induction baseline in each of the following items: o SF at each post baseline visit o RB at each post baseline visit o ES (Week 40 only) o The sum of the SF and RB subscores at each post baseline visit
• To evaluate the efficacy of mirikizumab compared to placebo in maintaining clinical response at Week 40 among patients induced into **clinical response** with mirikizumab	• Clinical response at Week 40. Clinical response is defined as: o A decrease in the MMS of ≥2 points and ≥30% decrease from induction baseline, and o A decrease of ≥1 point in the RB subscore or an RB subscore = 0 or 1

• To evaluate the efficacy of mirikizumab compared to placebo in reducing corticosteroid use over the course of maintenance treatment among patients induced into **clinical response** with mirikizumab and who entered the maintenance study on corticosteroids	• The change and percent change in daily (average) corticosteroid dose (prednisone equivalent) from maintenance baseline to end of maintenance study (Week 40), among clinical responders to mirikizumab induction who entered the maintenance study on corticosteroids
• To evaluate the effect of mirikizumab compared to placebo in health outcome endpoints at Week 40	• Change from induction baseline in: o IBDQ score at Week 40 o EQ-5D 5L index at Week 40 o WPAI:UC score at Week 40 o SF-36, V2 physical and mental component and domain scores at Week 40
• To evaluate the efficacy of mirikizumab compared to placebo in inducing combined clinical remission, with normalization of fecal calprotectin, and histologic remission	• The proportion of patients with all of the following at Week 40: o In clinical remission, defined as: o SF subscore = 0 or SF = 1 with a ≥1-point decrease from induction baseline, and o RB subscore = 0, and o ES = 0 or 1 (excluding friability) o In histologic remission, as defined in the SAP o Fecal calprotectin within limits of normal
• To evaluate the effect of mirikizumab compared to placebo on changes in inflammatory biomarkers	• Change from baseline at various time points in the following biomarkers: o C-reactive protein o Fecal calprotectin
• To evaluate the efficacy of mirikizumab compared to placebo in achieving 24-week corticosteroid-free remission without surgery among patients induced into **clinical response** with mirikizumab and receiving corticosteroids at induction baseline	• Corticosteroid-free remission without surgery at Week 40, defined as: o Clinical remission at Week 40, and o Symptomatic remission at Week 28, and o No corticosteroid use for ≥24 weeks prior to Week 40
• To evaluate the effect of mirikizumab compared to placebo on changes in Abdominal pain at Week 40	• Change from induction baseline at Week 40 in the Abdominal pain NRS score
• To evaluate the efficacy of mirikizumab in reducing the proportion of patients undergoing surgery for UC, colectomy, and hospitalization for UC	• The proportion of patients undergoing: o Surgery for UC (including colectomy) o Hospitalization for UC

• To evaluate the treatment of mirikizumab compared with placebo on achieving symptomatic remission	• The proportion of patients with symptomatic remission at various time points, defined as: o SF = 0, or SF = 1 with a ≥1-point decrease from induction baseline, and o RB = 0
• To evaluate key efficacy endpoints in biologic-failed and conventional-failed subgroups of patients (except those major secondary objectives noted above)	• Key efficacy endpoints in the subgroup of patients in whom biologic agents have failed or caused intolerance, and in whom conventional therapies have failed or caused intolerance
• To evaluate key efficacy endpoints in the subgroups of patients on concomitant treatment for UC	• Key efficacy endpoints in the subgroups of patients on concomitant medication for UC (corticosteroids and immunomodulators)
• To evaluate clinical remission, clinical response and endoscopic remission rates with extended induction in patients who did not respond to mirikizumab with initial induction	• At Week 12 (Week 24 of continuous therapy), o Clinical remission, defined as: o SF subscore = 0, or SF = 1 with a ≥1-point decrease from induction baseline, and o RB subscore = 0; and o ES = 0 or 1 (excluding friability) o Clinical response, defined as: o A decrease in MMS of ≥2 points and ≥30% decrease from induction baseline, and o A decrease of ≥1 point in the RB subscore from induction baseline or a RB score of 0 or 1 o Endoscopic remission, defined as: o ES = 0 or 1 (excluding friability)
• To evaluate the efficacy of mirikizumab compared to placebo on maintaining endoscopic remission at Week 40 among patients induced into **endoscopic remission** with mirikizumab	• The proportion of patients in durable endoscopic remission at Week 40, defined asES = 0 or 1 (excluding friability)
• Evaluate the pharmacokinetics and pharmacokinetic/pharmacodynamic relationship of mirikizumab	• Clearance and volume of distribution of mirikizumab • Relationship between mirikizumab exposure and efficacy
• To evaluate the potential development of anti-mirikizumab antibodies and their potential relationship with efficacy, safety, and mirikizumab exposure	• Relationship between TE-ADA and efficacy • Relationship between TE-ADA and safety • Relationship between TE-ADA and mirikizumab pharmacokinetics

• To evaluate the efficacy of mirikizumab compared to placebo in UCEIS endoscopic remission at Week 40 among patients induced into **clinical response** with mirikizumab	• The proportion of patients with a UCEIS score of ≤1 at Week 40
• To evaluate the efficacy of mirikizumab compared to placebo in mucosal healing at Week 40 among patients induced into **clinical response** with mirikizumab	• The proportion of patients with mucosal healing at Week 40, defined as achieveing both: o Histologic remission, as described in the SAP, and o Endoscopic remission, defined as ES = 0 or 1 (excluding friability)
• To evaluate the effect of mirikizumab compared to placebo on change in fatigue at Week 40	• Change from induction baseline at Week 40 in the Fatigue NRS score

Abbreviations: EQ-5D 5L = European Quality of Life 5-Dimensions 5 Level; ES = endoscopic subscore; IBDQ = Inflammatory Bowel Disease Questionnaire; MMS = modified Mayo Score; NRS = numeric rating scale; RB = rectal bleeding; SAP = statistical analysis plan; SF = stool frequency; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; UC = ulcerative colitis; WPAI:UC = Work Productivity and Activity Impairment Questionnaire Ulcerative Colitis; TE-ADA = treatment-emergent anti-drug antibody; UCEIS = Ulcerative Colitis Endoscopic Index of Severity.

[a] All primary and major secondary endpoints will be evaluated for mirikizumab versus placebo. All primary and major secondary endpoint analyses will utilize the multiplicity control approach based on 'graphical multiple testing procedure' to control the overall family-wise type I error rate at a 2-sided alpha level of 0.05. The graphical multiple testing procedure described in Bretz et al. (2009) will be used.

[b] The order of testing of the major secondary endpoints will be determined from the results of the statistical simulations. Therefore, the order of the secondary endpoints does not reflect the order of the statistical testing.

Summary of Study Design:

Study AMBG is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-arm study evaluating the safety and efficacy of 200 mg mirikizumab every 4 weeks (Q4W) subcutaneous (SC) in maintaining treatment response at Week 40 (that is, at Week 52 of continuous study drug treatment).

The study population includes patients with moderately to severely active UC who completed Study AMAN. Study AMAN includes patients who have an inadequate response to, loss of response to, or are intolerant to conventional (nonbiologic) therapy for UC ("conventional-failed"), and those who have an inadequate response to, loss of response to, or are intolerant to biologic therapy for UC ("biologic-failed").

Treatment Arms and Duration:

Patients who achieved clinical response with blinded mirikizumab treatment during Study AMAN will be randomized 2:1 to blinded 200 mg mirikizumab Q4W SC or blinded placebo. Patients who responded to blinded placebo in their induction study will remain on blinded placebo in Study AMBG. Open-label rescue therapy with 300 mg mirikizumab Q4W intravenous (IV) will be administered for 3 doses if these patients lose response.

Patients who did not achieve clinical response with either blinded mirikizumab or blinded placebo during Study AMAN will receive open-label extended induction therapy with 300 mg mirikizumab Q4W IV administered for 3 doses. Patients who achieve delayed clinical response (defined using induction study baseline) will then receive open-label 200 mg mirikizumab Q4W SC. Induction study nonresponders who do not achieve clinical response at Week 12 of Study AMBG will be discontinued.

> **Lead-in Period**: Visit [V] 1 (Week 0) should occur no more than 10 days from start of V5 (Week 12) of Study AMAN.
>
> **Treatment Period**: 40 weeks.
>
> **Follow-up Period**: Up to 16 weeks.
>
> **Extension Period**: N/A. Patients who complete Study AMBG will be eligible for extension Study I6T-MC-AMAP.
>
> **Continued Access Period**: N/A.

Number of Patients:

Enrolled: Approximately 1044.

Statistical Analysis:

Assuming that 90% of patients complete Study AMAN (which is expected to randomize approximately 1160 patients), Eli Lilly and Company (Lilly) anticipates approximately 1044 patients will enroll in Study AMBG. It is expected that approximately 470 of these patients will enter Study AMBG as clinical responders to mirikizumab and then will be randomized 2:1

to 200 mg mirikizumab SC (approximately 313 patients) and placebo (approximately 157 patients). Among the expected 470 mirikizumab clinical responders, approximately 180 mirikizumab clinical remitters will be randomized to 200 mg mirikizumab SC (approximately 120 patients) and placebo (approximately 60 patients). This assumes that:

- The induction study (AMAN, which has a mixed population with approximately 50% biologic-failed patients) is expected to have an overall clinical remission rate of 23% and response rate of 60% with mirikizumab.
- 75% of induction patients receive treatment with mirikizumab, based on a 3:1 randomization ratio for the induction study.
- 10% dropout rate from induction to maintenance.

The primary endpoint, clinical remission at Week 40, will be assessed on patients who achieved clinical response to mirikizumab induction treatment. Assuming mirikizumab and placebo clinical remission rates of 47% and 27%, respectively, this study based on the 470 mirikizumab induction responders is expected to have >95% power to demonstrate that mirikizumab is superior to placebo by using a chi-square test with a 2-sided significance level of 0.05. In addition, the sample size is expected to provide adequate power (>80%) to demonstrate that mirikizumab is superior to placebo for endoscopic remission, histologic remission, and corticosteroid-free remission at Week 40, among responders to mirikizumab induction treatment by using a chi-square test with a 2-sided significance level of 0.05.

Summary statistics for continuous variables may include mean, standard deviation, median, and minimum and maximum values. Categorical variables will be presented as counts and percentages. Unless otherwise specified, variables will be analyzed in the original scale on which they are measured. All hypothesis tests of treatment effects will be 2-sided, unless otherwise stated.

For assessments of the primary endpoint and other categorical efficacy endpoints among induced responders, the Cochran-Mantel-Haenszel (CMH) chi-square test will be used to compare mirikizumab and placebo with stratification factors: (a) previous biologic therapy failure (yes or no), (b) baseline corticosteroid use (yes or no), (c) region (North America/Europe/Other), (d) induction remission status (yes/no). The CMH chi-square p-value and the relative risk along with its 95% 2-sided confidence interval will be provided.

Treatment comparisons of continuous efficacy and health outcome variables with a single post-baseline time point will be made using analysis of covariance with: (a) treatment group, (b) previous biologic therapy failure (yes or no), (c) corticosteroid use (yes or no), (d) region (North America/Europe/Other), (e) baseline value in the model, and (f) induction remission status.

A prespecified multiple testing scheme based on graphical approach (Bretz et al. 2009, 2011) will be used to test the primary and major secondary hypotheses at overall family wise type 1 error rate (FWER) of 0.05. The graphical approach is a closed testing procedure, hence, it strongly controls the FWER across all endpoints (Alosh et al. 2014). Details of the specific graphical testing scheme (including testing order, interrelationships, type I error allocation for

the major secondary endpoints, and the associated propagation) will be prespecified in the statistical analysis plans (SAPs) prior to first unblinding of efficacy.

The Fisher exact test will be used to perform the between-treatment group comparisons for adverse events (AEs), discontinuations, and other categorical safety data. The change from baseline in continuous vital signs, physical characteristics, and other continuous safety variables, including laboratory variables, will be summarized by visit and treatment. Shift tables for categorical safety analyses (for example, "high" or "low" laboratory results) will also be produced.

No multiplicity control approach will be used for testing of other secondary endpoints.

2. Schedule of Activities

Table AMBG.2.1. Schedule of Activities – Responders from Induction Study

Procedure	Randomized Maintenance Period													Post-treatment Follow-up		Notes
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	N/A	V997	801	802	
Week	0	4	8	12	16	20	24	28	32	36	40 LV	ETV	UV	LV or ETV +4	LV or ETV +12/16[b]	
Day and/or Visit Interval Tolerance	1[a]	29 +/-7	57 +/-7	85 +/-7	113 +/-7	141 +/-7	169 +/-7	197 +/-7	225 +/-7	253 +/-7	281 +/-7	N/A	N/A	+/-10	+/-10	
Informed consent	X															Patients may consent between the start of V5 of Study AMAN and before any procedures at V1/Week 0 are performed.
Inclusion and exclusion criteria	X															Can begin at Week 12 of induction and continue until dosing is initiated in Study AMBG.
Concomitant medication	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	
Tobacco/nicotine use	X[c]			X			X				X	X				
IP Administration																
IWRS/Randomization	X															
IP SC administration	X	X	X	X	X	X	X	X	X	X						
Rescue mirikizumab IV dosing				X[d]												X[d]: Three Q4W IV rescue doses administered instead of SC dosing, if secondary loss of response (LOR) is confirmed. The IV dosing must start no later than V8/Week 28. The IV dosing visit window may shift if first rescue dose is given outside of SC dosing visit window. Rescue IV doses to be given Q4W with visit window tolerance of +/- 3 days.
Physical Examination																
Vital signs (T, BP, and PR)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight	X[c]						X				X	X				

Procedure	Randomized Maintenance Period													Post-treatment Follow-up		Notes
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	N/A	V997	801	802	
Week	0	4	8	12	16	20	24	28	32	36	40 LV	ETV	UV	LV or ETV +4	LV or ETV +12/16[b]	
Day and/or Visit Interval Tolerance	1[a]	29 +/-7	57 +/-7	85 +/-7	113 +/-7	141 +/-7	169 +/-7	197 +/-7	225 +/-7	253 +/-7	281 +/-7	N/A	N/A	+/-10	+/-10	
Physical examination	X[c]			X[d]							X	X	X[d]			X[d]: A targeted physical exam to be performed as appropriate for patients with secondary LOR.
Evaluate for EIMs	X	X	X	X	X	X	X	X	X	X	X	X	X			See Section 9.1.3.2.
12-lead ECG	X[c]										X	X				
Laboratory Investigations																
Urine pregnancy test	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[d]	X[c,d]			X[d]			X[d]				X[d]	X[d]				X[d]: For patients who were HBsAg-, anti-HBc+, and HBV DNA not detected in Study AMAN. See Section 9.4.5.2.
Hematology	X[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry	X[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Fasting lipid profile[e]	X[c]										X	X				
hsCRP[e]	X[c]										X	X				
FSH (optional in women to confirm nonchild-bearing potential)[e]	X															Optional, to confirm post-menopausal status in women ≥50 years with amenorrhea for >1 year.
Serum and plasma for cytokines	X[c]						X				X	X				

Procedure	Randomized Maintenance Period													Post-treatment Follow-up		Notes
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	N/A	V997	801	802	
Week	0	4	8	12	16	20	24	28	32	36	40 LV	ETV	UV	LV or ETV +4	LV or ETV +12/16[b]	
Day and/or Visit Interval Tolerance	1[a]	29 +/-7	57 +/-7	85 +/-7	113 +/-7	141 +/-7	169 +/-7	197 +/-7	225 +/-7	253 +/-7	281 +/-7	N/A	N/A	+/-10	+/-10	
PK assessment	X[c]	X		X	X[d]	X[d]	X	X[d]	X[d]	X[d]	X	X	X[d]		X	Serum for PK assessment [redacted] See Section 9.5. In addition, patients with potential hypersensitivity or infusion-related event should have sample taken as soon as possible after event occurs, at 4 and 12 to16 weeks after the event. X[d]: Patients with confirmed secondary LOR should have samples taken prior to IV mirikizumab rescue dosing, and 4 and 12 weeks after rescue initiation.
ADA assessment	X[c]	X		X	X[d]	X[d]	X	X[d]	X[d]	X[d]	X	X	X[d]		X	See Section 9.4.4. In addition, patients with possible hypersensitivity or infusion-related event should have sample taken as soon as possible after event occurs, at 4 and 12 to 16 weeks after the event. X[d]: Patients with confirmed secondary LOR should have samples taken prior to IV mirikizumab rescue dosing, and 4 and 12 weeks after rescue initiation.
Serum, plasma and whole blood for exploratory biomarkers	X[c]			X			X				X	X				
Additional Patient-Reported Tests																
C-SSRS, Self-Harm Supplement Form, and Self-Harm "Follow-Up" Form	X															
QIDS-SR16	X[c]			X			X				X	X				

Procedure	Randomized Maintenance Period													Post-treatment Follow-up		Notes
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	N/A	V997	801	802	
Week	0	4	8	12	16	20	24	28	32	36	40 LV	ETV	UV	LV or ETV +4	LV or ETV +12/16[b]	
Day and/or Visit Interval Tolerance	1[a]	29 +/-7	57 +/-7	85 +/-7	113 +/-7	141 +/-7	169 +/-7	197 +/-7	225 +/-7	253 +/-7	281 +/-7	N/A	N/A	+/-10	+/-10	
Stool Samples																
C. difficile testing			X[d]									X	X[d]			X[d]: Collection only at time of the first LOR assessment. Additional local stool testing (e.g., ova and parasites) is allowed at the investigator's discretion.
Fecal calprotectin and exploratory fecal biomarkers	X[c]		X[d]								X	X	X[d]			X[d]: Collection at time of the first LOR assessment.
Endoscopic Procedure																
Endoscopy with biopsies				X[d]							X	X	X[d]			X[d]: At least 1 endoscopy is performed at Week 40/ETV or if LOR is confirmed. LOR confirmation based on endoscopy can only occur at a scheduled or unscheduled visit between V4 and V8. Please refer to Section 9.1.1.3 for procedure clarification.
UC Activity Assessments																
Patient diary device dispensed	X															
Patient diary compliance review		X	X	X	X	X	X	X	X	X	X	X	X			
PGA	X[c]			X[d]							X	X	X[d]			X[d]: Performed at the second of 2 LOR assessments which may occur at a scheduled or unscheduled visit, at least 7 days from first LOR assessment. See Section 5.1.

Procedure	Randomized Maintenance Period													Post-treatment Follow-up		Notes
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	N/A	V997	801	802	
Week	0	4	8	12	16	20	24	28	32	36	40 LV	ETV	UV	LV or ETV +4	LV or ETV +12/16[b]	
Day and/or Visit Interval Tolerance	1[a]	29 +/-7	57 +/-7	85 +/-7	113 +/-7	141 +/-7	169 +/-7	197 +/-7	225 +/-7	253 +/-7	281 +/-7	N/A	N/A	+/-10	+/-10	
Review modified Mayo Score	X[c]			X[d]							X	X	X[d]			X[d:] Performed at the second of 2 LOR assessments which may occur at a scheduled or unscheduled visit, at least 7 days from first LOR assessment. See Section 5.1.
Patient diary device collected											X	X				
Health Outcome Assessment																
IBDQ	X[c]			X[d]							X	X	X[d]			X[d]: To be performed for patients who have LOR confirmed by endoscopy before rescue dosing.
EQ-5D 5L	X[c]			X[d]							X	X	X[d]			
PGRC				X[d]							X	X	X[d]			X[d]: To be performed for patients who have LOR confirmed by endoscopy before rescue dosing.
SF-36	X[c]										X	X				
WPAI:UC	X[c]										X	X				

Footnotes for Table AMBG.2.1

Abbreviations: ADA = anti-drug antibody; AE = adverse event; anti-HBc+ = positive for anti-hepatitis B core antibody; BP = blood pressure; C-SSRS = Columbia-Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EIM = extraintestinal manifestation; EQ-5D-5L = European Quality of Life 5-Dimension 5 Level; ETV = early termination visit; FSH = follicle-stimulating hormone; HBsAg- = negative for hepatitis B surface antigen; HBV = hepatitis B virus ; hsCRP = high-sensitivity C-reactive protein; IBDQ = Inflammatory Bowel Disease Questionnaire; IP = investigational product; IV = intravenous; IWRS = interactive web-response system; LOR = loss of response; LV = last visit; N/A = not applicable; PGA = Physician's Global Assessment; PGRC = Patient's Global Rating of Change; PK = pharmacokinetic; PR = pulse rate; Q4W = every 4 weeks; QIDS-SR16 = Quick Inventory of Depressive Symptomatology—Self-Report (16 Items); SC = subcutaneous; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; T = temperature; UV = unscheduled visit; V = visit; WPAI:UC = Work Productivity and Activity Impairment Questionnaire Ulcerative Colitis.

Notes: All activities should be completed prior to any study drug administration unless otherwise stated. Last visit or ETV is last visit prior to entering long term extension Study AMAP or post-treatment follow-up. Post-treatment follow-up visits should only occur if the patient is not proceeding to long term extension Study AMAP or if they discontinue treatment in Study AMBG early.

[a] V1 (Week 0) should occur no more than 14 days from the start of the Visit 5/Week 12 visit of Study AMAN.

[b] Patients who discontinue study drug with last dose administered IV will return for an LV +16 week post-treatment follow-up visit without a 12 week follow-up. Patients who discontinue study drug with last dose administered SC will return for an LV + 12 week post-treatment follow-up visit without a 16 week follow-up.

[c] Results from Week 12 of Study AMAN will be used for Week 0 of this study.

[d] Activity to be performed on a subpopulation of patients. See Notes column in table.

[e] These tests will be run from the "chemistry" sample.

Table AMBG.2.2. Schedule of Activities – Nonresponders from Induction Study

Procedure	Extended Induction			Open-Label Maintenance Period									Post-treatment Follow-up			Notes
Visit	V1	V2	V3	V4[a]	V5	V6	V7	V8	V9	V10	V11		V997	801	802	
Week	0	4	8	12	16	20	24	28	32	36	40 LV	ETV	UV	LV +4	LV +12/16[c]	
Day and/or Visit Interval Tolerance	1[b]	29 +/-3	57 +/-3	85 +/-7	113 +/-7	141 +/-7	169 +/-7	197 +/-7	225 +/-7	253 +/-7	281 +/-7		N/A	+/-10	+/-10	
Informed consent	X															Patients may consent between the start of V5 of Study AMAN and before any procedures at V1/Week 0 are performed.
Inclusion and exclusion criteria	X															Can begin at Week 12 of induction and continue until dosing is initiated in Study AMBG.
Concomitant medication	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	
Tobacco/nicotine use	X[d]			X			X				X	X				
IP Administration																
IWRS/Randomization	X															
Open-label mirikizumab extended IV dosing	X	X	X													
Open-label mirikizumab SC dosing				X	X	X	X	X	X	X						
Physical Examination																
Vital signs (T, BP, and PR)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight	X[d]			X			X				X	X				
Physical examination	X[d]										X	X				
Evaluate for EIMs	X	X	X	X	X	X	X	X	X	X	X	X	X			See Section 9.1.3.2.
12-lead ECG	X[d]										X	X				
Laboratory Investigations																
Urine pregnancy test	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.

Procedure	Extended Induction			Open-Label Maintenance Period									Post-treatment Follow-up		Notes
Visit	V1	V2	V3	V4[a]	V5	V6	V7	V8	V9	V10	V11		V997	801	802	
Week	0	4	8	12	16	20	24	28	32	36	40 LV	ETV	UV	LV +4	LV +12/16[c]	
Day and/or Visit Interval Tolerance	1[b]	29 +/-3	57 +/-3	85 +/-7	113 +/-7	141 +/-7	169 +/-7	197 +/-7	225 +/-7	253 +/-7	281 +/-7		N/A	+/-10	+/-10	
HBV DNA[e]	X[d,e]			X[e]			X[e]				X[e]	X[e]				X[e] For patients who were HBsAg-, anti-HBc+, and HBV DNA not detected at V0 in Study AMAN. See Section 9.4.5.2.
Hematology	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Fasting lipid profile[f]	X[d]										X	X				
hsCRP[f]	X[d]			X							X	X				
FSH (optional in women to confirm nonchild-bearing potential)[f]	X															Optional, to confirm post-menopausal status in women ≥50 years with amenorrhea for >1 year.
Serum and plasma for cytokines	X[d]			X			X				X	X				
PK assessment	X[d]	X		X			X				X	X	X		X	Serum for PK assessment [redacted] See Section 9.5. In addition, patients with potential hypersensitivity or infusion-related event should have sample taken as soon as possible after event occurs, at 4 and 12 to16 weeks after the event.
ADA assessment	X[d]	X		X			X				X	X	X		X	See Section 9.4.4. In addition, patients with possible hypersensitivity or infusion-related event should have sample taken as soon as possible after event occurs, at 4 and 12 to 16 weeks after the event.
Serum, plasma and whole blood for exploratory biomarkers	X[d]			X			X				X	X				

Procedure	Extended Induction			Open-Label Maintenance Period										Post-treatment Follow-up		Notes
Visit	V1	V2	V3	V4[a]	V5	V6	V7	V8	V9	V10	V11		V997	801	802	
Week	0	4	8	12	16	20	24	28	32	36	40 LV	ETV	UV	LV +4	LV +12/16[c]	
Day and/or Visit Interval Tolerance	1[b]	29 +/-3	57 +/-3	85 +/-7	113 +/-7	141 +/-7	169 +/-7	197 +/-7	225 +/-7	253 +/-7	281 +/-7		N/A	+/-10	+/-10	
Additional Patient-Reported Tests																
C-SSRS, Self-Harm Supplement Form, and Self-Harm "Follow-Up" Form	X															
QIDS-SR16	X[d]			X			X				X	X				
Stool Samples																
C. difficile testing	X			X[e]								X				X[e]: Should be performed if clinical response is not achieved with extended induction. In addition, may be performed if loss of clinical benefit, per investigator discretion, on OL SC maintenance dosing. Additional local stool testing (e.g., ova and parasites) is allowed at the investigator's discretion. V1 C. difficile testing does not need to be completed before the patient can start study drug therapy.
Fecal calprotectin and exploratory fecal biomarkers	X[d]			X							X	X				
Endoscopic Procedure																
Endoscopy with biopsies				X							X	X				Please refer to Section 9.1.1.3 for procedure clarification.
UC Activity Assessments																
Patient diary device dispensed	X															

Procedure	Extended Induction			Open-Label Maintenance Period									Post-treatment Follow-up		Notes
Visit	V1	V2	V3	V4[a]	V5	V6	V7	V8	V9	V10	V11		V997	801	802	
Week	0	4	8	12	16	20	24	28	32	36	40 LV	ETV	UV	LV +4	LV +12/16[c]	
Day and/or Visit Interval Tolerance	1[b]	29 +/-3	57 +/-3	85 +/-7	113 +/-7	141 +/-7	169 +/-7	197 +/-7	225 +/-7	253 +/-7	281 +/-7		N/A	+/-10	+/-10	
Patient diary compliance review		X	X	X	X	X	X	X	X	X	X	X	X			
PGA	X[d]			X							X	X				
Review Modified Mayo Score	X[d]			X							X	X				In addition, may be performed if loss of clinical benefit, per investigator discretion, on OL SC maintenance dosing
Patient diary device collected											X	X				
Health Outcome Assessments																
IBDQ	X[d]			X							X	X				
EQ-5D 5L	X[d]			X							X	X				
PGRC				X							X	X				
SF-36	X[d]										X	X				
WPAI:UC	X[d]										X	X				

Footnotes for Table AMBG.2.2

Abbreviations: ADA = anti-drug antibody; AE = adverse event; anti-HBc+ = positive for anti-hepatitis B core antibody; BP = blood pressure; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EIM = extraintestinal manifestation; EQ-5D 5L = European Quality of Life 5-Dimension 5 Level; ETV = early termination visit; FSH = follicle-stimulating hormone; HBsAg- = negative for hepatitis B surface antigen; HBV = hepatitis B virus; hsCRP = high-sensitivity C-reactive protein; IBDQ = Inflammatory Bowel Disease Questionnaire; IP = investigational product; IV = intravenous; IWRS = interactive web-response system; LV = last visit; N/A = not applicable; PGA = Physician's Global Assessment; PGRC = Patient's Global Rating of Change; PK = pharmacokinetic; PR = pulse rate; QIDS-SR16 = Quick Inventory of Depressive Symptomatology—Self-Report (16 Items); SC = subcutaneous; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; T = temperature; UV = unscheduled visit; V = visit; WPAI:UC = Work Productivity and Activity Impairment Questionnaire Ulcerative Colitis.

Notes: All activities should be completed prior to any study drug administration unless otherwise stated. Last visit or ETV is last visit prior to entering long term extension Study AMAP or post-treatment follow-up. Post-treatment follow-up visits should only occur if the patient is not proceeding to long term extension Study AMAP or if they discontinue treatment in Study AMBG early (i.e. patients who do not achieve delayed clinical response).

[a] For patients who cannot continue beyond V4 because they did not achieve delayed clinical response, ETV activites that are performed as part of V4 do not need to be repeated. Only those ETV activities that are not part of V4 should be completed during the ETV.

[b] V1 (Week 0) should occur no more than 14 days from the start of the Visit 5/Week 12 visit of Study AMAN.

[c] Patients who discontinue study drug with last dose administered IV will return for an LV +16 week post-treatment follow-up visit without a 12 week follow-up. Patients who discontinue study drug with last dose administered SC will return for an LV + 12 week post-treatment follow-up visit without a 16 week follow-up.

[d] Results from V5 (Week 12) of Study AMAN will be used for Week 0 of this study.

[e] Activity to be performed on a subpopulation of patients. See Notes column in table.

[f] These tests will be run from the "chemistry" sample

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-AMBG (AMBG) is a Phase 3 clinical study that is designed to evaluate the safety and efficacy of mirikizumab in maintaining remission of ulcerative colitis (UC) at Week 40 in patients who completed the 12-week induction study I6T-MC-AMAN (AMAN). Study AMAN includes patients with moderate to severely active UC who have an inadequate response to, loss of response to, or are intolerant to conventional (nonbiologic) therapy for UC ("conventional-failed"), and those who have an inadequate response to, loss of response to, or are intolerant to biologic therapy for UC ("biologic-failed").

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 trials). In both clinical practice and clinical trials, 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-aminosalicylic 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-$\alpha_4\beta_7$ 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 up 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

Interleukin (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).

Interleukin-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 to 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 16T-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 (Leonardi et al. 2008; Papp 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/IFN-γ 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 and Sandborn 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 AMBG 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 AMBG 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 adverse events (AEs) of mirikizumab are to be found in the IB.

4. Objectives and Endpoints

Table AMBG.4.1 shows the objectives and endpoints of the study.

Table AMBG.4.1. Objectives and Endpoints

Objective(s)/Endpoints:

Objectives	Endpoints
Primary[a]	
• To test the hypothesis that mirikizumab is superior to placebo in achieving clinical remission at Week 40 (Week 52 of continuous therapy) among patients induced into **clinical response** with mirikizumab in Study AMAN	• The proportion of patients in clinical remission at Week 40, defined as: o Stool frequency (SF) subscore = 0, or SF = 1 with a ≥1-point decrease from induction baseline, and o Rectal bleeding (RB) subscore = 0, and o Endoscopic subscore (ES) = 0 or 1 (excluding friability).
Major Secondary[a,b]	
• To evaluate the efficacy of mirikizumab compared to placebo in maintaining clinical remission at Week 40 (Week 52 of continuous therapy) among patients induced into **clinical remission** with mirikizumab	• The proportion of patients who were in clinical remission at Week 40 among patients in clinical remission at Week 12 in Study AMAN (i.e. durable clinical remission). Clinical remission is defined as: o SF subscore = 0 or SF = 1 with a ≥1-point decrease from induction baseline, and o RB subscore = 0, and o ES subscore = 0 or 1 (excluding friability)
• To evaluate the efficacy of mirikizumab compared to placebo on endoscopic remission at Week 40 among patients induced into **clinical response** with mirikizumab	• The proportion of patients in endoscopic remission at Week 40, defined as: o ES = 0 or 1 (excluding friability)
• To evaluate the efficacy of mirikizumab compared to placebo in achieving corticosteroid-free remission without surgery among patients induced into **clinical response** with mirikizumab and receiving corticosteroids at induction baseline	• Corticosteroid-free remission without surgery at Week 40, defined as: o Clinical remission at Week 40, and o Symptomatic remission at Week 28, and o No corticosteroid use for ≥12 weeks prior to Week 40
• To evaluate the efficacy of mirikizumab compared to placebo on histologic remission at Week 40 among patients induced into **clinical response** with mirikizumab	• Proportion of patients in histologic remission at Week 40, as defined in the SAP

• To evaluate the efficacy of mirikizumab compared to placebo on stable maintenance of symptomatic remission among patients who were induced into **clinical response** and **symptomatic remission** with mirikizumab	• The proportion of patients in symptomatic remission defined as being in symptomatic remission for at least 7 out of 9 visits from Week 4 to Week 36 and being in symptomatic remission at Week 40 among patients in symptomatic remission at Week 12 of Study AMAN. • Symptomatic remission is defined as: o SF = 0, or SF = 1 with a ≥1-point decrease from induction baseline and o RB = 0
• To evaluate the efficacy of mirikizumab compared to placebo on bowel movement urgency improvement at Week 40, among patients who: (1) had bowel urgency symptoms at induction baseline and (2) were induced into clinical response with mirikizumab	• The proportion of patients with bowel movement urgency improvement at Week 40 as defined in the study SAP.
Other Secondary	
• To evaluate the efficacy of mirikizumab compared to placebo in achieving clinical remission at Week 40 among patients induced into **clinical response** with mirikizumab, in the subgroup of patients in whom biologic agents have failed or caused intolerance.	• Clinical remission at Week 40 in the subgroup of patients in whom biologic agents have failed or caused intolerance. Clinical remission is defined as: o SF subscore = 0 or SF = 1 with a ≥1-point decrease from induction baseline, and o RB subscore = 0, and o ES = 0 or 1 (excluding friability)
• To evaluate the efficacy of mirikizumab compared to placebo in achieving endoscopic remission at Week 40 among patients induced into **clinical response** with mirikizumab, in the subgroup of patients in whom biologic agents have failed or caused intolerance.	• Endoscopic remission at Week 40 in the subgroup of patients in whom biologic agents have failed or caused intolerance. Endoscopic remission is defined as: ES = 0 or 1 (excluding friability)
• To evaluate the efficacy of mirikizumab as compared to placebo in maintaining clinical remission at Week 40 (Week 52 of continuous therapy) among patients induced into clinical remission with mirikizumab, in the subgroup of patients in whom biologic agents have failed or caused intolerance	• The proportion of patients who were in clinical remission at Week 40 among patients in clinical remission at Week 12 in Study AMAN (i.e. durable clinical remission) in whom biologic agents have failed or caused intolerance. Clinical remission is defined as: o SF subscore = 0 or SF = 1 with a ≥1-point decrease from induction baseline, and o RB subscore = 0, and o ES = 0 or 1 (excluding friability)
• To evaluate the efficacy of mirikizumab compared to placebo in achieving corticosteroid-free remission without surgery among patients induced into **clinical remission** with mirikizumab and receiving corticosteroids at induction baseline	• Corticosteroid-free remission without surgery at Week 40 among induction clinical remitters, defined as: o Clinical remission at Week 40, and o No corticosteroid use for ≥12 weeks prior to Week 40

• To evaluate the efficacy of mirikizumab compared to placebo in achieving clinical remission (using a more stringent ES) at Week 40 among patients induced into **clinical response** with mirikizumab	• The proportion of patients with clinical remission (using a more stringent ES) at Week 40, with clinical remission defined as: o SF subscore = 0, or SF = 1 with a ≥1-point decrease from induction baseline, and o RB subscore = 0; and o ES = 0
• To evaluate the efficacy of mirikizumab compared to placebo on achieving ES of 0 at Week 40 among patients induced into **clinical response** with mirikizumab	• The proportion of patients achieving ES = 0
• To evaluate the efficacy of mirikizumab compared to placebo in achieving an endoscopic response at Week 40 among patients induced into **clinical response** with mirikizumab	• The proportion of patients in endoscopic response at Week 40 defined as: o A decrease in ES of ≥1 point from induction baseline.
• To evaluate the treatment of mirikizumab compared with placebo on achieving the symptomatic components of clinical remission as defined by the modified Mayo score (MMS) at Week 40	• The proportion of patients at Week 40 with SF subscore = 0, or SF = 1 with a ≥1-point decrease from induction baseline • The proportion of patients at Week 40 with RB subscore = 0
• To evaluate the numerical value and change from baseline of the individual MMS subscores and the composite symptom subscore over time during maintenance between mirikizumab and placebo	• The numerical value and change from induction baseline in each of the following items: o SF at each post baseline visit o RB at each post baseline visit o ES (Week 40 only) o The sum of the SF and RB subscores at each post baseline visit
• To evaluate the efficacy of mirikizumab compared to placebo in maintaining clinical response at Week 40 among patients induced into **clinical response** with mirikizumab	• Clinical response at Week 40. Clinical response is defined as: o A decrease in the MMS of ≥2 points and ≥30% decrease from induction baseline, and o A decrease of ≥1 point in the RB subscore or an RB subscore = 0 or 1
• To evaluate the efficacy of mirikizumab compared to placebo in reducing corticosteroid use over the course of maintenance treatment among patients induced into **clinical response** with mirikizumab and who entered the maintenance study on corticosteroids	• The change and percent change in daily (average) corticosteroid dose (prednisone equivalent) from maintenance baseline to end of maintenance study (Week 40), among clinical responders to mirikizumab induction who entered the maintenance study on corticosteroids

• To evaluate the effect of mirikizumab compared to placebo in health outcome endpoints at Week 40	• Change from induction baseline in: o IBDQ score at Week 40 o EQ-5D 5L index at Week 40 o WPAI:UC score at Week 40 o SF-36, V2 physical and mental component and domain scores at Week 40
• To evaluate the efficacy of mirikizumab compared to placebo in inducing combined clinical remission, with normalization of fecal calprotectin, and histologic remission	• The proportion of patients with all of the following at Week 40: o In clinical remission, defined as: o SF subscore = 0 or SF = 1 with a ≥1-point decrease from induction baseline, and o RB subscore = 0, and o ES = 0 or 1 (excluding friability) o In histologic remission, as defined in the SAP o Fecal calprotectin within limits of normal
• To evaluate the effect of mirikizumab compared to placebo on changes in inflammatory biomarkers	• Change from baseline at various time points in the following biomarkers: o C-reactive protein o Fecal calprotectin
• To evaluate the efficacy of mirikizumab compared to placebo in achieving 24-week corticosteroid-free remission without surgery among patients induced into **clinical response** with mirikizumab and receiving corticosteroids at induction baseline	• Corticosteroid-free remission without surgery at Week 40, defined as: o Clinical remission at Week 40, and o Symptomatic remission at Week 28, and o No corticosteroid use for ≥24 weeks prior to Week 40
• To evaluate the effect of mirikizumab compared to placebo on changes in Abdominal pain at Week 40	• Change from induction baseline at Week 40 in the Abdominal pain NRS score
• To evaluate the efficacy of mirikizumab in reducing the proportion of patients undergoing surgery for UC, colectomy, and hospitalization for UC	• The proportion of patients undergoing: o Surgery for UC (including colectomy) o Hospitalization for UC
• To evaluate the treatment of mirikizumab compared with placebo on achieving symptomatic remission	• The proportion of patients with symptomatic remission at various time points, defined as: o SF = 0, or SF = 1 with a ≥1-point decrease from induction baseline, and o RB = 0
• To evaluate key efficacy endpoints in biologic-failed and conventional-failed subgroups of patients (except those major secondary objectives noted above)	• Key efficacy endpoints in the subgroup of patients in whom biologic agents have failed or caused intolerance, and in whom conventional therapies have failed or caused intolerance

• To evaluate key efficacy endpoints in the subgroups of patients on concomitant treatment for UC	• Key efficacy endpoints in the subgroups of patients on concomitant medication for UC (corticosteroids and immunomodulators)
• To evaluate clinical remission, clinical response and endoscopic remission rates with extended induction in patients who did not respond to mirikizumab with initial induction	• At Week 12 (Week 24 of continuous therapy), o Clinical remission, defined as: o SF subscore = 0, or SF = 1 with a ≥1-point decrease from induction baseline, and o RB subscore = 0; and o ES = 0 or 1 (excluding friability) o Clinical response, defined as: o A decrease in MMS of ≥2 points and ≥30% decrease from induction baseline, and o A decrease of ≥1 point in the RB subscore from induction baseline or a RB score of 0 or 1 o Endoscopic remission, defined as: o ES = 0 or 1 (excluding friability)
• To evaluate the efficacy of mirikizumab compared to placebo on maintaining endoscopic remission at Week 40 among patients induced into **endoscopic remission** with mirikizumab	• The proportion of patients in durable endoscopic remission at Week 40, defined asES = 0 or 1 (excluding friability)
• Evaluate the pharmacokinetics and pharmacokinetic/pharmacodynamic relationship of mirikizumab	• Clearance and volume of distribution of mirikizumab • Relationship between mirikizumab exposure and efficacy
• To evaluate the potential development of anti-mirikizumab antibodies and their potential relationship with efficacy, safety, and mirikizumab exposure	• Relationship between TE-ADA and efficacy • Relationship between TE-ADA and safety • Relationship between TE-ADA and mirikizumab pharmacokinetics
• To evaluate the efficacy of mirikizumab compared to placebo in UCEIS endoscopic remission at Week 40 among patients induced into **clinical response** with mirikizumab	• The proportion of patients with a UCEIS score of ≤1 at Week 40
• To evaluate the efficacy of mirikizumab compared to placebo in mucosal healing at Week 40 among patients induced into **clinical response** with mirikizumab	• The proportion of patients with mucosal healing at Week 40, defined as achieveing both: o Histologic remission, as described in the SAP, and o Endoscopic remission, defined as ES = 0 or 1 (excluding friability)

• To evaluate the effect of mirikizumab compared to placebo on change in fatigue at Week 40	• Change from induction baseline at Week 40 in the Fatigue NRS score

Abbreviations: EQ-5D 5L = European Quality of Life 5-Dimensions 5 Level; ES = endoscopic subscore; IBDQ = Inflammatory Bowel Disease Questionnaire; MMS = modified Mayo Score; NRS = numeric rating scale; RB = rectal bleeding; SAP = statistical analysis plan; SF = stool frequency; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; UC = ulcerative colitis; WPAI:UC = Work Productivity and Activity Impairment Questionnaire Ulcerative Colitis; TE-ADA = treatment-emergent anti-drug antibody; UCEIS = Ulcerative Colitis Endoscopic Index of Severity.

[a] All primary and major secondary endpoints will be evaluated for mirikizumab versus placebo. All primary and major secondary endpoint analyses will utilize the multiplicity control approach based on 'graphical multiple testing procedure' to control the overall family-wise type I error rate at a 2-sided alpha level of 0.05. The graphical multiple testing procedure described in Bretz et al. (2009) will be used.

[b] The order of testing of the major secondary endpoints will be determined from the results of the statistical simulations. Therefore, the order of the secondary endpoints does not reflect the order of the statistical testing.

5. Study Design

5.1. Overall Design

Study AMBG is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-arm study evaluating the safety and efficacy of 200 mg mirikizumab Q4W SC in maintaining treatment response at Week 40 (that is, 52 weeks of continuous therapy). The study also will evaluate the safety and efficacy of: (a) extended induction with 300 mg mirikizumab IV for patients who did not have a clinical response at Week 12 of Study AMAN, and (b) rescue induction for patients who achieved clinical response in Study AMAN and subsequently lose clinical response during Study AMBG.

Patient Population

Patients with moderately to severely active UC who completed Study AMAN and who meet eligibility requirements will enroll in this study. The study will enroll patients who achieve clinical response or clinical remission with blinded mirikizumab or placebo dosing in Study AMAN, as well as patients who do not achieve clinical response with blinded mirikizumab or placebo during Study AMAN.

Treatment Assignments

Maintenance study treatment assignment will be dependent on whether patients responded to study drug dosing in AMAN and whether they experience a loss of response (LOR) during this study as follows:

- **Mirikizumab Responders from Study AMAN**

  Patients who achieve clinical response with blinded mirikizumab in induction Study AMAN will be randomized to receive blinded 200 mg mirikizumab Q4W SC or blinded placebo SC Q4W (randomized withdrawal) in a 2:1 ratio. Randomization will be stratified to achieve between-group comparability, based on biologic-failed status (yes or no), induction remission status (yes or no), baseline corticosteroid use (yes or no), and region (North America/Europe/Other).

  Patients will continue on the randomized treatment assignment for the remainder of Study AMBG unless they develop secondary LOR.

  Loss of Response (LOR) is defined as:

  - ≥2-point increase from Study AMBG baseline in the combined SF + RB scores AND combined SF + RB score of ≥4, on 2 consecutive visits (≥7 days apart), and with confirmation of negative *C. difficile* testing (first assessment can start as early as Week 8/Visit 3),

    AND

  - Confirmed by centrally read endoscopic subscore (ES) of 2 or 3 not sooner than Week 12/Visit 4.

SC dosing should be continued according to dosing schedule until endoscopy determines whether LOR is confirmed. If LOR is confirmed based on endoscopy at or after Week 12 (and *C. difficile* stool toxin testing is negative), patients will be rescued with open-label 300 mg mirikizumab Q4W IV for 3 doses. The first IV rescue dose may be administered as soon as LOR is confirmed by centrally read endoscopy, if ≥7 days from the most recent SC dose. Subsequent doses will be given every 4 weeks for total of 3 doses.

If endoscopy does not confirm secondary LOR, patients are encouraged to continue SC study drug dosing, maintaining the scheduled dosing interval. If study drug dosing is continued, an additional endoscopy would be performed at Week 40, early termination visit (ETV) or unscheduled visit (UV).

Patients who, in the opinion of the investigator, receive clinical benefit after completion of the LOR rescue therapy (12 weeks after first IV rescue dose) may be considered for enrollment into the long term extension study I6T-MC-AMAP (AMAP) to receive further SC dosing. Once the LOR IV rescue therapy is initiated, no further SC dosing will be available in AMBG.

If study drug is discontinued, procedures for early termination from study drug will be performed and the patient should undergo post-treatment follow-up as described in the schedule of activities (Section 2).

- **Placebo Responders from Study AMAN**

  Patients who achieve clinical response with blinded placebo in the induction study will continue to receive blinded placebo for the remainder of the maintenance study. Placebo SC injections will be administered Q4W to maintain study blind. If LOR is confirmed based on endoscopy at or after Week 12 (and *C. difficile* stool toxin testing is negative), patients will be rescued with open-label mirikizumab 300 mg Q4W IV for 3 doses. The same LOR assessments and procedures should be performed as described for the mirikizumab responders from Study AMAN.

- **Mirikizumab and Placebo Nonresponders from Study AMAN**

  Patients who do not achieve clinical response to blinded mirikizumab or blinded placebo in Study AMAN will receive open-label extended induction therapy with 300 mg mirikizumab IV at Weeks 0, 4, and 8, and undergo endoscopy at Week 12.

  Patients who achieve delayed clinical response (compared to induction study baseline) with extended mirikizumab induction therapy at Week 12 may subsequently receive open-label 200 mg mirikizumab Q4W SC starting at Week 12. Patients will continue on this dose regimen and undergo endoscopy at Week 40. Patients who, in the opinion of the investigator, receive clinical benefit may be considered for enrollment into the long term extension study AMAP to receive further SC dosing. Patients who discontinue study drug before Week 40 will undergo endoscopy and procedures for early termination of the study drug, including post-treatment follow-up as described in the schedule of activities (Section 2).

Patients who do not achieve clinical response to mirikizumab IV extended induction therapy at Week 12, compared to induction baseline, will discontinue study drug and undergo procedures for early termination of the study drug, including post-treatment follow-up as described in the schedule of activities (Section 2).

Post-Treatment Follow-up Period

Patients will undergo a maximum 16-week post-treatment follow-up period:

- Patients who discontinue study drug with **last dose administered IV** will return for post-treatment follow-up visits (Visit 801 and 802) at 4 and 16 weeks after the end-of-treatment visit.
- Patients who discontinue study drug with **last dose administered SC** will return for post-treatment follow-up visits (Visit 801 and 802) at 4 and 12 weeks after the end-of-treatment visit.
- Patients who subsequently enter the long term extension study AMAP do not need to complete the post-treatment follow-up period.

Figure AMBG.5.1 illustrates the study design. Study governance considerations are described in detail in Appendix 3.

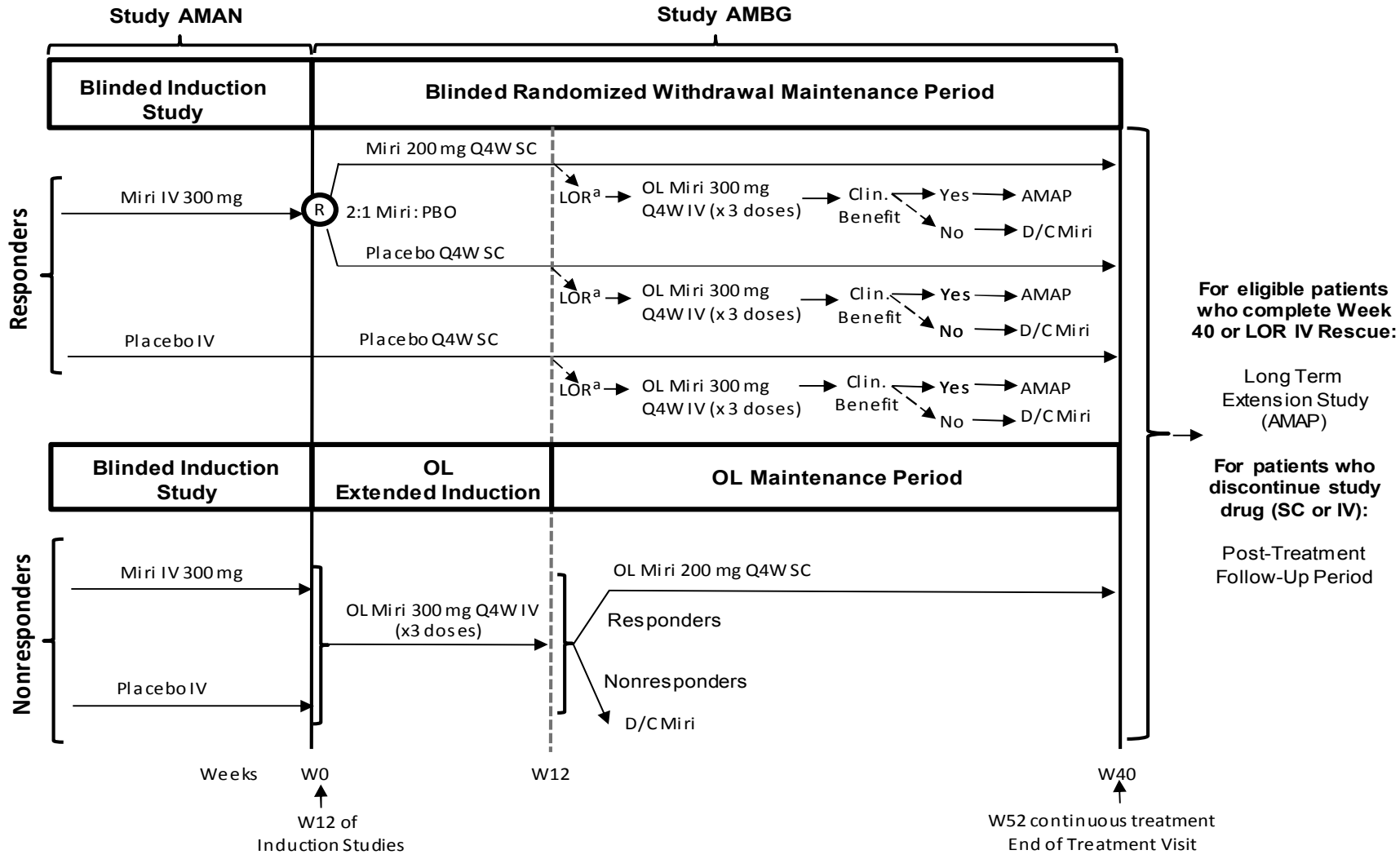

Figure AMBG.5.1. Illustration of study design for Clinical Protocol I6T-MC-AMBG.

Footnotes for Figure AMBG.5.1
Abbreviations: D/C = discontinue; IV = intravenous; LOR = loss of response; Miri = mirikizumab; OL = open-label; PBO = placebo; Q4W = every 4 weeks; R = randomization; RB = rectal bleeding; SC = subcutaneous; SF = stool frequency; W = week.
Note: LOR is defined as ≥2-point increase from maintenance baseline in the combined SF + RB scores, AND combined SF + RB score of ≥4 on 2 consecutive visits, AND confirmed by an endoscopic subscore of 2 or 3.
a = Loss of response at or after Week 12 and up to and including Week 28.

5.2. Number of Participants

The number of participants in Study AMBG will depend on the number of patients completing the induction study and who fulfill the enrollment criteria. It is estimated that approximately 1044 patients will enter Study AMBG from the induction study AMAN as either induction responders or nonresponders.

5.3. End of Study Definition

End of 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 AMBG is designed to evaluate the maintenance of efficacy with blinded 200 mg mirikizumab Q4W in patients induced into clinical response with mirikizumab during the 12-week induction study, Study AMAN. Study AMAN includes patients with moderate to severely active UC.

Randomized withdrawal of mirikizumab clinical responders from Study AMAN to either placebo or continuation of mirikizumab administered SC, will enable evaluation of the benefits of maintenance dosing of mirikizumab following induction dosing.

Because randomized withdrawal of mirikizumab clinical responders to placebo may precipitate secondary LOR, 300 mg mirikizumab IV rescue will be provided to LOR patients who lose response after patients have completed at least 12 weeks of the maintenance study. Loss of response will be defined based on symptomatic criteria (that is, SF and RB) confirmed by endoscopic criteria (see Section 5.1).

The 40-week duration of this study provides a total of 52 weeks of continuous therapy (induction and maintenance) for mirikizumab patients who complete the 12-week induction study. The 40-week duration of randomized withdrawal in the maintenance study is expected to provide

adequate time for separation of efficacy effects between mirikizumab and placebo arms based on the approximate 10-day half-life of mirikizumab.

The primary endpoint tests whether mirikizumab maintains clinical remission among patients who achieved clinical remission to induction treatment with mirikizumab. Clinical remission is a clinically relevant composite endpoint, as it combines symptomatic improvement as well as endoscopic remission (anti-inflammatory effect) in the individual patient.

Patients are allowed to remain on a stable background dose regimen of conventional UC therapies during the study, except for oral corticosteroids. Corticosteroid tapering using a standardized algorithm will be mandated per protocol for patients who achieve clinical response to study drug in Study AMAN, or with extended induction for nonresponders from Study AMAN (see Section 7.7).

Patients randomized to placebo in Study AMAN and who achieved clinical response will be assigned to blinded placebo maintenance dosing in Study AMBG. These patients provide "true" placebo data for evaluation of safety and efficacy outcomes. Patients will continue on blinded placebo unless they meet the criteria for LOR, at which point they will receive rescue treatment with mirikizumab 300 mg Q4W IV for 3 doses.

An extended induction is available to patients who do not achieve clinical response at the end of the induction study. The extended induction dosing will only include IV mirikizumab and is intended to increase the likelihood of the patient achieving clinical response. Patients who did not respond to blinded placebo therapy in the previous induction study will receive IV mirikizumab for the first time in Study AMBG.

A daily diary will be used to record PROs, including SF and RB. Use of a daily diary to collect data over a short recall period offers potential advantages over collecting data intermittently at clinic visits. Daily diary entries will be used to assess the effect of mirikizumab on achieving the primary and secondary endpoints.

5.5. Justification for Dose

The maintenance dose regimen selected for this study was 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 300 mg Q4W (IV) LOR dose regimen proposed relative to the NOAEL level in the 6-month nonclinical toxicology study in cynomolgus monkeys is 6.5, based on area under the plasma concentration versus time curve. The MOS for the maintenance dose of 200 mg Q4W (SC) is 23.

Considerations of Efficacy and Exposure-Response Relationship

200 mg SC Q4W Maintenance Dose Regimen

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 timecourse 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 concentration 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 maintenance dose regimen of 200 mg SC Q4W was selected for Study AMBG.

300 mg IV Q4W Loss of Response Dose Regimen

The dose regimen selected for patients that lose response during maintenance is the same dose and regimen as used during the 12-week induction study, AMAN. The induction dose and regimen was based on the observed data in the Phase 2 study, AMAC, that showed significant efficacy relative to placebo at Week 12 in the 50-mg and 200-mg IV Q4W cohorts. Due to the application of exposure-based dose adjustments in Study AMAC, the overall average induction dose received by subjects in the 50- and 200-mg cohorts were 100 and 250 mg, respectively. Although exposure increased in proportion to dose, patients in the 600-mg mirikizumab cohort did not respond better to treatment at Week 12 than patients in the 200-mg mirikizumab cohort.

Examination of the relationship between observed individual subject mirikizumab exposures and Week 12 clinical response and remission, and model based analyses of these relationships, suggests that the probability of a subject achieving these clinical endpoints was not strongly dependent on exposure within the range of exposures that were evaluated in Study AMAC. However, model based analyses of the relationship between mirikizumab exposure and reduction in the modified Mayo Score (MMS) at Week 12 indicated that doses below 300 mg may lead to decreased efficacy, while doses above 300mg are not likely to provide meaningful improvements in efficacy. Furthermore, a dose of 300 mg is expected to produce a median average concentration that covers approximately 90% of individual subject exposures observed in the 200-mg cohort in Study AMAC.

Therefore, the observed results in Study AMAC and the analyses of exposure-response relationships support the selection of 300 mg IV Q4W for subjects that lose response during maintenance in Study AMBG.

6. Study Population

Study AMBG is a continuation of the induction Study AMAN. The AMBG patient population will consist of patients who complete Study AMAN through Week 12 and who meet all Study AMBG enrollment criteria, irrespective of their treatment assignment in Study AMAN and their clinical response to the investigational product in that study.

Patients will enter Study AMBG directly from Study AMAN once they sign a study-specific Institutional Review Board/Ethics Committee-approved informed consent. A patient is considered enrolled into the study once the patient is randomized and assigned to treatment. Besides a maximum 14-day window between the start of the Visit 5 (Week 12) visit of the induction study AMAN and the start of Visit 1 (Week 0) of Study AMBG, no screening period is allowed for Study AMBG. Data collected during the last visit of the induction study AMAN, including laboratory evaluations, endoscopy, and PRO data, will be used to review enrollment criteria for Study AMBG. A visit window (14 days) is provided to allow laboratory results and central reading of the endoscopy to be available for the investigator to appropriately evaluate a patient and to ensure compliance with enrollment criteria. 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 prior to study entry, as long as all testing is completed within 14 calendar days from the start of the Visit 5 (Week 12) visit of Study AMAN. Patients who terminate from the induction study early for any reason or permanently discontinue study drug during the induction study are not eligible to enter Study AMBG.

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 maintenance study baseline, unless specifically defined:

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.

Patient Characteristics

[2.] Have completed Study AMAN through the Week 12 visit (Visit 5) and have a Visit 5 MMS and have received at least 1 study drug administration without early termination of study drug.

[3.] Are willing and able to complete the scheduled study assessments, including endoscopy and daily diary entry.

[4.] Contraception

[4a.] Male patients:

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

[4b.] Female patients:

Women of childbearing potential:

A. Must test negative for pregnancy prior to initiation of treatment as indicated by a negative urine pregnancy test at Visit 1/Week 0 of this study.

AND

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 20 weeks

i. 2 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 (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives or intrauterine devices).

Women not of childbearing 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

- Cessation of menses for at least 1 year or
- At least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone (FSH) >40 mIU/mL; or

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.

[5.] Have documentation of the following:

[5a.] A surveillance colonoscopy (performed according to local standard) within 12 months before baseline for:

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

OR

[5b.] In patients for whom Inclusion Criterion [5a] does not apply, up-to-date screening for colorectal cancer (performed according to local standard).

A full colonoscopy can be performed as part of the Week 12 procedures in Study AMAN to satisfy this inclusion criterion for Study AMBG.

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at maintenance study baseline, unless specifically defined:

Gastrointestinal Exclusion Criteria

[6.] Have been diagnosed during the previous induction study AMAN with Crohn's disease or Inflammatory Bowel Disease-Unclassified (IBD-U, formerly known as indeterminate colitis).

[7.] Have had bowel resection or other surgery for the treatment of UC during the previous induction study AMAN, or are likely to require surgery for the treatment of UC during Study AMBG.

[8.] Have evidence of colonic dysplasia (including dysplasia in flat mucosa or dysplasia-associated lesion or mass [DALM]) at maintenance baseline (Study AMAN Visit 5 [Week 12] endoscopy) or have been diagnosed with cancer of the gastrointestinal tract during Study AMAN.

[9.] Have current adenomatous polyps that have not been removed. Once removed, the patient may be eligible for study after confirming no dysplasia or malignancy on local histology report.

Infectious Disease Exclusion

[10.] Have been diagnosed with clinically important infection including, but not limited to, hepatitis B, hepatitis C, HIV/AIDS, and active tuberculosis (TB) during the induction study AMAN.

[11.] Have detectable hepatitis B virus (HBV) DNA detected at any time in Study AMAN

[12.] Have been diagnosed with latent TB during the induction study AMAN and are not willing to comply with completing TB treatment as appropriate.

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

General Exclusion Criteria

[14.] Initiation of a new prohibited medication (see Appendix 8) during the induction study AMAN.

[15.] Presence of a hepatic or hematologic laboratory abnormality prior to Visit 1/Week 0 that would require permanent discontinuation from study drug (see Section 8.1.1).

[16.] 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;

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.

[17.] 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 malignancy that would potentially affect patient safety within the study or confound efficacy assessment.

[18.] Have a known systemic 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.

[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 (or within 20 weeks if patient received less than 2 SC doses and decides to terminate study participation early for any reason during Study AMBG).

[20.] Became 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 previous induction study AMAN.

[21.] Have enrolled in another clinical trial involving an investigational product or nonapproved use of a drug or device during Study AMAN, OR 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.

[22.] Have previously completed or withdrawn from Study AMBG or any other study investigating mirikizumab, except for completion of 12 weeks of induction study AMAN.

[23.] Are unwilling or unable to comply with the use of a data collection device to directly record data from the patient daily for the duration of Study AMBG, or are unable to complete other study procedures.

6.3. Lifestyle Restrictions

Study participants should be instructed not to donate blood or blood products during the study and for 20 weeks following their last dose (if last dose is given IV) or for 16 weeks following their last dose (if last dose is given SC). In order to participate in the study, patients must agree to the contraception, reproduction and breastfeeding criteria detailed in inclusion criterion [4] and exclusion criterion [19].

6.4. Screen Failures

As described in Section 6, patients will be entered into Study AMBG directly from Study AMAN, with a maximum 14-day window between start of the Visit 5 (Week 12) visit of the induction study AMAN and start of Visit 1 (Week 0) of Study AMBG.

Data collected during the last visit of the induction trial will be used to review enrollment criteria and the suitability of an induction patient proceeding to Study AMBG. Patients who do not meet enrollment criteria may have one or more blood measures repeated one time, at the investigator's discretion, prior to study entry as long as all testing is completed within 14 calendar days from the start of the last induction visit.

7. Treatments

7.1. Treatments Administered

The treatments to which patients will be randomized or assigned to will depend upon their clinical response at Visit 5 (Week 12) of induction study AMAN (Figure AMBG.5.1). Patients who achieved clinical response during the induction study (defined in Table AMBG.9.1) will follow the treatment regimens described in Table AMBG.7.1. Patients who did not achieve clinical response during the induction study will follow the treatment regimens described in Table AMBG.7.2. Importantly, to preserve the study blind:

- All Study AMAN responders, regardless of Study AMBG treatment assignment, will be administered study drug in Study AMBG in the same manner:
    - Blinded SC study drug for maintenance dosing, and open-label 300 mg mirikizumab IV rescue dosing if they develop secondary LOR.
- All Study AMAN nonresponders will be administered study drug in Study AMBG in the same manner:
    - Open-label 300 mg mirikizumab IV, followed by open-label 200 mg mirikizumab SC dosing if they demonstrate delayed clinical response with extended induction.

Patients who meet all criteria for enrollment and **who have achieved clinical response to mirikizumab** at the end of induction study AMAN will be randomized 2:1 to double-blind treatment with either 200 mg mirikizumab Q4W SC or placebo Q4W SC at Visit 1. Patients who **achieved clinical response to placebo** at the end of the induction study AMAN will continue to receive blinded placebo Q4W SC during the maintenance study starting at Visit 1.

If the patient experiences LOR to either 200 mg mirikizumab Q4W SC or to placebo Q4W SC at or after Week 12 of Study AMBG, they will receive rescue with open-label 300 mg mirikizumab IV Q4W for 3 doses. Induction-study placebo responders who experience LOR on SC placebo will also receive open-label mirikizumab IV 300 mg Q4W for 3 doses. No further treatment adjustments are permitted. Once IV LOR dosing is complete, patients who, in the opinion of the investigator, are receiving clinical benefit from mirikizumab therapy may be considered for enrollment into the long term extension study AMAP to receive further SC dosing. Patients who are not considered by the investigator to be receiving clinical benefit from mirikizumab IV rescue therapy, will be discontinued and proceed to post-treatment follow-up.

Patients who meet all enrollment criteria and who **did not respond to study drug (either mirikizumab or placebo)** in induction study AMAN will enter Study AMBG as nonresponders. All induction nonresponders will receive open-label extended induction dosing with 300 mg mirikizumab IV Q4W for 3 doses. Patients who achieve delayed clinical response to mirikizumab IV extended induction therapy at Week 12, compared to induction baseline, will subsequently receive open-label 200 mg mirikizumab Q4W SC injections for the remainder of the 40-week treatment period. Patients who do not achieve clinical response to mirikizumab IV extended induction therapy at Week 12 will discontinue study drug and undergo early termination procedures and proceed to post-treatment follow-up.

Table AMBG.7.1. Treatment Regimens: Induction Clinical Responders

Regimen		Dose Weeks 0-8	Dose Weeks 12-40
Responders to blinded mirikizumab in induction study			
Randomized 2:1	Blinded 200 mg mirikizumab Q4W SC	Weeks 0, 4, 8	• Continue **blinded** 200 mg mirikizumab SC at Weeks 12, 16, 20, 24, 28, 32, 36 **Or, if LOR anytime between Weeks 12 and 28 (inclusive):** • Change to **open-label 300 mg mirikizumab IV Q4W** for 3 doses **If no clinical benefit after 3 doses of rescue IV induction with mirikizumab, then discontinue mirikizumab** **If clinical benefit, may proceed to Study AMAP**
	Blinded Placebo Q4W SC	Weeks 0, 4, 8	• Continue **blinded** placebo at Weeks 12, 16, 20, 24, 28, 32, 36 **Or, if LOR anytime between Weeks 12 and 28 (inclusive):** • Change to **open-label 300 mg mirikizumab IV Q4W** for 3 doses **If no clinical benefit after 3 doses of rescue IV induction with mirikizumab, then discontinue mirikizumab** **If clinical benefit, may proceed to Study AMAP**
Responders to blinded placebo in induction study			
Blinded Placebo Q4W SC		Weeks 0, 4, 8	• Continue **blinded** placebo at Weeks 12, 16, 20, 24, 28, 32, 36 **Or, if LOR anytime between Weeks 12 and 28 (inclusive):** • Change to **open-label 300 mg mirikizumab IV Q4W** for 3 doses **If no clinical benefit after 3 doses of rescue IV induction with mirikizumab, then discontinue mirikizumab** **If clinical benefit, may proceed to Study AMAP**

Abbreviations: IV = intravenous; LOR = loss of response (defined as ≥2-point increase from maintenance baseline in the combined SF + RB scores, AND combined SF + RB score of ≥4 on 2 consecutive visits, AND confirmed by endoscopic subscore of 2 or 3); OL = open-label; Q4W = every 4 weeks; RB = rectal bleeding; SC = subcutaneous; SF = stool frequency.

Table AMBG.7.2. Treatment Regimens: Induction Clinical Nonresponders

Regimen	Dose Weeks 0-8	Dose Weeks 12-40
Nonresponders to blinded mirikizumab IV in induction study		
Open-label 300 mg mirikizumab IV	Weeks 0, 4, 8	**Week 12 Extended Induction Responders** • Open-label 200 mg mirikizumab SC at Weeks 12, 16, 20, 24, 28, 32, 36; then may proceed to Study AMAP • If clinical benefit is lost, discontinue mirikizumab and enter post-treatment follow-up period **Week 12 Extended Induction Nonresponders:** • Discontinue mirikizumab
Nonresponders to blinded placebo in induction study		
Open-label 300 mg mirikizumab IV	Weeks 0, 4, 8	**Week 12 Extended Induction Responders** • Open-label 200 mg mirikizumab SC at Weeks 12, 16, 20, 24, 28, 32, 36; then may proceed to Study AMAP • If clinical benefit is lost, discontinue mirikizumab and enter post-treatment follow-up period **Week 12 Extended Induction Nonresponders:** • Discontinue mirikizumab

Abbreviations: IV = intravenous; SC = subcutaneous.

Study Drug Administration

Subcutaneous administration of mirikizumab or placebo will be given in 2 injections (maximum volume is 1 mL per injection).

Intravenous infusion of mirikizumab will occur over at least 30 minutes. All patients should be monitored for 1 hour or longer after dosing, or longer according to investigator practice or local standard of care. Sites must have resuscitation equipment, emergency medications, and appropriately trained staff available during the infusion and monitoring period. Detailed instructions for investigational product administration will be provided separately by the sponsor.

Investigational product will be prepared at the site by blinded pharmacists or other trained and qualified personnel as designated by the investigator. Investigational product will be administered at the site by a blinded nurse, pharmacist, or other trained and qualified personnel as designated by the investigator.

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

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

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

7.1.1. Packaging and Labeling

Mirikizumab and placebo will be supplied to the investigator by Lilly or its designee. Clinical trial materials will be labeled according to the country's regulatory requirements. All 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 pre-filled syringe containing mirikizumab or placebo. The 1-mL syringe of mirikizumab is manufactured to deliver 100 mg.
- Single-use solution vial containing mirikizumab. The 15-mL vial of mirikizumab is manufactured to deliver 300 mg (20 mg/ml).

Mirikizumab cannot be distinguished visually from placebo.

Study drug will be provided with study-specific labels. Syringes and vials 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

Assignment to treatment groups for patients entering Study AMBG as clinical responders will be determined by a computer-generated random sequence using an interactive web-response system (IWRS) in a double-blind manner. To achieve between-group comparability, patients will be stratified to these arms based upon biologic-failed status (yes or no), baseline corticosteroid use (yes or no), region (North America/Europe/Other), and induction remission status (yes or no). This stratification will be controlled by IWRS.

7.2.1. Selection and Timing of Doses

The doses will be administered at each scheduled visit as described in the Schedule of Activities (Section 2). The actual time of all dose administrations will be recorded in the patient's electronic case report form (eCRF). Doses, other than rescue mirikizumab IV doses, should not be administered during unscheduled visits, unless the unscheduled visit occurs during the next scheduled dosing window. Rescue mirikizumab IV doses may be administered during unscheduled visits if LOR has been confirmed and if it is ≥7 days from the most recent SC dose. Subsequent rescue mirikizumab IV doses will be given every 4 weeks (+/- 3 days) for total of 3 doses.

7.3. Blinding

This is a double-blind study. To preserve the blinding of the study, a minimum number of Lilly personnel will have access to the randomization table and treatment assignments before the study

is complete. These personnel will not have communication with site personnel. No unblinding at the investigational site for investigational product preparation will be required. A blinded study site pharmacist or other trained and qualified person will prepare the investigational product.

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

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

If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study drug and must complete the ETV and post-treatment follow-up as per protocol. In cases where there are ethical reasons to have the patient remain on study drug, the investigator must obtain specific approval from the sponsor or designee for the patient to continue in the study.

7.4. Dosage Modification

Dose adjustments, other than the dose regimen change provided to patients who demonstrate a LOR, described in Section 7.1, 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.

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 and placebo 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 at the study site by 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 in the Concomitant Medication eCRF. All patients are encouraged to maintain their usual medication regimens for concomitant conditions or diseases throughout the study, unless those medications are specifically excluded (Appendix 8).

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 9. Patients taking oral corticosteroids are to follow the corticosteroid taper instructions described below. 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 8) 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 medications. 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 8 and Appendix 9, respectively.

Corticosteroid Taper

Patients who enter Study AMBG on corticosteroid therapy for treatment of their UC and who achieved clinical response in the induction study AMAN will initiate corticosteroid tapering, as described below, at Week 0 of Study AMBG. Clinical nonresponders who undergo extended IV induction with mirikizumab will begin corticosteroid tapering if clinical response is achieved at Week 12 of the extended induction dosing, or earlier if symptomatic improvement, based on investigator discretion, is evident at any time after starting extended IV induction dosing.

For patients who cannot tolerate the corticosteroid taper without recurrence of clinical symptoms, corticosteroid taper may be paused and/or corticosteroid dose may be increased up to the original dose at induction baseline (should not exceed induction baseline dose). In such cases, attempts to reinitiate corticosteroid tapering should be made within 2 weeks of interruption of taper, with a goal to complete tapering no later than Week 12 of Study AMBG.

The recommended tapering schedule for oral corticosteroids (other than budesonide extended release tablets [budesonide MMX] or beclomethasone dipropionate [gastro-resistant prolonged-release tablet]) is as follows:

- Dose >10 mg/day prednisone or equivalent: taper daily dose by 5 mg/week until receiving 10 mg/day, and then continue tapering at 2.5 mg/week until 0 mg/day.
- Dose ≤10 mg/day prednisone or equivalent: taper daily dose by 2.5 mg/week until 0 mg/day.

The recommended tapering schedule for patients receiving oral budesonide MMX 9 mg/day is to reduce tablets to 9 mg every other day for 2 weeks, followed by 9 mg every third day for 2 weeks, and then discontinue.

The recommended tapering schedule for patients receiving oral beclomethasone dipropionate (gastro-resistant prolonged-release tablet) 5 mg/day is to reduce tablets to 5 mg every other day for 4 weeks, and then discontinue.

7.8. Treatment after the End of the Study

7.8.1. Study Extensions

Patients who complete Week 40 in Study AMBG will be assessed for eligibility to enter the open-label extension study (Study AMAP). There is no extension period within Study AMBG. If patients do not meet enrollment criteria for Study AMAP or opt not to continue into Study

AMAP, they will be asked to complete the post-treatment follow-up period, as described in the Schedule of Activities (Section 2), which will complete their study participation.

7.8.2. Treatment after Study Completion

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

7.8.3. Special Treatment Considerations

7.8.3.1. Premedication for Infusions

Premedication for the study drug infusions or injections is not planned. Any premedication for infusions or injections should be discussed with the medical monitor. Any premedication given will be documented as a concomitant therapy.

7.8.3.2. Management of Hypersensitivity, Infusion-Related Events, Infusion Site Reactions and Injection Site Reactions

During and after study drug administration, patients should be closely monitored for signs or symptoms of AEs, including hypersensitivity events, other infusion-related events, and infusion or 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 10 for additional information):

- Study drug infusion should be stopped immediately and appropriate supportive care provided according to local standard practice (for example, administration of epinephrine, anti-histamine, systemic steroids, and/or bronchodilators).
- After patient's stabilization, an anti-drug antibody (ADA) and PK sample should be collected; additional samples should be obtained 4 and 12-16 weeks after the event. These samples will also be used for tryptase, complement (C3/C4), and cytokine panel assays.
- 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.

Other Infusion-Related Events and Infusion Site Reactions

If a patient experiences a reaction consisting of headache, rigors and/or temperature >38°C (in the absence of signs or symptoms of a systemic hypersensitivity reaction), or an infusion site reaction, including urticaria, pruritus, or angioedema localized to the IV infusion site (in the absence of other systemic hypersensitivity signs or symptoms), during or up to 6 hours after an infusion of study drug, the following guidance should be followed:

- Study drug infusion should be interrupted and appropriate medical care should be administered (for example, NSAIDS, anti-pyretics or antihistamines).
- An ADA and PK sample should be collected at the time of the event (or as soon as possible after the event occurs), and 4 and 12-16 weeks after the event. These samples will also be used for tryptase, complement (C3/C4), and cytokine panel assays.
- Resumption of study drug infusion after interruption, possibly at a slower rate of administration, can be considered if symptoms resolve and it is deemed to be medically appropriate based on the investigator's discretion, and considering the risk/benefit of readminstration.
- If the patient develops systemic hypersensitivity symptoms or signs, they should be managed as described above for a systemic hypersensitivity reaction. Patient should remain in observation, as is clinically appropriate for the patient's symptoms.
- Premedication prior to subsequent study drug administration may be considered, if judged by the investigator to be appropriate for the individual patient.

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. Patients who discontinue study treatment early will undergo early termination procedures, which include an ETV and post-treatment follow-up visits. The investigator will also complete any AE reporting and follow-up that may be required (if applicable, see Section 9.2).

If a patient's study treatment is discontinued before the end of the Maintenance Study Dosing Period, the patient should complete the ETV and post-treatment follow-up period as follows:

- Patients who discontinue investigational product during **extended induction IV dosing** or **before receiving any SC dosing** will return for post-treatment follow-up visits (Visit 801 and 802) 4 and 16 weeks after the end-of-treatment visit.
- Patients who discontinue study drug **after having received ≥1 SC dose** will return for post-treatment follow-up visits (Visit 801 and 802) 4 and 12 weeks after the end-of-treatment visit.

Possible reasons leading to permanent discontinuation of investigational product include the following (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%)

Discontinuation due to Lack of Clinical Benefit or Disease Worsening

- Induction study responders who experience LOR and do not receive clinical benefit from mirikizumab IV rescue induction
- Induction study nonresponders who do not achieve clinical response with 3 doses of mirikizumab IV extended induction
- Induction study nonresponders who achieve clinical response with mirikizumab extended IV induction, but subsequently lose clinical benefit with open-label mirikizumab SC dosing, should be discontinued. Loss of clinical benefit may be based on demonstrating LOR criteria (see Section 5.1) or by other criteria according to investigator discretion
- Patients who require treatment with a prohibited UC medication (Appendix 8), an increase in immunomodulatory medication, or a course of corticosteroids that exceeds the baseline dose
- Patients who undergo surgery for UC

Safety Criteria for Study Drug Discontinuation

- The patient requires a prohibited medication to treat their UC (Appendix 8). 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, proctocolectomy, or partial 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 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 9.4.5.2).
- A diagnosis of hepatitis C during the study or development of detectable hepatitis C virus (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 participant has an AE or SAE which, in the opinion of the investigator or sponsor, would preclude the participant from continuing to receive study drug.

- Systemic hypersensitivity event or anaphylaxis to study drug.

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

- If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study drug and continue to post-treatment follow-up. In cases where there are ethical reasons to have the patient continue on study drug, the investigator must obtain specific approval from the sponsor or designee for the patient to continue in the study.
- Inadvertent enrollment (see Section 8.1.3)

Patients discontinuing from the investigational product prematurely for any reason should complete AE 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) of 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 during the study, including latent tuberculosis infection (LTBI).
- 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-MP 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 (that is, 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 recommence 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
- 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 discontinued 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 AMBG.9.1. Endpoint Definitions in Study AMBG

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 baseline, and • A decrease of ≥1 point in the RB subscore from baseline or a RB score of 0 or 1
Corticosteroid-free remission without surgery at Week 40[a]	• Clinical remission at Week 40, and • Symptomatic remission at Week 28, and • No corticosteroid use for ≥12 weeks prior to Week 40
Endoscopic remission	• ES = 0 or 1 (excluding friability)
Endoscopic response	• A decrease in the ES of ≥1 point compared to baseline
Histologic remission	• This definition will be specified in the SAP
Mucosal healing	• Histologic remission as described in the SAP and • endoscopic remission defined as ES = 0 or 1 (excluding friability)
Symptomatic remission	• SF = 0, or SF = 1 with a ≥1-point decrease from induction baseline, and • RB = 0
Stable maintenance of symptomatic remission[b]	• Symptomatic remission for at least 7 out of 9 visits from Week 4 to Week 36 • Symptomatic in remission at Week 40
Bowel movement urgency improvement	• The definition will be specified in the study SAP

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

[a] Among patients induced into clinical response with mirikizumab during the induction study and who were receiving corticosteroids at induction baseline.

[b] Among patients in symptomatic remission at Week 12 of Study AMAN.

9.1.1. Primary Efficacy Assessments

9.1.1.1. Primary Endpoint

The primary endpoint is **clinical remission** at Week 40, among patients induced into clinical response with mirikizumab induction treatment (Study AMAN). Clinical remission is based on the MMS and is defined in Table AMBG.9.1.

9.1.1.2. Mayo Score

This study utilizes components of the Mayo Score (Schroeder et al. 1987) to assess UC disease activity for the primary and major secondary endpoints (see Appendix 6). **Complete and accurate recording of the Mayo SF and RB subscores by patients in their daily electronic diary is necessary for the success of the study.** Adequate bowel preparation and an endoscopy with adequate visualization of the mucosa will enable calculation of the Mayo ES.

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

SF Subscore: The SF subscore is a patient-reported measure. This item reports the number of stools in a 24-hour period, relative to the normal number of stools for that patient in the same period, on a 4-point scale (see Appendix 6). **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 absolute number of stools passed in a 24-hour period will be recorded by the patient in a daily electronic diary. The reference "normal" SF for that patient will be recorded electronically at the induction study screening visit. Study software will use the patient-reported daily SF and the reference normal SF to automatically calculate the Mayo SF subscore. The patient will record this in an electronic diary (Appendix 7). Further details on the analysis of diary items are contained in the statistical analysis plan (SAP).

Normal SF: The Normal SF is a patient-reported measure. This item reports the number of stools in a 24-hour period when the patient was in remission or, if the patient has never achieved remission, the reported SF before initial onset of signs and symptoms of UC. Remission refers to a period of time since being diagnosed with UC when the patient is not experiencing any signs or symptoms relating to UC. This period of time may last a few weeks or a few months or may even last several years. The patient will record this electronically as source data in the tablet device at the screening study visit of Study AMAN.

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 6). The patient will record this in a daily electronic diary (Appendix 7). Further details on the analysis of diary items are contained in the SAP.

Endoscopic Subscore (ES): 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 6). Determination of the ES is further detailed in Section 9.1.1.3. 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 Physician's Global Assessment (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 6). The investigator will record the PGA electronically as source data in the tablet device 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 MMS 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.

9.1.1.3. 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 [5]), or for other clinically indicated reasons, in the judgement of the investigator and after discussion with the medical monitor as appropriate.

Endoscopic disease activity assessed at Week 12 of Study AMAN will serve as the baseline assessment of endoscopic disease activity in Study AMBG.

In patients who enter Study AMBG in clinical response or clinical remission, endoscopy will be performed at Week 40, ETV, UV, or if LOR is suspected in these patients based on SF/RB scores, endoscopy can be performed at or after Week 12 to confirm secondary LOR. Secondary LOR must be confirmed endoscopically before rescue mirikizumab IV induction dosing is initiated. If endoscopy does not confirm secondary LOR, patients are encouraged to continue study drug dosing. If study drug dosing is continued, an additional endoscopy would be performed at Week 40, ETV, or UV.

In patients who enter Study AMBG as induction study nonresponders, endoscopy will be performed at Week 12, following extended mirikizumab IV induction. An additional endoscopy will be performed at Week 40, ETV, or UV. Patients who plan to continue in the long term extension study AMAP and who require an annual surveillance colonoscopy to remain up-to-date in screening for colorectal cancer (see Inclusion Criterion [5]), will undergo colonoscopy as the endoscopy method at Week 40.

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

If a patient undergoes early termination soon after baseline, loss of response, or at the end of extended induction endoscopy, the need for ETV endoscopy should be discussed with the medical monitor.

The endoscopy report and histopathology report (if biopsies are sent to a 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 colonoscopies. 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 centrally-read Mayo ES at each colonoscopy in a blinded manner, as detailed in the image review charter.

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

9.1.1.4. Endoscopic Biopsies

Biopsies will be obtained at each endoscopy to support assessment of the histopathology endpoints in this study, and where permitted, for the assessment of exploratory biomarkers. These will be sent to the central study laboratory for processing. 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 specimen transfer, processing, slide preparation, and digitization of slides for histopathologic scoring. Centrally read histopathology results will not be made available to study sites.

9.1.2. Secondary Efficacy Assessments

9.1.2.1. Major Secondary Endpoints

The major secondary endpoints are as follows (see Table AMBG.9.1 for definitions):

- Clinical **remission** at Week 40, among patients induced into clinical **remission** with mirikizumab at Week 12 of induction study (Study AMAN)
- Endoscopic remission at Week 40, among patients induced into clinical **response** with mirikizumab at Week 12 of the induction study
- Corticosteroid-free remission without surgery at Week 40, among patients induced into clinical **response** with mirikizumab at Week 12 of the induction study and were receiving corticosteroids at induction baseline
- Histologic remission at Week 40, among patients induced into clinical **response** with mirikizumab at Week 12 of induction study
- Stable maintenance of symptomatic remission, among patients induced into clinical **response** with mirikizumab and were in symptomatic remission at Week 12 of induction study
- Bowel movement urgency improvement among patients induced into clinical **response** with mirikizumab at Week 12 of induction study

9.1.2.1.1. Histopathology Scoring Instruments

The histopathology instruments that will be used for the evaluation of microscopic inflammation and histopathologic disease activity will be specified in the histopathology charter.

9.1.2.1.2. Patient Reported Outcome Instruments

The Urgency NRS (see Appendix 7 for description) is a PRO instrument used to collect bowel movement urgency data in the patient eDiary. The Urgency NRS will be used to determine the secondary endpoint for bowel movement urgency improvement (see Table AMBG.4.1 for definition).

9.1.2.2. Other Secondary Endpoints

Other secondary endpoints are found in Table AMBG.4.1.

9.1.2.2.1. Physician Reported Instrument

The Ulcerative Colitis Endoscopic Index of Severity (UCEIS) is a physician reported instrument for measuring the endoscopic disease activity of UC on flexible sigmoidoscopy or colonoscopy, that includes 3 descriptors of vascular pattern, bleeding, and erosions/ulcerations (Arai et al. 2016; Ikeya et al. 2016; Tontini et al. 2014). Only blinded central reading of endoscopies will be used to determine the UCEIS score for each endoscopy.

9.1.2.2.2. PRO Instruments Used to Assess Secondary Endpoints

The following are additional PRO instruments collected using a patient electronic diary (eDiary). Please see Appendix 7 for additional descriptions.

- Abdominal Pain Numeric Rating Scale (NRS)
- Fatigue NRS (collected at site visits until Visit 10 when collected via electronic diary)

The following are additional PRO instruments collected using a tablet device. Please see Appendix 7 for additional descriptions.

- Inflammatory Bowel Disease Questionnaire (IBDQ)
- European Quality of Life 5-Dimension 5 Level (EQ-5D 5L)
- Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) Version 2
- Work Productivity and Activity Impairment Questionnaire: Ulcerative Colitis (WPAI:UC)

9.1.3. Exploratory Endpoints

Exploratory endpoints are defined in the SAP.

9.1.3.1. Inflammatory Biomarkers

C-reactive protein (CRP): CRP is an acute phase protein expressed by hepatocytes in response to inflammatory cytokines, particularly IL-6, tumor necrosis factor, and IL-1β (Sands 2015). C-reactive protein will be obtained at the time points described in the Schedule of Activities (Section 2). Investigators will be blinded to CRP results.

Fecal calprotectin: Fecal calprotectin is a complex consisting of the calcium-binding proteins S100A8 and S100A9 (Sands 2015). It is expressed by activated neutrophils (and to a lesser extent by macrophages and monocytes) and fecal levels correlate with the number of neutrophils in the gut. It is used as a biomarker of intestinal inflammation in clinical practice. Fecal calprotectin will be obtained at time points described in the Schedule of Activities (Section 2). Investigators will be blinded to fecal calprotectin results.

9.1.3.2. Extraintestinal Manifestations

Review of extraintestinal manifestations (EIMs) will be performed at the time points described in the Schedule of Activities (Section 2). If new events are reported or ongoing events change in severity, they are to be reported as AEs. 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.

9.1.3.3. PRO Instruments Used to Assess Exploratory Endpoints

The Patient UC Symptom Diary is a set of 8 items that assess UC-related symptoms in the past 24 hours (Appendix 7). In addition to the SF, RB, abdominal pain, and urgency items mentioned above, the diary also includes items that asks the patient to report stool consistency, the frequency of night-time stools, and overall disease severity.

The following exploratory endpoints will be assessed via the electronic diary tool and/or at applicable study visits using the tablet device:

- Nocturnal Stool (collected at site visits until Visit 10 when collected via electronic diary)
- Patient's Global Rating of Severity (PGRS) (collected via electronic diary)
- Bristol Stool Scale (collected at site visits until Visit 10 when collected via electronic diary)

In addition to those exploratory endpoints assessed by the Symptom Diary, the PGRC will be administered at applicable study visits using the tablet device. Additional descriptions of these PRO instruments can be found in Appendix 7.

9.1.4. 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 eCRF 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 protocol procedure or 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 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 SAP, 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 7.8.3.2.

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, electrocardiogram (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.

9.4.2. Electrocardiograms

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

Electrocardiograms 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. Electrocardiograms 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.

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). Retesting is allowed 1 time between the last induction visit and Visit 1 of Study AMBG.

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 childbearing potential, outlined in Inclusion Criterion [4b].

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 FSH levels can assist in determining if a woman meets the definition of "postmenopausal," as outlined in Inclusion Criterion [4b]. Follicle-stimulating hormone 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 [4b].

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 will be collected at the same time points. Samples for ADA and accompanying PK analysis should be taken prior to dosing.

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 12-16 weeks after the event. These samples will also be used for tryptase, complement (C3/C4), and cytokine panel assays. 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 is mandated at Week 40 (or ETV), and must also be performed at Week 0 if not performed at Week 12 of induction study. 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

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 the United States Centers for Disease Control and Prevention guidance (CDC [WWW]) for the United States or the World Health Organization guidance for the treatment of LTBI for all countries outside of the United States (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.

9.4.5.3. Hepatitis B

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

- HBV DNA is not detected at Visit 5 (Week 12) of Study AMAN *and*
- If HBV DNA was tested at other times in Study AMAN, HBV DNA was not detected *and*
- The other inclusion/exclusion criteria of Study AMBG are met.

Such patients will undergo HBV DNA testing at the following time points:

- Weeks 12, 24, and 40 (or 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 AMBG, 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 AE:

- “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 ETV 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 the induction study AMAN 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 during the study (test positive for HCV RNA) will be discontinued from study treatment, undergo ETV and post-treatment follow-up, and 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 at Week 0, Week 12, Week 24, and Week 40 or ETV. These assessments are described below, and further information is provided in Appendix 11.

> **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 recorded in the eCRF.
>
> **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 is then documented in the eCRF.
>
> **Quick Inventory of Depressive Symptomatology—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 electronically as source data in the tablet device according to the Schedule of Activities (Section 2).

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.

9.4.5.6. Stool Testing

In assessing secondary LOR, a stool sample for *C. difficile* toxin will be obtained at the first of the LOR assessments. *C. difficile* testing will also be performed at UVs and ETV when UC disease exacerbation is suspected.

This assay tests for the presence of *C. difficile* toxin protein, followed by a confirmatory test for *C. difficile* toxin gene expression in the stool sample. *C. difficile* testing must be negative for patients to be eligible to receive IV mirikizumab rescue dosing. If the *C. difficile* test confirms active *C. difficile* infection, patients should be treated as considered appropriate by the investigator, and study treatment dosing may be withheld if infection is assessed to be clinically important (Section 8.1.2). An AE should be reported if, in the judgement of the investigator, the patient's signs, symptoms, and positive *C. difficile* test results are consistent with a *C. difficile* infection.

In the event of a positive test, re-testing is allowed if, in the judgement of the investigator, the patient's symptoms or signs are not consistent with *C. difficile* infection.

Additional local stool culture/testing is allowed at the investigator's discretion at the time of LOR evaluation or as deemed appropriate by the investigator.

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 an 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. It is not intended that samples collected from placebo-treated patients will be analyzed. 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.

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

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

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9.6. Pharmacodynamics

See Section 9.8.

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[redacted]

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

Assuming that 90% of patients complete Study AMAN (which is expected to randomize approximately 1160 patients), Eli Lilly and Company (Lilly) anticipates approximately 1044 patients will enroll in Study AMBG. It is expected that approximately 470 of these patients will enter Study AMBG as clinical responders to mirikizumab and then will be randomized 2:1 to 200 mg mirikizumab SC (approximately 313 patients) and placebo (approximately 157 patients). Among the expected 470 mirikizumab clinical responders, approximately 180 mirikizumab clinical remitters will be randomized to 200 mg mirikizumab SC (approximately 120 patients) and placebo (approximately 60 patients). This assumes that:

- The induction study (AMAN, which has a mixed population with approximately 50% biologic-failed patients) is expected to have an overall clinical remission rate of 23% and response rate of 60% with mirikizumab.
- 75% of induction patients receive treatment with mirikizumab, based on a 3:1 randomization ratio for the induction study.
- 10% dropout rate from induction to maintenance.

The primary endpoint, clinical remission at Week 40, will be assessed on patients who achieved clinical response to mirikizumab induction treatment. Assuming mirikizumab and placebo clinical remission rates of 47% and 27%, respectively, this study based on the 470 mirikizumab induction responders is expected to have >95% power to demonstrate that mirikizumab is superior to placebo by using a chi-square test with a 2-sided significance level of 0.05. In addition, the sample size is expected to provide adequate power (>80%) to demonstrate that mirikizumab is superior to placebo for endoscopic remission, histologic remission, and corticosteroid-free remission at Week 40, among responders to mirikizumab induction treatment by using a chi-square test with a 2-sided significance level of 0.05.

10.2. Populations for Analyses

For purposes of analysis, the populations described in Table AMBG.10.1 are defined.

Table AMBG.10.1. Analysis Populations in Study AMBG

Population	Description
Intent-to-treat (ITT) Population	All randomized/assigned patients. Patients will be analyzed according to the treatment to which they were assigned
Modified Intent-to-treat (mITT) Population	All randomized/assigned patients who received at least 1 dose of study treatment in Study AMBG, regardless of whether correct treatment was administered or whether protocol was followed, will be analyzed according to the treatment to which they were assigned.
Safety Population	Same as mITT Population
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). Qualifications and identification of the specific significant protocol deviations that result in exclusion from the PP population will be determined while the study remains blinded, prior to the database lock
Pharmacokinetic Evaluable	All patients who received at least 1 dose of investigational product and have sufficient blood sampling to allow for pharmacokinetic evaluation

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

Four analysis cohorts have been defined (Table AMBG.10.2).

Table AMBG.10.2. Analysis Cohorts in Study AMBG

Cohort ID	Cohort	Description
1	Main cohort (mirikizumab induction responders)	Patients who are randomized and responded to mirikizumab induction dosing and then are rerandomized to 200 mg mirikizumab SC or placebo
2	Mirikizumab induction nonresponders	Patients who are randomized and did not respond to mirikizumab induction dosing and then are enrolled into Study AMBG
3	Placebo induction responders	Patients who are randomized and responded to placebo in induction study and then enrolled into Study AMBG
4	Placebo induction nonresponders	Patients who are randomized and did not respond to placebo in induction study and then enrolled into Study AMBG

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

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

Both efficacy and safety analysis will be conducted on the modified intent-to-treat (mITT) population. The efficacy analysis of the primary endpoint and major secondary endpoints will be repeated for intent-to treat population and the per-protocol population in the main cohort (mirikizumab induction responders). Additional analyses may be performed as deemed appropriate.

For efficacy analysis, the baseline will be defined as the initial baseline value before the patient is randomized into the induction study (Study AMAN), unless otherwise specified. For safety analysis, the baseline will be defined as the visit at Week 12 value in the induction study and prior to enrollment in Study AMBG, unless otherwise specified.

Unless otherwise specified, the main efficacy and safety analyses will be conducted on the main cohort for patients who respond to mirikizumab induction dosing and then are rerandomized to 200 mg mirikizumab SC dosing or placebo. For other cohorts of patients, efficacy and safety will be descriptive without statistical testing.

Summary statistics for continuous variables may include mean, standard deviation, median, and minimum and maximum values. Categorical variables will be presented as counts and percentages. Unless otherwise specified, variables will be analyzed in the original scale on which they are measured. The parametric approach will be employed by default for statistical analysis, except when nonparametric analysis, such as by a rank-based method, is assessed to be more fitting. Additional exploratory analyses of the data may be conducted as deemed appropriate. All hypothesis tests of treatment effects will be 2-sided, unless otherwise stated.

For assessments of the primary endpoint and other categorical efficacy endpoints among induced responders, the CMH chi-square test will be used to compare mirikizumab and placebo with stratification factors: (a) previous biologic therapy failure (yes or no), (b) baseline corticosteroid use (yes or no), (c) region (North America/Europe/Other), and (d) induction remission status (yes/no). The CMH chi-square p-value and the relative risk along with its 95% 2-sided confidence interval (CI) will be provided. In addition, the absolute treatment difference in proportions will be provided along with the 95% 2-sided CI estimate. The differences between mirikizumab and placebo will also be tested separately using a logistic regression model that controls for the stratification factors. If deemed necessary, additional analyses of categorical efficacy variables may be conducted to address sparse data and/or small sample sizes.

Treatment comparisons of continuous efficacy and health outcome variables will be made using mixed-effects model of repeated measures (MMRM) analysis. When the MMRM model is used, the model includes: (a) treatment group, (b) previous biologic therapy failure (yes or no), (c) corticosteroid use (yes or no), (d) region (North America/Europe/Other), (e) baseline value in the model, (f) visit, (g) induction remission status (if analysis is among induced responders), and (h) the interactions of treatment-by-visit and baseline-by-visit as fixed factors. The covariance structure to model the within-patient errors will be unstructured. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure will be used. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III sums of squares for the least squares (LS) means will be used for the statistical comparison; the 95% CI will also be reported.

Treatment comparisons of continuous efficacy and health outcome variables with a single post-baseline time point will be made using analysis of covariance with: (a) treatment group, (b) previous biologic therapy failure (yes or no), (c) corticosteroid use (yes or no), (d) region

(North America/Europe/Other), (e) baseline value in the model, and (f) induction remission status. Type III sums of squares for LS means will be used for statistical comparison between treatment groups. The LS mean difference, standard error, p-value, and 95% CI, unless otherwise specified, will also be reported.

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

10.3.1.1. Missing Data Imputation:

While every effort will be made to reduce missing data, the missing data imputation methods described below will be used to provide a conservative approach for assessing 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 dosing with mirikizumab prior to the time point of interest.
- Mixed-effects model of 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. The data collected after rescue medication will be censored in the primary analysis. No additional imputation methods will be applied to the MMRM analysis.

Sensitivity analyses, including additional methods of handling missing data or analyzing the data that may be required to satisfy regulatory needs will be specified in the SAP.

10.3.1.2. Multiplicity Control

A prespecified multiple testing scheme based on graphical approach (Bretz et al. 2009, 2011) will be used to test the primary and major secondary hypotheses at overall family wise type 1 error rate (FWER) of 0.05. The graphical approach is a closed testing procedure; hence, it strongly controls the FWER across all endpoints (Alosh et al. 2014). Details of the specific graphical testing scheme (including testing order, interrelationships, type I error allocation for the major secondary endpoints, and the associated propagation) will be prespecified in the SAPs prior to first unblinding of efficacy.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

The number of enrolled patients will be summarized by cohort and by treatment. Frequency counts and percentages of all patients who are enrolled and complete the study or discontinue the

study drug/study early will be presented. Reasons for discontinuing the study drug/study will be summarized.

10.3.2.2. Patient Characteristics

Year of birth, sex, weight, smoking habits, prior biologic therapy, and other demographic and disease characteristics will be summarized for all enrolled patients. Age and body mass index will be calculated. Demographic and baseline disease characteristics will be summarized for each treatment group and by cohort. Certain characteristics, such as weight, that are collected after baseline, will be reported as a listing.

10.3.2.3. Concomitant Therapy

Concomitant therapy will be collected at each visit, and the reported term will be classified by the World Health Organization drug dictionary. Medications started prior to randomization and medications started on study after randomization will be presented separately in frequency tables by drug name and by cohort for all enrolled patients.

Patients who are noncompliant will be listed by treatment and by cohort. The details of noncompliance will be defined in SAP. A contingency table of numbers of noncompliant patients by treatment and by cohort will be provided.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary endpoint is the proportion of patients with clinical remission at Week 40 (Week 52 of continuous therapy) among the patients who are responders to 300 mg mirikizumab IV at 12 weeks of induction dosing.

For study visits that include endoscopy as a study procedure (for example, Visit 11 [Week 40]), the SF and RB subscores of the Mayo score will be calculated from daily electronic diary data by averaging the most recent 3 valid days (possibly nonconsecutive) in the 7 days prior to commencing bowel preparation for endoscopy. At other study visits, where endoscopy is not performed, SF and RB subscores will be calculated from the daily electronic diary data by averaging the most recent 3 valid days (possibly nonconsecutive) in the 7 days prior to that study visit. If data for fewer than 3 valid days are available, the subscores will be considered missing. Patient diary data obtained on the following days will be excluded: (i) days when bowel preparation was taken prior to endoscopy, (ii) the day of the endoscopy, and (iii) the day after the endoscopy.

Rates of clinical remission at Week 40 among induction responders will be analyzed. Patients who do not achieve clinical remission or who do not reach the Week 40 assessment will be considered to be nonremitters. In addition, patients who take rescue dosing with mirikizumab will be considered nonremitters.

The primary endpoint analysis will utilize the CMH test as described in Section 10.3.1.

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

10.3.3.2. Secondary Analyses

The secondary efficacy and health outcome endpoints of the trial are presented in Table AMBG.4.1 and details of the analysis methods that will be utilized are provided in Section 10.3.1.

The endpoints for the major secondary objectives will be analyzed using the similar CMH test used for the primary endpoint. Multiplicity adjustment for type 1 error control to the major secondary endpoints is described in Section 10.3.1.2.

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

10.3.3.3. Exploratory Analyses

Details of the analysis of exploratory endpoints will be fully detailed in the SAP. Additional analyses of exploratory health outcome endpoints may be considered and will be fully detailed in the SAP.

10.3.4. Safety Analyses

Safety will be assessed by evaluating exposure, AE (for example, treatment-emergent AE [TEAE], SAE, treatment related AE, discontinuation due to AE), AESI (for example, infection, MACE, injection site event, hypersensitivity event, etc.), laboratory analytes, vital signs, ECGs, C-SSRS, etc.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities and summarized by system organ class, preferred term, severity, and relationship to investigational product. A TEAE is defined as an event that first occurred or worsened in severity after baseline, which is the on-study AE recorded at Week 12 in the induction study. For each event classification term, the number of patients experiencing a TEAE with that classification term will be tabulated.

The safety analyses for the main cohort will compare mirikizumab to placebo during the maintenance treatment. For other cohorts, the safety data will be summarized without treatment comparison.

The Fisher exact test will be used to perform the between-treatment group comparisons for AEs, discontinuations, and other categorical safety data. The change from baseline in continuous vital signs, physical characteristics, and other continuous safety variables, including laboratory variables, will be summarized by visit and treatment. The change from baseline to last observation value will be analyzed with the ANOVA model with baseline as a covariate. The last non-missing observation in the treatment period will be used as the last observation.

Shift tables for categorical safety analyses (for example, “high” or “low” laboratory results) will also be produced.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

The PK of mirikizumab will be characterized using graphical evaluations and mixed-effect (population PK) modeling approaches. Various structural and error models will be evaluated

during development of the mixed-effect model. Intrinsic factors (such as, age, body weight, gender, ADAs, etc.) and extrinsic factors (such as, co-medications) will be investigated to assess their influence on model parameters. Model evaluation will include a visual predictive check. Estimates of PK model parameters and covariate effects and the corresponding 90% CIs will be reported.

Analyses of exposure-response relationships will be conducted using both exploratory graphical approaches and model based approaches. Exploratory graphical analysis approaches may consist of graphs showing the percentage of patients who achieve clinical response, clinical remission, and endoscopic remission at different percentiles (for example, quartiles) of exposure of mirikizumab at Week 40. Measures of exposure may include population PK estimated average concentrations (C_{avg}) between Week 0 and Week 40, or estimated or observed trough concentrations at Week 40. Model based analyses will utilize population exposure-response logistic regression models, where maximum effect (E_{max}) or other model structures may be used to relate exposure to the probability of achieving clinical response, clinical remission, and endoscopic remission. These models may be used to evaluate patient factors that may impact the relationship between exposure and the probability of achieving the endpoint. Longitudinal exposure-response models for SF and RB subscores may be developed, which relate the time course and magnitude of mirikizumab exposure to the time course of these subscores.

Additional analyses may be conducted if they are deemed appropriate. Data from this study may be combined with other study data, if appropriate. Further details on PK and PK/PD analyses will be provided in the PK/PD analysis plan.

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, may be assessed.

10.3.7. Other Analyses

10.3.7.1. Subgroup Analyses

Subgroup analyses will be conducted for the primary endpoint and selected major secondary endpoints. Subgroups to be evaluated will include sex, age category, body weight, race, geographic region, baseline disease severity, duration of disease, previous biologic-failed status (yes or no), corticosteroid use (yes or no), UC concomitant therapy use (corticosteroid, immunomodulators), induction remission status (yes or no) for endpoints among induction responders. The treatment-by-subgroup interaction will be tested at the significance level

of 0.10. If any treatment group within the subgroup is less than 10% of the total mITT population for the main cohort, only summaries of the efficacy data will be provided (that is, no inferential testing will be done).

Detailed subgroup analysis 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 the 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 be detailed in the DMC charter for the UC adult program.

A primary database lock is planned after all patients complete the Week 40 visit or the ETV. The analysis based on data from the primary database lock will be conducted by the sponsor or a designee and no further multiplicity adjustment will be implemented. The final database lock will occur after all patients complete the entire study, including safety follow-up.

The DMC is authorized to evaluate unblinded interim efficacy and safety analyses during the periodic safety review. The DMC will make recommendation to the Lilly Research Laboratories Senior Management Designee, who may order the immediate implementation of the DMC recommendation, or may convene an internal review committee (IRC), which is independent from the study team, to review the recommendation according to standard Lilly policy. Study sites will receive information about interim results ONLY if they need to know for the safety of their patients.

In addition to DMC, SAC, and potential IRC, a limited number of pre-identified individuals may gain access to the limited unblinded data, as specified in the unblinding plan, prior to the interim or final database lock, in order to initiate the final population PK/PD model development processes for interim or final analyses. Information that may unblind the study during the analyses will not be shared to the study sites or the blinded study team until the study has been unblinded. Unblinding details will be specified in the unblinding plan section of the SAP or a separate unblinding plan document.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ADA	Anti-drug antibody
ADR	adverse drug reactions
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 events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
anti-HBc	anti-hepatitis B core antibody
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.
CI	confidence interval
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.
CMH	Cochran-Mantel-Haenszel
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.
CRP	C-reactive protein
CSR	clinical study report

C-SSRS	Columbia-Suicide Severity Rating Scale
DALM	dysplasia-associated lesion or mass
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
eCRF	electronic case report form
EIM	extraintestinal manifestations
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.
EQ-5D 5L	European Quality of Life 5-Dimension 5 Level
ERB	ethical review board
ES	endoscopic subscore(s)
ETV	early termination visit
EUDRA	European Union Drug Regulatory Authorities
FSH	follicle-stimulating hormone
FWER	family-wise type I error rate
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)
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
IB	Investigator's Brochure
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	informed consent form

ICH	International Council for Harmonisation
IgG4	immunoglobulin G4
IL	interleukin
IRC	internal review committee
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.
IWRS	interactive web-response system
LOR	Loss of Response
LS	least squares
LTBI	latent tuberculosis infection
mITT	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 of repeated measures
MMS	modified Mayo Score
MOS	margin of safety
NOAEL	no-observed-adverse-effect level
NRI	nonresponder imputation
NRS	numeric rating scale
PASI	Psoriasis Area and Severity Index
PD	pharmacodynamic(s)

PGA	Physician's Global Assessment
PGRC	Patient's Global Rating of Change
PGRS	Patient's Global Rating of Severity
PK	pharmacokinetic(s)
PRO	patient-reported outcomes
Q4W	every 4 weeks
QIDS-SR16	Quick Inventory of Depressive Symptomatology —Self-Report (16 Items)
RB	rectal bleeding
SAE	serious adverse event
SAC	statistical analysis center
SAP	statistical analysis plan
SC	subcutaneous
SF	stool frequency
SF-36	Medical Outcomes Study 36-Item Short Form Health Survey
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TBL	total bilirubin level
TE-ADA	treatment-emergent antidrug antibody
TEAE	treatment-emergent adverse event
UC	ulcerative colitis
UCEIS	Ulcerative Colitis Endoscopic Index of Severity
ULN	upper limit of normal
UV	unscheduled visit
WPAI:UC	Work Productivity and Activity Impairment Questionnaire Ulcerative Colitis

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 (ALP)
Lymphocytes	Alanine aminotransferase (ALT)
Monocytes	Aspartate aminotransferase (AST)
Eosinophils	Gamma-Glutamyl Transferase (GGT)
Basophils	Blood urea nitrogen (BUN)
Platelets	Creatinine
	Uric acid
	Calcium
	Glucose
	Albumin
	Cholesterol (total)
	Triglycerides
	Lipid Panel (fasting)[c]
	HDL cholesterol
	LDL cholesterol
	Creatine kinase (CK)
	Other Tests[a]
	Hepatitis B DNA PCR (if indicated)[b,d]
	Pregnancy test (urine[e])
	FSH[b,e]
	CCI [redacted]
	Anti-mirikizumab antibodies (immunogenicity)
	Serum mirikizumab concentration (PK)
	C-reactive protein, high-sensitivity
	Clostridium difficile[f,g] and Stool Culture[g]
	Fecal calprotectin
	Exploratory cytokines
	Tryptase[h]
	Complement (C3/C4)[h]
	Cytokine panel[h]

Footnotes on next page.

Abbreviations: ADA = anti-drug antibody; anti-HBc+ = positive anti-hepatitis B core antibody; DNA = deoxyribonucleic acid; FSH = follicle-stimulating hormone; HBsAg- = negative hepatitis B surface antigen; HBV = hepatitis B virus; HDL = high density lipoprotein; LDL = low density lipoprotein PCR = polymerase chain reaction; PK = pharmacokinetic; RBC = red blood cell; RNA = ribonucleic acid; SC = subcutaneous; 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] For the fasting lipid profile, patients should not eat or drink anything except water for 12 hours prior to test.

[d] Hepatitis B PCR testing will be performed in patients known from induction study to be HBsAg-, anti-HBc+, and in whom HBV DNA was not detected.

[e] Urine pregnancy test will be evaluated locally. 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 [4b].

[f] To be performed only for patients with secondary loss of response after at least 3 maintenance SC doses to determine eligibility for rescue dosing.

[g] Can be done locally by investigator as needed

[h] Performed only in the event of systemic allergic/hypersensitivity events, along with ADA and PK.

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.
- Answering 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's 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 clinical study report (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 CSR coordinating investigator will be selected by the study team. 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 electronic case report forms (eCRFs), and study procedures.

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

An eCRF system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided eCRF system. The eCRF data will be encoded and stored in a clinical trial database.

Electronic clinical outcome assessments (eCOA) measures (questionnaires, scales, self-reported diary data, etc.) will be collected by the patients and site personnel at the time that the information is obtained. In these instances, where there is no prior written or electronic source data at the site, the eCOA data record will serve as the source. The eCOA data will be stored at a third party site. Investigator sites will have continuous access to the source documents during the study and will receive an archival copy at the end of the study for retention. Any data for which the eCOA instrument record will serve to collect source data will be identified and documented by each site in that site's study file.

Data managed by a central vendor, such as laboratory test data or endoscopy 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-AMBG (AMBG) 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	**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	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 = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cell; WBC = white blood cell.

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

Appendix 5. 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 6. Mayo Scoring System for the Assessment of Ulcerative Colitis Activity

Stool Frequency (SF) Subscore	Score
Normal number of stools for subject	0
1 to 2 stools more than normal	1
3 to 4 stools more than normal	2
5 or more stools than normal	3
Rectal Bleeding (RB) 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 (ES)	**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 (PGA)	**Score**
Normal	0
Mild disease	1
Moderate disease	2
Severe disease	3
Mayo Score = Stool Frequency (SF) + Rectal Bleeding (RB)+ Endoscopic Subscore (ES) + Physician's Global Assessment (PGA)	

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 ES of 1. Consistent with current clinical practice and regulatory guidance, this study excludes friability from the definition of an ES of 1.

Stool frequency reports the number of stools in a 24-hour period, relative to the normal number of stools for that patient. The reference "normal" stool frequency for that patient will be recorded electronically at the screening visit in Study AMAN. The Normal SF refers to when the patient was in remission or, if the patient has never achieved remission, the reported SF before initial onset of signs and symptoms of ulcerative colitis. Remission refers to a period of time since being diagnosed with ulcerative colitis when the patient is not experiencing any signs or symptoms relating to ulcerative colitis. This period of time may last a few weeks or a few months or may even last several years. The patient will record this electronically as source data in the tablet device at the screening study visit in Study AMAN.

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

Appendix 7. Patient-Reported Outcome Instruments

Daily Diary Review
Rectal Bleeding[a]
Stool Frequency[a]
Urgency NRS[a]
Abdominal Pain NRS[a]
PGRS[a]
Nocturnal Stool[b]
Fatigue NRS[b]
Bristol Stool Scale[b]

Abbreviations: NRS = numeric rating scale; PGRS = Patient's Global Rating of Severity

[a] Question will be administered daily through Week 40 or early termination visit.

[b] Question will be administered at Visits 2 through 10 (Weeks 4 through 36), and daily between Visit 10 and Visit 11.

The following are descriptions of additional patient-reported outcome instruments used in Study AMBG using Patient eDiary or tablet device:

- **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 be provided with an electronic diary tool during screening to record information daily pertaining to their severity of urgency.
- **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 (worst possible pain). Patients will be provided with an electronic diary tool during screening to record information daily pertaining to their worst abdominal pain experience.
- **Patient's Global Rating of Severity (PGRS):** The PGRS is a 1-item patient-rated questionnaire designed to assess the patients' rating of their disease symptom severity over the past 24 hours. Responses are graded on a 6-point scale in which a score of 1 indicates that the patient has no symptoms (that is, "none") and a score of 6 indicates that the patient's symptom(s) are "very severe." Patients will be provided with an electronic diary tool during screening to record information daily pertaining to their disease experience.
- **Nocturnal Stool**: The Nocturnal Stool instrument is a single item asking the patient to record the number of stools they had during the night (or day, for shift workers), causing them to waken from sleep. Patients will be provided with an electronic diary tool during screening to record information daily pertaining to their nocturnal stool count during appropriate time periods. Patients will also record their response to the nocturnal stool count electronically as source data in the tablet device at appropriate visits.
- **Fatigue NRS**: The Fatigue NRS is a single item that measures the "worst fatigue (weariness, tiredness) in the past 24 hours" using an 11-point NRS ranging from 0 (no fatigue) to 10 (fatigue as bad as you can imagine). Patients will be provided with an electronic diary tool during screening to record information daily pertaining to their worst fatigue experience during appropriate time periods. Patients will also record their

response to the Fatigue NRS electronically as source data in the tablet device at appropriate visits.

- **Bristol Stool Scale:** The Bristol Stool Scale is a single item that provides a pictorial and verbal description of stool consistency and form, ranging from Type 1 (hard lumps) to Type 7 (watery/liquid). Patients will be provided with an electronic diary tool during screening to record information daily pertaining to their stool during appropriate time periods. Patients will also record their response to the Bristol Stool Scale electronically as source data in the tablet device at appropriate visits.
- **Patient's Global Rating of Change (PGRC):** The PGRC scale is a patient-rated instrument designed to assess the patients' rating of change in their symptom(s). Responses are graded on a 7-point Likert scale, in which a score of 1 indicates that the subject's symptom(s) is "very much better," a score of 4 indicates that the subject's symptom(s) has experienced "no change," and a score of 7 indicates that the subject's symptom(s) is "very much worse." Patients will record their response to the PGRC electronically as source data in the tablet device at appropriate visits.
- **Inflammatory Bowel Disease Questionnaire (IBDQ)**: 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 et al.1989; Irvine et al. 1994, 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 electronically as source data in the tablet device at appropriate visits.
- **European Quality of Life 5-Dimension 5 Level (EQ-5D 5L):** A widely used, generic questionnaire that assesses health status (Herdman et al. 2011; EuroQol Group 2015). The questionnaire consists of 2 parts. The first part assesses 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that have 5 possible levels of response (no problems, slight problems, moderate problems, severe problems, extreme problems). This part of the EQ-5D can be used to generate a health state index score, which is often used to compute quality-adjusted life years (QALY) for utilization in health economic analyses. The health state index score is calculated based on the responses to the 5 dimensions, providing a single value on a scale from less than 0 (where zero is a health state equivalent to death; negative values are valued as worse than dead) to 1 (perfect health), with higher scores indicating better health utility (EuroQol Group [WWW]). The second part of the questionnaire consists of a visual analog scale (VAS) on which the patient rates their perceived health state from 0 (the worst health you can imagine) to 100 (the best health you can imagine). Patients will record their responses to the EQ-5D 5L electronically as source data in the tablet device at appropriate visits.
- **Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) Version 2:** A patient-reported, generic, health-related quality of life instrument originally published in 1992, with some item wordings and response options revised in 2000 (Ware and Sherbourne 1992; Ware 2000). It consists of 36 questions measuring 8 health domains: physical functioning, bodily pain, role limitations due to physical problems, role

limitations due to emotional problems, general health perceptions, mental health, social function, and vitality. The patient's responses are solicited using Likert scales that vary in length, with 3 – 6 response options per item. The SF-36 can be scored into the 8 health domains named above and 2 overall summary scores: physical component summary (PCS) and mental component summary (MCS) scores. The domain and summary scores range from 0 to 100; higher scores indicate better levels of function and/or better health. The SF-36 version 2 (standard version) will be used, which utilizes the recall period of "the past 4 weeks" (Ware and Sherbourne 1992; Maruish 2011). Patients will record their responses to the SF-36 Version 2 electronically as source data in the tablet device at appropriate visits.

- **Work Productivity and Activity Impairment Questionnaire: Ulcerative Colitis (WPAI:UC):** A patient-reported instrument developed to measure the impact on work productivity and regular activities attributable to a specific health problem (WPAI:UC). It contains 6 items that measure: 1) employment status, 2) hours missed from work due to the specific health problem, 3) hours missed from work for other reasons, 4) hours actually worked, 5) degree health affected productivity while working, and 6) degree health affected productivity in regular unpaid activities. Four scores are calculated from the responses to these 6 items: absenteeism, presenteeism, work productivity loss, and activity impairment (Reilly Associates [WWW]). Scores are calculated as impairment percentages (Reilly et al. 1993), with higher numbers indicating greater impairment and less productivity, that is, worse outcomes (Reilly Associates [WWW]). Patients will record their responses to the WPAI:UC electronically as source data in the tablet device at appropriate visits.

Appendix 8. 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
Rectally administered investigational preparations for UC such as arsenic preparations	Prohibited throughout treatment period
Intravenous corticosteroids for UC	A course of IV corticosteroids for UC is prohibited
Systemic corticosteroids for non-UC indications (oral or IV)	Patients requiring systemic corticosteroids for non-UC conditions are excluded. Exceptions include corticosteroids to treat adrenal insufficiency, premedication for IP infusion, or locally administered corticosteroids (e.g., inhaled, intranasal, intra-articular, topical) (see Appendix 10)
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 attenuated 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; IL = interleukin; IV = intravenous; JAK = Janus Kinase; TNF = tumor necrosis factor; UC = ulcerative colitis.

Appendix 9. Permitted Medications with Dose Stabilization

Drug Class	Comments
Oral 5-ASAs (for example, mesalamine, balsalazide, olsalazide) and sulfasalazine for UC	May continue during study with stable doses encouraged
Oral corticosteroids for UC (prednisone ≤20 mg/day or equivalent, budesonide MMX 9 mg/day, or beclomethasone dipropionate [gastro-resistant prolonged-release tablet] 5 mg/day)	Responder patients who are receiving oral corticosteroids at the start of Study AMBG will start corticosteroid taper at the beginning of the study. Clinical nonresponders who undergo extended IV induction with mirikizumab will begin corticosteroid tapering if symptomatic response or symptomatic improvement based on investigator discretion is achieved at any time after starting extended induction (see *Corticosteroid Taper* in Section 7.7).
Corticosteroids for non-UC indications: corticosteroids to treat adrenal insufficiency, as premedication for IP infusion, or locally administered corticosteroids (e.g. inhaled, intranasal, intra-articular, topical).	May continue corticosteroids to treat adrenal insufficiency or locally administered corticosteroids during study with stable dose encouraged. Single doses of oral or IV corticosteroids as premedication to IP administration are allowed in patients with prior IP or other previous biologic injection reactions.
Immunomodulators (for example, AZA, 6-MP, or methrotrexate	Prescribed dose will remain stable throughout the 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-aminosalicyclic acid; 6-MP = 6-mercaptopurine; AZA = azathioprine; IV = intravenous; IP = investigational product; UC = ulcerative colitis.

Appendix 10. 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 11. 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.

Appendix 12. Protocol Amendment I6T-MC-AMBG(a) Summary A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Arm, Placebo-Controlled Maintenance Study of Mirikizumab in Patients with Moderately to Severely Active Ulcerative Colitis LUCENT 2

Overview

Protocol I6T-MC-AMBG, A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Arm, Placebo-Controlled Maintenance Study of Mirikizumab in Patients with Moderately to Severely Active Ulcerative Colitis LUCENT 2 has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

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

Amendment Summary for Protocol I6T-MC-AMBG Amendment (a)

Section # and Name	Description of Change	Brief Rationale
Section 1 Synopsis, Objective(s), Endpoints	Added/modified/removed Primary, Major secondary and Other secondary objectives/endpoints	Match Section 4 Objectives and Endpoints
Section 1 Synopsis, Statistical Analysis	Clarified primary endpoint statistics	Match Section 10 Statistical Considerations
Section 2 Table AMBG.2.1 Schedule of Activities, Induction Responders, Informed consent	Added that patients may consent between the start of V5 of Study AMAN	Clarification of consent window
Section 2 Table AMBG.2.1 Schedule of Activities, Induction Responders, FSH	Added that FSH is optional in women to confirm nonchild-bearing potential	Clarification of the patient for whom FSH should be performed
Section 2 Table AMBG.2.1 Schedule of Activities, Induction Responders, PK Assessment and ADA Assessment	Clarified that patients with potential hypersensitivity or infusion-related event should have sample taken as soon as possible after event occurs and at 4 and 12 to 16 weeks after the event.	Clarification to be consistent with management of hypersensitivity and infusion related event section
Section 2 Table AMBG.2.1 Schedule of Activities, Induction Responders, C. Difficile Testing and Fecal Calprotectin and Exploratory Fecal Biomarkers	Expanded the timeframe for C. Difficile, Fecal Calprotectin and Exploratory Fecal Biomarkers testing to as early as V3 during the loss of response assessment	Since loss of response assessment can start as early as V3, the window for C. Difficile, Fecal Calprotectin and Fecal Biomarkers were expanded to facilitate this assessment
Section 2 Table AMBG.2.1 Schedule of Activities, Induction	Clarified that loss of response has to be confirmed with endoscopy and	Clarification of Table AMBG.2.2 Schedule of Activities comment for

Section # and Name	Description of Change	Brief Rationale
Responders, Endoscopy with biopsies	added clarification to refer to Section 9.1.1.3 of the protocol for specification of what endoscopic procedure can be performed when	Endoscopy with biopsies
Section 2 Table AMBG.2.1 Schedule of Activities, Induction Responders, IBDQ, EQ-5D 5L, and PGRC	Added that health outcome assessments are to be performed for patients who have LOR confirmed by endoscopy before rescue dosing instead of for those with secondary LOR at the second of 2 LOR assessments	Clarification of when health outcome assessments for LOR should be performed
Section 2 Table AMBG.2.1 Schedule of Activities, Induction Responders, Abbreviations	Added abbreviation: DNA = deoxyribonucleic acid	Clarification of acronym in Table
Section 2 Table AMBG.2.1 Schedule of Activities, Induction Responders, Footnote section	Clarified the options that patients have after completing the last visit in AMBG or the ETV in AMBG	Clarification provided since Study AMBG does not have an open label extension period but patients may qualify for the long term extension Study I6T-MC-AMAP
Section 2 Table AMBG.2.1 Schedule of Activities, Induction Responders, footnote a	Changed that V1 (Week 0) should occur no more than 14 days instead of 10 days from the start of the Visit 5/Week 12 visit of Study AMAN	Changes make the transition from AMAN to AMBG operationally acceptable while enabling AMAN Week 12 endoscopy to represent baseline status of disease severity in AMBG
Section 2 Table AMBG.2.2 Schedule of Activities, Induction Non-responders	Footnote letters reordered	Editorial change
Section 2 Table AMBG.2.2 Schedule of Activities	Updated window for V4	Allow more time for V4
Section 2 Table AMBG.2.2 Schedule of Activities, Induction Non-responders, Informed consent	Added that patients may consent between the start of V5 of AMAN and before any procedures at V1/Week 0 are performed instead of between the time of induction consent and before any procedures at V1/Week 0 are performed	Clarification of consent window
Section 2 Table AMBG.2.2 Schedule of Activities, Induction Non-responders, FSH	Added that FSH is optional in women to confirm nonchild-bearing potential	Clarification of the patient for whom FSH should be performed
Section 2 Table AMBG.2.2 Schedule of Activities, Induction Non-responders, PK and ADA	Clarified that patients with potential hypersensitivity or infusion-related event should have sample taken as soon as possible after event occurs and at 4 and 12 to 16 weeks after the event	Clarification to be consistent with management of hypersensitivity and infusion related event section

Section # and Name	Description of Change	Brief Rationale
Section 2 Table AMBG.2.2 Schedule of Activities, Induction Non-responders, *C. difficile* testing	Clarified that V1 C. difficile testing does not need to be completed before the patient can start study drug therapy	Clarification of *C. difficile* testing procedure at V1
Section 2 Table AMBG.2.2 Schedule of Activities, Induction Non-responders, Endoscopy with biopsies	Added clarification to refer to Section 9.1.1.3 of the protocol for specification of what procedure can be performed when	Clarification for Endoscopy with biopsies
Section 2 Table AMBG.2.2 Schedule of Activities, Induction Non- responders, Footnote section	Added "Notes" section describing when study procedures should be performed and patient options post study completion or early termination	Information added to be consistent with the induction responder path of Study AMBG
Section 2 Table AMBG.2.2 Schedule of Activities, Induction Non-responders, footnote a	Added that for patients who cannot continue beyond V4 because they did not achieve delayed clinical response, ETV activities that are performed as part of V4 do not need to be repeated. Only those ETV activities that are not part of V4 should be completed during the ETV	Clarification to minimize study procedures for patients who discontinue AMBG soon after completing V4
Section 2 Table AMBG.2.2 Schedule of Activities, Induction Non-responders, footnote b	Clarified that V1 (Week 0) should occur no more than 14 days instead of 10 days from the start of the Visit 5/Week 12 visit of Study AMAN	Changes make the transition from AMAN to AMBG operationally acceptable while enabling AMAN Week 12 endoscopy to represent baseline status of disease severity in AMBG
Section 4 Objectives and Endpoints, Table AMBG.4.1	Moved "To test the hypothesis that mirikizumab is superior to placebo in achieving clinical remission at Week 40 among patients induced into **clinical response** with mirikizumab in Study AMAN" from first Major Secondary Objective/Endpoints to Primary Objective/Endpoints	In order to align with recent external biologic clinical trials in UC, primary endpoint changed to clinical remission among responders, and clinical remission among remitters moved to a Major secondary
Section 4 Objectives and Endpoints, Table AMBG.4.1	To evaluate the efficacy of mirikizumab compared to placebo in maintaining clinical remission at Week 40 (Week 52 of continuous therapy) among patients induced into clinical remission with mirikizumab has been moved from primary to first major secondary	In order to align with recent external biologic clinical trials in UC, primary endpoint changed to clinical remission among responders, and clinical remission among remitters moved to a Major secondary.
Section 4 Objectives and Endpoints, Table AMBG.4.1	Moved "Clinical remission at Week 40 in the subgroup of patients in whom biologic agents have failed or	In order to align with recent external biologic clinical trials in UC and associated enrollment trends, this

Section # and Name	Description of Change	Brief Rationale
	caused intolerance." and definition of "clinical remission" from Major Secondary Objective/Endpoints to Other Secondary Objectives/Endpoints	objective/endpoints was moved to other secondary objective/endpoints
Section 4 Objectives and Endpoints, Table AMBG.4.1	Moved "Endoscopic remission at Week 40 in the subgroup of patients in whom biologic agents have failed or caused intolerance." and definition of "endoscopic remission" from Major Secondary Objective/Endpoints to Other Secondary Objectives/Endpoints	In order to align with recent external biologic clinical trials in UC and associated enrollment trends, this objective/endpoints was moved to other secondary objective/endpoints
Section 4 Objectives and Endpoints, Table AMBG.4.1	Added "The proportion of patients in symptomatic remission defined as being in symptomatic remission for at least 7 out of 9 visits from Week 4 to Week 36 and in symptomatic remission at Week 40 among patients in symptomatic remission at Week 12 of AMAN." and definition of "Symptomatic remission" to Major Secondary Objective/Endpoints	This endpoint (and associated objective) was added in order to assess the stability of efficacy with mirikizumab throughout the maintenance period
Section 4 Objectives and Endpoints, Table AMBG.4.1	Moved and modified "The proportion of patients with bowel movement urgency improvement at Week 40 as defined in the study SAP" to Major Secondary Objective/Endpoints	Moved and modified endpoint to assess improvement in urgency. Published literature shows that improvement in urgency is a clinically meaningful endpoint and supports urgency as one of the most bothersome symptoms experienced by patients with UC. Therefore, this endpoint has been moved from an Other Secondary endpoint to a Major secondary endpoint
Section 4 Objectives and Endpoints, Table AMBG.4.1	Deleted from Other Secondary Objective/Endpoints: The percentage of the total time (in weeks) during maintenance study treatment that patients achieve: SF = 0, or SF = 1 with a ≥1-point decrease from induction baseline, and RB subscore = 0	Other Secondary Objective/Endpoints for symptom free duration removed and replaced with new Major Secondary Objective/Endpoints of stable maintenance of symptomatic remission
Section 4 Objectives and Endpoints, Table AMBG.4.1	Removed redundant text in Other Secondary Objective/Endpoints: "…among subgroup of patients on corticosteroids at induction study baseline" from Corticosteroid-free	Editorial change

Section # and Name	Description of Change	Brief Rationale
	remission without surgery at Week 40 endpoint.	
Section 4 Objectives and Endpoints, Table AMBG.4.1	Deleted from Other Secondary Objective/Endpoints related to patient reported outcomes the reference to Urgency NRS score following change from induction baseline at Week 40	Other Secondary Objective/Endpoints for bowel movement urgency removed and replaced with new Major Secondary Objective/Endpoints bowel movement urgency improvement endpoint was added to Major secondary endpoints. This objective/endpoint now focuses on the patient reported outcome of abdominal pain only
Section 4 Objectives and Endpoints, Table AMBG.4.1	Added to Other Secondary Objective/Endpoints: The proportion of patients with a UCEIS score of ≤1 at Week 40	The UCEIS is considered to be an important endpoint assessing endoscopic disease activity and thus has been added as an other secondary endpoint. The UCEIS has been included in all endoscopy central readings from the onset of the study
Section 4 Objectives and Endpoints, Table AMBG.4.1	Added "The proportion of patients with mucosal healing at Week 40, defined as achieving both histologic remission and endoscopic remission" and their definitions to Other Secondary Objective/Endpoints	In order to align with recent UC clinical trials and FDA guidance, protocol definition of mucosal healing was updated to include histologic and endoscopic healing. This is the same endpoint – note that histologic remission is already and has always been a secondary endpoint. The location of the histologic remission/response definition has been clarified throughout the protocol amendment
Section 4 Objectives and Endpoints, Table AMBG.4.1	Other Secondary Objectives/Endpoints added	Fatigue is a common symptom for patients with active disease and published literature supports fatigue as an important symptom experienced by patients with UC. Therefore, this endpoint has been added to Other Secondary Endpoint
Section 4 Objectives and Endpoints, Table AMBG.4.1	Abbreviations have been added under the table	Editorial change
Section 5 Study Design	Added "baseline" to corticosteroid use stratification criteria	Clarified that baseline corticosteroid use (yes or no) will be used to stratify patients
Section 5 Study Design	Clarified definition of "loss of response"	Clarification that the loss of response assessment can start as early as Week 8/V3 but the endoscopic confirmation of loss of response cannot occur any

Section # and Name	Description of Change	Brief Rationale
		earlier than Week 12/V4
Section 6.0 Study population	Changed the duration for the maximum window from the start of AMAN Week 12/V5 to the start of Week 0/V1 from 10 to 14 days	Changes make the transition from AMAN to AMBG operationally acceptable while enabling AMAN Week 12 endoscopy to represent baseline status of disease severity in AMBG
Section 6.1 Inclusion Criteria, Patient Characteristics	Added text to clarify that patients require a Visit 5/Week 12 of Study AMAN MMS, not just an endoscopy	Clarification that not only is an endoscopy required but a MMS is needed in order to enroll in AMBG from AMAN
6.2 Exclusion Criteria, General Exclusion Criteria	The term “malignancy” was added to Exclusion Criterion [17]	Added to be consistent with exclusion criteria in induction study AMAN
Section 6.4 Screen Failures	Changed the duration for the maximum window from the start of AMAN Week 12/V5 to the start of Week 0/V1 from 10 to 14 days	Changes make the transition from AMAN to AMBG operationally acceptable while enabling AMAN Week 12 endoscopy to represent baseline status of disease severity in AMBG
Section 7.1 Treatments Administered, Study Drug Administration	Added that intravenous infusion of mirikizumab (not placebo) will occur over at least 30 minutes	Clarification that placebo will not be administered IV
Section 7.2 Method of Treatment Assignment	Added “baseline” to corticosteroid use stratification criteria	Clarified that baseline corticosteroid use (yes or no) will be used to stratify patients
Section 7.7 Concomitant Therapy, Corticosteroid Taper	Added “or beclomethasone dipropionate (gastro-resistant prolonged-release tablet)” including tapering schedule	Based on wide use of this corticosteroid in certain countries, tapering instructions were added

Section # and Name	Description of Change	Brief Rationale
Section 7.8.3.2. Management of Hypersensitivity, Infusion Related Events, Infusion Site Reactions and Injection Site Reactions	Added "These samples will also be used for tryptase, complement (C3/C4), and cytokine panel assays."	Additional assessments added to better understand the possible etiology if a drug hypersensitivity event is observed, including markers of basophil/mast cell activation (i.e. tryptase), immune complex formation (i.e. C3/C4 levels) and cytokine release (i.e., cytokine panel). No additional blood is required for this sample collection.
Section 7.8.3.2. Management of Hypersensitivity, Infusion Related Events, Infusion Site Reactions and Injection Site Reactions	Under "Other Infusion-Related Events and Infusion Site Reactions": added the word "other" in sentence describing reaction consisting of headache, rigors and/or temperature >38°C	Clarification of reaction consisting of headache, rigors and/or temperature >38°C
Section 8.1.1. Permanent Discontinuation from Study Treatment, Safety Criteria for Study Drug Discontinuation	Added to safety criteria for study drug discontinuation: "proctocolectomy or partial colectomy".	Clarification of safety criteria for drug discontinuation
Section 8.1.1. Permanent Discontinuation from Study Treatment, Safety Criteria for Study Drug Discontinuation	Added to safety criteria for study drug discontinuation that the patient has an AE or SAE which, in the opinion of the investigator or sponsor, would preclude the participant from continuing to receive study drug.	Study drug discontinuation related to AEs or SAEs is now consistent with wording in AMAN
Section 8.1.1. Permanent Discontinuation from Study Treatment, Safety Criteria for Study Drug Discontinuation	Mirikizumab changed to "study drug"	Clarification since study drug may be blinded
Section 9.1 Efficacy Assessments: Table AMBG.9.1 Endpoint Definitions in Study AMBG	Added endpoint, definition, and footnote for corticosteroid-free remission without surgery at Week 40	Defined corticosteroid-free remission without surgery at Week 40
Section 9.1 Efficacy Assessments: Table AMBG.9.1 Endpoint Definitions in Study AMBG	Term mucosal healing deleted from histologic remission endpoint definition	Clarification of term "histologic remission"
Section 9.1 Efficacy Assessments: Table AMBG.9.1 Endpoint Definitions in Study AMBG	Added mucosal healing endpoint definition	Defined mucosal healing endpoint
Section 9.1 Efficacy Assessments: Table AMBG.9.1 Endpoint Definitions in Study AMBG	Added stable maintenance of symptomatic remission	This endpoint was added in order to assess the stability of efficacy with mirikizumab throughout the maintenance period
Section 9.1 Efficacy Assessments:	Added bowel movement urgency	Now included as a major secondary

Section # and Name	Description of Change	Brief Rationale
Table AMBG.9.1 Endpoint Definitions in Study AMBG	improvement	endpoint because of unmet patient needs and the symptom being one of the most meaningful and important symptoms from patient perspective
Section 9.1 Efficacy Assessments: Table AMBG.9.1 Endpoint Definitions in Study AMBG	Added footnote: " [a]Among patients induced into clinical response with mirikizumab during the induction study and who were receiving corticosteroids at induction baseline."	Added footnote clarifying the applicable patient population for this endpoint
Section 9.1 Efficacy Assessments: Table AMBG.9.1 Endpoint Definitions in Study AMBG	Added footnote: "[b]Among patients in symptomatic remission at Week 12 of AMAN"	Added footnote clarifying the applicable patient population for this endpoint
Section 9.1.1.1. Primary Endpoint	Terminology changed from "durable clinical remission" to "clinical remission"; "remission" changed to "response" with mirikizumab induction treatment.	Change made due to change in primary endpoint of the study
9.1.1.2. Mayo Score	Deleted from SF Subscore and expanded to its own sub-section: 'Normal SF for that patient is based on reported SF when the patient was in remission or reported SF before initial onset of signs and symptoms of UC."	Sentence moved to new description of Normal SF and to provide additional detail regarding the definition
Section 9.1.1.3. Endoscopy	Wording added to clarify when colonoscopy can be performed instead of flexible sigmoidoscopy in the judgement of the investigator and after discussion with the medical monitor as appropriate	Clarification of importance to discuss with medical monitor the need for colonoscopy vs. flexible sigmoidoscopy to assure appropriate consideration for patient safety
Section 9.1.1.3. Endoscopy	Added that allowances may be made for not performing ETV endoscopy if ETV occurs soon after a recent study required endoscopy, based on approval by the medical monitor	Change made to assure patient safety by not performing unnecessary repeat endoscopies soon after a recent endoscopy procedure
9.1.2.1. Major Secondary Endpoints	Multiple changes made in major secondary endpoints to match Section 1 and Section 4	To align with Section 1 Synopsis and Section 4 Objectives and Endpoints.
9.1.2.1.2. Patient Reported Outcome Instruments	Description of Urgency NRS added under major secondary endpoints section	Moved definition of Urgency NRS to major secondary endpoints to be consistent with changes in objective and endpoint sections (Section 1 and Section 4)
9.1.2.2.1. Physician Reported Instrument	Added description of UCEIS	Due to the addition of the objective/endpoint, added description

Section # and Name	Description of Change	Brief Rationale
		of the instrument
9.1.2.2.2. PRO Instruments Used to Assess Secondary Endpoints	Urgency NRS deleted from PRO instruments used to assess other secondary endpoints; Fatigue NRS added	Moved definition of Urgency NRS out of other secondary endpoints and added Fatigue NRS to be consistent with changes in objectives
9.1.3.3. PRO Instruments Used to Assess Exploratory Endpoints	Collection conditions for the following added: • Nocturnal Stool • Patient's Global Rating of Severity • Bristol Stool Scale Fatigue NRS deleted	Clarification of data collection conditions
Section 9.4.4. Immunogenicity Assessments	Added that tryptase, complement (C3/C4), and cytokine panel samples will be collected in the event of a drug hypersensitivity event, other infusion related events and infusion site reactions	Additional assessments added to better understand the possible etiology if a drug hypersensitivity event is observed, including markers of basophil/mast cell activation (i.e. tryptase), immune complex formation (i.e. C3/C4 levels) and cytokine release (i.e., cytokine panel). No additional blood is required for this sample collection.
Section 9.4.5.2. Tuberculosis, Diagnosis of LTBI during Study	For the treatment of LTBI, added that CDC guidelines are to be used for the USA and the WHO guidelines are to be followed for countries outside of the USA	Clarification of guidance for LTBI treatment
Section 9.5 Pharmacokinetics	CCI [redacted]	CCI [redacted]
Section 10.1 Sample Size Determination	Primary endpoint statistical changes	Match with Section 1 Synopsis and Section 4 Objectives and Endpoints. Due to changes in primary and major secondary endpoints, sample size has been recalculated.
10.2. Populations for Analyses, Table AMBG.10.1 Analysis Populations in Study AMBG	Intent-to-treat (ITT) Population changed from enrolled to randomized/assigned	Clarification of the definition of "enrolled" in the ITT population
10.2. Populations for Analyses, Table AMBG.10.1 Analysis Populations in Study AMBG	Modified Intent-to-treat (mITT) Population changed to "All randomized/assigned patients who received at least 1 dose of study treatment, regardless of whether	Definition clarified of the mITT population

Section # and Name	Description of Change	Brief Rationale
	correct treatment was administered or whether protocol was followed."	
10.3.1. General Statistical Considerations	Changed that induced responders instead of induced remitters were among those assessed. Induction remission status of yes or no was added. "Baseline" was added to corticosteroid use.	Change made due to change in primary endpoint of the study. Clarified that baseline corticosteroid use (yes or no) will be used to stratify patients
10.3.1.1. Missing Data Imputation	Deleted "In addition, the patients who require UC surgery, increase UC medication dose from baseline, or initiate new UC medications will be considered as nonresponders" from the description of nonresponder imputation.	Modifications made to align with other recent UC clinical trials and to clarify that patients who require UC surgery, require an increase in UC medication dose from baseline, or require treatment with new UC medications should be discontinued from the trial as described in Section 8.1.1 of the protocol. Therefore, imputing such patients as non-responders will be performed because the data will be missing
10.3.2.3 Concomitant Therapy	Changed description of how concomitant therapy will be presented in frequency tables	Clarification
10.3.3.1. Primary Analyses	Primary analysis was changed from "durable clinical remission" to "clinical remission" and "remitters" to "responders."	Change made due to change in primary endpoint of the study.
10.3.3.1. Primary Analyses	Nonremitter description changed	Change made due to clarification of NRI
10.3.7.1 Subgroup Analyses	Removed "The major subgroup analysis is for the primary and major secondary endpoints for biologic-failed patients described in Section 9.1.2.1. Multiplicity adjustment described in Section 10.3.1.2. will be used to control type I error."	Change made due to changes in the major secondary endpoints
Section 11. References	References added	Editorial change
Appendix 1. Abbreviations and Definitions	Term added	Editorial Change
Appendix 2. Clinical Laboratory Tests	Other tests along with their associated footnote added	Clarification of procedures. Updates made to align with Section 7.8.3.2 of the protocol
Appendix 3.1.7. Final Report Signature	Deleted that the investigator with most enrolled patients will be selected by the study team to act as the CSR coordinating investigator	This change reflects that the selection of CSR coordinating investigator is not dependent on number of patients enrolled
Appendix 6. Mayo Scoring System	Note added to table for stool	Definition of normal stool frequency

Section # and Name	Description of Change	Brief Rationale
for the Assessment of Ulcerative Colitis Activity	frequency	when in remission from UC to align with Section 9.1.1.2 of the protocol
Appendix 7. Patient Reported Outcome Instruments	Replaced language in definition of Abdominal Pain Numeric Rating Scale (NRS) and Fatigue NRS	Clarification of definitions of ranges
Appendix 8. Prohibited Medications	Added rectally administered investigational preparations for UC and restrictions	Arsenic and other therapies were added because it was recognized that there are other treatments for UC in certain countries that need to be considered as prohibited medications
Appendix 8. Prohibited Medications	Added "for UC" to Intravenous corticosteroids category	Clarification of restrictions for IV corticosteroid use for UC vs. non UC indication
Appendix 8. Prohibited Medications	Added that patients requiring systemic corticosteroids for non-UC indications are "excluded". Added "Exceptions include: premedication for IP infusion, or locally".	Added allowance for single limited dose for study drug administration premedication. This would be a single limited dose that would not be expected to affect efficacy. Other minor editorial changes were made.
Appendix 9. Permitted Medications with Dose Stabilization	Added to Drug Class: oral 5-ASAs "and sulfasalazine for UC"	Clarification of drug class
Appendix 9. Permitted Medications with Dose Stabilization	Added to Drug Class: oral corticosteroids "for UC" indications clarification	Clarified that oral corticosteroids are allowed for UC indication
Appendix 9. Permitted Medications with Dose Stabilization	Added beclomethasone dipropionate [gastro-resistant prolonged-release tablet] 5 mg/day	Based on wide use of this corticosteroid in certain countries, this medication was added as permitted medication during the study along with prednisone or equivalent or budesonide MMX
Appendix 9. Permitted Medications with Dose Stabilization	Added to Drug Class: "corticosteroids for non-UC indications" that are allowed	Added clarification to reinforce the exception to the prohibited concomitant medications

Revised Protocol Sections

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

The numbering system used for inclusion and exclusion criteria provides a unique number for each criterion and allows for efficiency in data collection.

In case an amendment to the protocol adds a criterion, that criterion will receive the next available number, regardless of whether it is an inclusion or exclusion criterion.

1. Synopsis

Objective(s)/Endpoints:

Objectives	Endpoints
Primary[a]	
• To test the hypothesis that mirikizumab is superior to placebo in achieving ~~maintaining~~ clinical remission at Week 40 (Week 52 of continuous therapy) among patients induced into **clinical response** ~~**remission**~~ with mirikizumab in Study AMAN	• The proportion of patients ~~who were~~ in clinical remission at Week ~~12 in AMAN and are in clinical remission at Week~~ 40, ~~that is, with durable clinical remission,~~ defined as: o Stool frequency (SF) subscore = 0 or SF = 1 with a ≥1-point decrease from induction baseline, and o Rectal bleeding (RB) subscore = 0, and o Endoscopic subscore (ES) = 0 or 1 (excluding friability)
Major Secondary[a,b]	
• To evaluate the efficacy of mirikizumab compared to placebo in ~~achieving~~ maintaining clinical remission at Week 40 (Week 52 of continuous therapy) among patients induced into **clinical remission** ~~**response**~~ with mirikizumab	• The proportion of patients who were in clinical remission at Week 40 among patients in clinical remission at Week 12 in Study AMAN (i.e., durable clinical remission). Clinical remission is defined as: o SF subscore = 0 or SF = 1 with a ≥1-point decrease from induction baseline, and o RB subscore = 0, and o ES subscore = 0 or 1 (excluding friability)
~~• To evaluate the efficacy of mirikizumab compared to placebo on endoscopic remission at Week 40 among patients induced into **clinical response** with mirikizumab~~	~~• The proportion of patients in endoscopic remission at Week 40, defined as:~~ ~~• ES = 0 or 1 (excluding friability)~~

• ~~To evaluate the efficacy of mirikizumab compared to placebo in achieving corticosteroid-free remission without surgery among patients induced into **clinical response** with mirikizumab and receiving corticosteroids at induction baseline~~	• ~~Corticosteroid-free remission without surgery at Week 40, defined as:~~ o ~~Clinical remission at Week 40, and~~ o ~~Symptomatic remission at Week 28, and~~ • ~~No corticosteroid use for ≥12 weeks prior to Week 40~~
• ~~To evaluate, in the subgroup of patients in whom biologic agents have failed or caused intolerance, clinical remission at Week 40 among patients induced into **clinical response** with mirikizumab~~	• ~~Clinical remission at Week 40 in the subgroup of patients in whom biologic agents have failed or caused intolerance. Clinical remission is defined as:~~ o ~~SF subscore = 0 or SF = 1 with a ≥1 point decrease from induction baseline, and~~ o ~~RB subscore = 0, and~~ o ~~ES = 0 or 1 (excluding friability)~~
• ~~To evaluate, in the subgroup of patients in whom biologic agents have failed or caused intolerance, endoscopic remission at Week 40 among patients induced into **clinical response** with mirikizumab~~	• ~~Endoscopic remission at Week 40 in the subgroup of patients in whom biologic agents have failed or caused intolerance. Endoscopic remission is defined as:~~ o ~~ES = 0 or 1 (excluding friability)~~
• To evaluate the efficacy of mirikizumab compared to placebo on histologic remission ~~(mucosal healing)~~ at Week 40 among patients induced into **clinical response** with mirikizumab	• Proportion of patients in histologic remission at Week 40, as defined in the ~~histopathology charter~~ SAP
• To evaluate the efficacy of mirikizumab compared to placebo on stable maintenance of symptomatic remission among patients who were induced into **clinical response** and **symptomatic remission** with mirikizumab	• The proportion of patients in symptomatic remission defined as being in symptomatic remission for at least 7 out of 9 visits from Week 4 to Week 36 and being in symptomatic remission at Week 40 among patients in symptomatic remission at Week 12 of Study AMAN. • Symptomatic remission is defined as: o SF = 0, or SF = 1 with a ≥1-point decrease from induction baseline and o RB = 0
• To evaluate the efficacy of mirikizumab compared to placebo on bowel movement urgency improvement at Week 40, among patients who: (1) had bowel urgency symptoms at induction baseline and (2) were induced into clinical response with mirikizumab	• The proportion of patients with bowel movement urgency improvement at Week 40 as defined in the study SAP.
Other Secondary	
• To evaluate the efficacy of mirikizumab compared to placebo in achieving clinical remission at Week 40 among patients induced into **clinical response** with mirikizumab, in the subgroup of patients in whom biologic agents have failed or caused intolerance~~,~~. ~~clinical remission at Week 40 among patients induced into **clinical remission** with~~	• ~~The proportion of patients who were in clinical remission at Week 12 in AMAN and are in e~~Clinical remission at Week 40 , ~~that is, with durable clinical remission,~~ in the subgroup of patients in whom biologic agents have failed or caused intolerance. Clinical remission is defined as:

~~mirikizumab~~	○ 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)
• To evaluate the efficacy of mirikizumab compared to placebo in achieving ~~on maintaining~~ endoscopic remission at Week 40 among patients induced into **clinical response** ~~**endoscopic remission**~~ with mirikizumab, in the subgroup of patients in whom biologic agents have failed or caused intolerance.	• ~~The proportion of patients in durable~~ ~~e~~Endoscopic remission at Week 40 in the subgroup of patients in whom biologic agents have failed or caused intolerance. Endoscopic remission is defined as: ES = 0 or 1 (excluding friability)
• To evaluate the efficacy of mirikizumab as compared to placebo in maintaining clinical remission at Week 40 (Week 52 of continuous therapy) among patients induced into clinical remission with mirikizumab, in the subgroup of patients in whom biologic agents have failed or caused intolerance.	• The proportion of patients who were in clinical remission at Week 40 among patients in clinical remission at Week 12 in Study AMAN (i.e., durable clinical remission) in whom biologic agents have failed or caused intolerance. 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)
• To evaluate the efficacy of mirikizumab compared to placebo in achieving clinical remission (using a more stringent ES) at Week 40 among patients induced into **clinical response**~~**mission**~~ with mirikizumab	• The proportion of patients with clinical remission (using a more stringent ES) at Week 40, with clinical remission defined as: ○ SF subscore = 0, or SF = 1 with a ≥1-point decrease from induction baseline, and ○ RB subscore = 0; and ○ ES = 0
• To evaluate the efficacy of mirikizumab compared to placebo in achieving an endoscopic response at Week 40 among patients induced into **clinical response** with mirikizumab	• The proportion of patients in endoscopic response at Week 40 defined as: ○ A decrease in ES of ≥1 point from induction baseline.
~~• To evaluate mirikizumab compared with placebo on symptom-free duration among patients induced into **clinical response** with mirikizumab~~	~~• The percentage of the total time (in weeks) during maintenance study treatment that patients achieve:~~ ~~• SF = 0, or SF = 1 with a ≥1-point decrease from induction baseline, and~~ ~~• RB subscore = 0~~
• To evaluate the efficacy of mirikizumab compared to placebo in achieving 24-week corticosteroid-free remission without surgery among patients induced into **clinical response** with mirikizumab and receiving corticosteroids at induction baseline	• Corticosteroid-free remission without surgery at Week 40, defined as: ○ Clinical remission at Week 40, and ○ Symptomatic remission at Week 28, and ○ No corticosteroid use for ≥24 weeks prior to Week 40 ~~among subgroup of patients on corticosteroids at induction study baseline~~

• To evaluate the effect of mirikizumab compared to placebo on changes in ~~patient reported outcome endpoints~~ Abdominal pain at Week 40	• Change from induction baseline at Week 40 in the ~~following:~~ ~~o Urgency NRS score~~ Abdominal pain NRS score
• To evaluate the efficacy of mirikizumab compared to placebo in UCEIS endoscopic remission at Week 40 among patients induced into **clinical response** with mirikizumab	• The proportion of patients with a UCEIS score of ≤1 at Week 40
• To evaluate the efficacy of mirikizumab compared to placebo in mucosal healing at Week 40 among patients induced into **clinical response** with mirikizumab	• The proportion of patients with mucosal healing at Week 40, defined as achieveing both: o Histologic remission, as described in the histopathology charter, and o Endoscopic remission, defined as ES = 0 or 1 (excluding friability)
• To evaluate the effect of mirikizumab compared to placebo on change in fatigue at Week 40	• Change from induction baseline at Week 40 in the Fatigue NRS score

Abbreviations: SAP = statistical analysis plan; UCEIS = Ulcerative Colitis Endoscopic Index of Severity.

Statistical Analysis

It is expected that approximately ~~459~~470 of these patients will enter Study AMBG as clinical responders to mirikizumab and then will be randomized 2:1 to 200 mg mirikizumab SC (~~306~~approximately 313 patients) and placebo (~~153~~approximately 157 patients). Among the ~~approximately~~ expected ~~459~~470 mirikizumab clinical responders, approximately ~~169~~180 mirikizumab clinical remitters will be randomized to 200 mg mirikizumab SC (~~113~~approximately 120 patients) and placebo (~~56~~approximately 60 patients). This assumes that:

- The induction study (AMAN, which has a mixed population with approximately ~~60~~50% biologic-failed patients) is expected to have an overall clinical remission rate of ~~21.6~~23% and response rate of ~~58.6~~60% with mirikizumab.
- 75% of induction patients receive treatment with mirikizumab, based on a 3:1 randomization ratio for the induction study.
- 10% dropout rate from induction to maintenance.

The primary endpoint, ~~maintenance of~~ clinical remission at Week 40, will be assessed on patients who achieved ~~remission~~clinical response to mirikizumab induction treatment. Assuming mirikizumab and placebo ~~maintenance of~~ clinical remission rates of ~~58.4~~47% and ~~23.6~~27%, respectively~~(biologic-failed patients: 44% and 13%; conventional-failed patients: 70% and 32%),~~ this study based on the ~~169~~470 mirikizumab induction ~~remitters~~ responders is expected to have >95~~0~~% power to demonstrate that mirikizumab is superior to placebo by using a chi-square test with a 2-sided ~~0.05~~ significance level of 0.05. ~~This sample size also provides 80% power to evaluate clinical remission among induction remitters in the biologic-failed subgroup of patients .~~In addition, ~~459 mirikizumab induction clinical responders are~~the sample size is expected to provide adequate power (>80%) to demonstrate that mirikizumab is superior to placebo for ~~the~~

~~major secondary endpoints (clinical remission [among patients induced into clinical response with mirikizumab],~~ endoscopic remission, histologic remission, and~~or~~ corticosteroid-free remission~~)~~ at Week 40, among responders to mirikizumab induction treatment by using a chi-square test with a 2-sided ~~0.05~~ significance level of 0.05.

For assessments of the primary endpoint and other categorical efficacy endpoints among induced ~~remitters~~responders, the Cochran-Mantel-Haenszel (CMH) chi-square test will be used to compare mirikizumab and placebo with stratification factors: (a) previous biologic therapy failure (yes or no), (b) baseline corticosteroid use (yes or no), ~~and~~ (c) region (North America/Europe/Other), (d) induction remission status (yes/no). The CMH chi-square p-value and the relative risk along with its 95% 2-sided confidence interval will be provided.

Treatment comparisons of continuous efficacy and health outcome variables with a single post-baseline time point will be made using analysis of covariance with: (a) treatment group, (b) previous biologic therapy failure (yes or no), (c) corticosteroid use (yes or no), (d) region (North America/Europe/Other), (e) baseline value in the model, and (f) induction remission status~~(if analysis is among induced responders)~~.

2. Schedule of Activites

Table AMBG.2.1. Schedule of Activities – Responders from Induction Study

Informed Consent Notes: Patients may consent between the start of V5 of Study AMAN ~~time of induction consent~~ and before any procedures at V1/Week 0 are performed.

Procedure: FSH (optional in women to confirm nonchild-bearing potential)[e]

PK Assessment: In addition, patients with potential hypersensitivity or infusion-related event should have sample taken as soon as possible after event occurs,

ADA Assessment: In addition, patients with possible hypersensitivity or infusion-related event should have sample taken as soon as possible after event occurs,

C. Difficile Testing: Table cell expaneded to include V3

Fecal Calprotectin and Exploratory Fecal Biomarkers: Table cell expaneded to include V3

Endoscopy with biopsies: ~~Flexible sigmoidoscopy is recommended for all patients. Colonoscopy can be performed instead of flexible sigmoidoscopy for clinically indicated reasons after discussion with the medical monitor (See section 9.1.1.3.)~~

X[d]: At least 1 endoscopy is performed at Week 40/ETV or if LOR is confirmed. LOR ~~assessments~~ confirmation based on endoscopy can only occur at a scheduled or unscheduled visit between V4 and V8. Please refer to Section 9.1.1.3 for procedure clarification.

IBDQ and EQ-5D 5L X[d]: To be performed for patients who have LOR confirmed by endoscopy before rescue dosing~~To be performed for patients with secondary LOR at the second of 2 LOR assessments~~.

PGRC: X[d]: To be performed for patients who have LOR confirmed by endoscopy before rescue dosing~~To be performed for patients with secondary LOR at the second of 2 LOR assessments~~.

Abbreviations: DNA = deoxyribonucleic acid;

Notes: Last visit or ETV is last visit prior to entering long term extension Study AMAP ~~open-label extension~~ or post-treatment follow-up.

Footnote: [a] V1 (Week 0) should occur no more than ~~10~~ 14 days from the start of the Visit 5/Week 12 visit of Study AMAN.

Table AMBG.2.2. Schedule of Activities – Nonresponders from Induction Study

Visit 4: 85 ± ~~4~~7

Informed Consent Notes: Patients may consent between the start of V5 of Study AMAN ~~time of induction consent~~ and before any procedures at V1/Week 0 are performed.

Procedure: FSH (optional in women to confirm nonchild-bearing potential)[f]

PK Assessment: In addition, patients with potential hypersensitivity or infusion-related event should have sample taken as soon as possible after event occurs,

ADA Assessment: In addition, patients with possible hypersensitivity or infusion-related event should have sample taken as soon as possible after event occurs,

C. *difficile* testing: V1 C. difficile testing does not need to be completed before the patient can start study drug therapy.

Endoscopy with biopsies: ~~See~~ Please refer to Section 9.1.1.3. for procedure clarification.

Notes: All activities should be completed prior to any study drug administration unless otherwise stated. Last visit or ETV is last visit prior to entering long term extension Study AMAP or post-treatment follow-up. Post-treatment follow-up visits should only occur if the patient is not proceeding to long term extension Study AMAP or if they discontinue treatment in Study AMBG early (i.e. patients who do not achieve delayed clinical response).

Footnote[a]: For patients who cannot continue beyond V4 because they did not achieve delayed clinical response, ETV activites that are performed as part of V4 do not need to be repated. Only those ETV activities that are not part of V4 should be completed during the ETV.

Footnote[b]: V1 (Week 0) should occur no more than ~~10~~ 14 days from the start of the Visit 5/Week 12 visit of Study AMAN.

Various footnotes re-lettered

4. Objectives and Endpoints

See Section 1 Synopsis Objective(s)/Endpoints above

5.1. Overall Design

Mirikizumab Responders from Study AMAN

Randomization will be stratified to achieve between-group comparability, based on biologic-failed status (yes or no), induction remission status (yes or no), baseline corticosteroid use (yes or no), and region (North America/Europe/Other).

Loss of Response (LOR) is defined as:

≥2-point increase from Study AMBG baseline in the combined SF + RB scores AND combined SF + RB score of ≥4, on 2 consecutive visits (≥7 days apart, and with confirmation of negative *C. difficile* testing~~)~~ (first assessment can start as early as Week 8/Visit 3),

AND

- Confirmed by centrally read endoscopic subscore (ES) of 2 or 3 not sooner than Week 12/Visit 4.

6. Study Population

Besides a maximum ~~10~~14-day window between the start of the Visit 5 (Week 12) visit of the induction study AMAN and the start of Visit 1 (Week 0) of Study AMBG, no screening period is allowed for Study AMBG. Data collected during the last visit of the induction study AMAN, including laboratory evaluations, endoscopy, and PRO data, will be used to review enrollment criteria for Study AMBG. A visit window (~~10~~14 days) is provided to allow laboratory results and central reading of the endoscopy to be available for the investigator to appropriately evaluate a patient and to ensure compliance with enrollment criteria. 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 prior to study entry, as long as all testing is completed within ~~10~~14 calendar days from the start of the Visit 5 (Week 12) visit of Study AMAN.

6.1. Inclusion Criteria

Patient Characteristics

[2.] Have completed Study AMAN through the Week 12 visit (Visit 5) and have a Visit 5 MMS and have ~~,~~received at least 1 study drug administration without early termination of study drug., ~~and underwent a Visit 5 (Week 12) endoscopy.~~

6.2. Exclusion Criteria

General Exclusion Criteria

[17.] 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 malignancy that would potentially affect patient safety within the study or confound efficacy assessment.

6.4. Screen Failures

As described in Section 6, patients will be entered into Study AMBG directly from Study AMAN, with a maximum ~~10~~14 day window between start of the Visit 5 (Week 12) visit of the induction study AMAN and start of Visit 1 (Week 0) of Study AMBG.

Patients who do not meet enrollment criteria may have one or more blood measures repeated one time, at the investigator's discretion, prior to study entry as long as all testing is completed within ~~10~~ 14 calendar days from the start of the last induction visit.

7.1. Treatments Administered

Study Drug Administration

Subcutaneous administration of mirikizumab or placebo will be given in 2 injections (maximum volume is 1 mL per injection).

Intravenous infusion of mirikizumab ~~or placebo~~ will occur over at least 30 minutes.

7.2. Method of Treatment Assignment

To achieve between-group comparability, patients will be stratified to these arms based upon biologic-failed status (yes or no), baseline corticosteroid use (yes or no), region (North America/Europe/Other), and induction remission status (yes or no). This stratification will be controlled by IWRS.

7.7. Concomitant Therapy

The recommended tapering schedule for oral corticosteroids (other than budesonide extended release tablets [budesonide MMX] or beclomethasone dipropionate [gastro-resistant prolonged-release tablet]) is as follows:

The recommended tapering schedule for patients receiving oral beclomethasone dipropionate (gastro-resistant prolonged-release tablet) 5 mg/day is to reduce tablets to 5 mg every other day for 4 weeks, and then discontinue.

7.8.3.2. Management of Hypersensitivity, Infusion-Related Events, Infusion Site Reactions and Injection Site Reactions

- After patient's stabilization, an anti-drug antibody (ADA) and PK sample should be collected; additional samples should be obtained 4 and 12-16 weeks after the event.

These samples will also be used for tryptase, complement (C3/C4), and cytokine panel assays.

Other Infusion-Related Events and Infusion Site Reactions

If a patient experiences a reaction consisting of headache, rigors and/or temperature >38°C (in the absence of signs or symptoms of a systemic hypersensitivity reaction), or an infusion site reaction, including urticaria, pruritus, or angioedema localized to the IV infusion site (in the absence of other systemic hypersensitivity signs or symptoms), during or up to 6 hours after an infusion of study drug, the following guidance should be followed:

- An ADA and PK sample should be collected at the time of the event (or as soon as possible after the event occurs), and 4 and 12-16 weeks after the event. These samples will also be used for tryptase, complement (C3/C4), and cytokine panel assays.

8.1.1. Permanent Discontinuation from Study Treatment

Safety Criteria for Study Drug Discontinuation

- The patient requires a colectomy, proctocolectomy, or partial colectomy during the study.
- ~~The patient experiences an AE or SAE that would preclude him/her from participating in the trial~~.The participant has an AE or SAE which, in the opinion of the investigator or sponsor, would preclude the participant from continuing to receive study drug.
- Systemic hypersensitivity event or anaphylaxis to ~~mirikizumab~~ study drug.

9.1. Efficacy Assessments

Table AMBG.9.1. Endpoint Definitions in Study AMBG

Endpoint	Definition
Corticosteroid-free remission without surgery at Week 40[a]	• Clinical remission at Week 40, and • Symptomatic remission at Week 28, and • No corticosteroid use for ≥12 weeks prior to Week 40
Histologic remission ~~(mucosal healing)~~	• This definition will be specified in the ~~histopathology charter~~SAP
Mucosal healing	• Histologic remission as described in the SAP and • endoscopic remission defined as ES = 0 or 1 (excluding friability)
Stable maintenance of symptomatic remission[b]	• Symptomatic remission for at least 7 out of 9 visits from Week 4 to Week 36 • Symptomatic in remission at Week 40
Bowel movement urgency improvement	The definition will be specified in the study SAP

Abbreviations: SAP = statistical analysis plan;

~~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.~~

[a] Among patients induced into clinical response with mirikizumab during the induction study and who were receiving corticosteroids at induction baseline.

[b] Among patients in symptomatic remission at Week 12 of Study AMAN.

9.1.1.1. Primary Endpoint

The primary endpoint is ~~durable~~ **clinical remission** at Week 40, among patients induced into clinical ~~remission~~ response with mirikizumab induction treatment (Study AMAN).

9.1.1.2. Mayo Score

SF Subscore: The reference "normal" SF for that patient will be recorded electronically at the induction study screening visit. ~~Normal SF for that patient is based on reported SF when the patient was in remission or reported SF before initial onset of signs and symptoms of UC.~~ Study software will use the patient-reported daily SF and the reference normal SF to automatically calculate the Mayo SF subscore.

Normal SF: The Normal SF is a patient-reported measure. This item reports the number of stools in a 24-hour period when the patient was in remission or, if the patient has never achieved remission, the reported SF before initial onset of signs and symptoms of UC. Remission refers to a period of time since being diagnosed with UC when the patient is not experiencing any signs or symptoms relating to UC. This period of time may last a few weeks or a few months or may even last several years. The patient will record this electronically as source data in the tablet device at the screening study visit of Study AMAN.

9.1.1.3. Endoscopy

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 [5]), or for other clinically indicated reasons, in the judgement of the investigator~~.~~, and after discussion with the medical monitor as appropriate.

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

If a patient undergoes early termination soon after baseline, loss of response, or at the end of extended induction endoscopy, the need for ETV endoscopy should be discussed with the medical monitor.

9.1.2.1. Major Secondary Endpoints

- Clinical **remission** at Week 40, among patients induced into clinical ~~**response**~~**remission** ~~(that is, demonstrating clinical response or clinical remission)~~ with mirikizumab at Week 12 of induction study (Study AMAN)
- Corticosteroid-free remission without surgery at Week 40, among patients induced into clinical **response** with mirikizumab at Week 12 of the induction study ~~during the induction study~~ and ~~who~~ were receiving corticosteroids at induction baseline. ~~For Week 40, this endpoint is defined as:~~
- ~~Clinical remission at Week 40, and~~
- ~~Symptomatic remission at Week 28, and~~

- ~~No corticosteroid use for ≥12 weeks prior to Week 40~~
- ~~Evaluate, in the subgroup of patients in whom biologic agents have failed or caused intolerance, clinical **remission** at Week 40 among patients induced into clinical **response** with mirikizumab~~
- ~~Evaluate, in the subgroup of patients in whom biologic agents have failed or caused intolerance, endoscopic remission at Week 40 among patients induced into clinical **response** with mirikizumab~~
- Histologic remission at Week 40, among patients induced into clinical **response** with mirikizumab at Week 12 of induction study
- Stable maintenance of symptomatic remission, among patients induced into clinical **response** with mirikizumab and were in symptomatic remission at Week 12 of induction study
- Bowel movement urgency improvement among patients induced into clinical **response** with mirikizumab at Week 12 of induction study
- ~~—~~

9.1.2.1.2. Patient Reported Outcome Instruments

The Urgency NRS (see Appendix 7 for description) is a PRO instrument used to collect bowel movement urgency data in the patient eDiary. The Urgency NRS will be used to determine the secondary endpoint for bowel movement urgency improvement (see Table AMBG.4.1 for definition).

9.1.2.2.1. Physician Reported Instrument

The Ulcerative Colitis Endoscopic Index of Severity (UCEIS) is a physician reported instrument for measuring the endoscopic disease activity of UC on flexible sigmoidoscopy or colonoscopy, that includes 3 descriptors of vascular pattern, bleeding, and erosions/ulcerations (Arai et al. 2016; Ikeya et al. 2016; Tontini et al. 2014). Only blinded central reading of endoscopies will be used to determine the UCEIS score for each endoscopy.

9.1.2.2.2. PRO Instruments Used to Assess Secondary Endpoints

The following are additional PRO instruments collected using a patient electronic diary (eDiary).

- Abdominal Pain Numeric Rating Scale (NRS)
- Fatigue NRS (collected at site visits until Visit 10 when collected via electronic diary)
- ~~Urgency NRS~~

9.1.3.3. PRO Instruments Used to Assess Exploratory Endpoints

The following exploratory endpoints will be assessed via the electronic diary tool and/or at applicable study visits using the tablet device:

- Nocturnal Stool (collected at site visits until Visit 10 when collected via electronic diary)
- ~~Fatigue NRS~~
- Patient's Global Rating of Severity (PGRS) (collected via electronic diary)

- Bristol Stool Scale (collected at site visits until Visit 10 when collected via electronic diary)

9.4.4. Immunogenicity Assessments

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 12-16 weeks after the event. These samples will also be used for tryptase, complement (C3/C4), and cytokine panel assays.

9.4.5.2. Tuberculosis

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,~~the United States Centers for Disease Control and Prevention guidance (CDC [WWW]) for the United States~~;~~ or the World Health Organization guidance for the treatment of LTBI for all countries outside of the United States (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.

9.5. Pharmacokinetics

CCI [redacted]

10.1. Sample Size Determination

It is expected that approximately ~~459~~470 of these patients will enter Study AMBG as clinical responders to mirikizumab and then will be randomized 2:1 to 200 mg mirikizumab SC (approximately 313~~06~~ patients) and placebo (approximately 157~~3~~ patients). Among the ~~approximately~~ expected 470~~459~~ mirikizumab clinical responders, approximately ~~169~~ 180 mirikizumab clinical remitters will be randomized to 200 mg mirikizumab SC (approximately ~~113~~120 patients) and placebo (approximately ~~56~~60 patients). This assumes that:

- The induction study (AMAN, which has a mixed population with approximately ~~60~~50% biologic-failed patients) is expected to have an overall clinical remission rate of 23~~21.6~~% and response rate of 60~~58.6~~% with mirikizumab.

The primary endpoint, ~~maintenance of~~ clinical remission at Week 40, will be assessed on patients who achieved clinical ~~remission~~ response to mirikizumab induction treatment. Assuming

mirikizumab and placebo ~~maintenance of~~ clinical remission rates of ~~58.4~~47% and ~~23.6~~27%, respectively~~(biologic-failed patients: 44% and 13%; conventional-failed patients: 70% and 32%)~~, this study based on the ~~169~~ 470 mirikizumab induction ~~remitters~~responders is expected to have >95~~0~~% power to demonstrate that mirikizumab is superior to placebo by using a chi-square test with a 2-sided ~~0.05~~ significance level of 0.05. ~~This sample size also provides 80% power to evaluate clinical remission among induction remitters in the subgroup of biologic-failed patients.~~ In addition, ~~459 mirikizumab induction clinical responders are~~ the sample size is expected to provide adequate power (>80%) to demonstrate that mirikizumab is superior to placebo for ~~the major secondary endpoints (clinical remission,~~ endoscopic remission, histologic remission, and ~~or~~ corticosteroid-free remission~~)~~ at Week 40, among responders to mirikizumab induction treatment by using a chi-square test with a 2-sided ~~0.05~~ significance~~t~~ level of 0.05.

10.2. Populations for Analyses

Table AMBG.10.1. Analysis Populations in Study AMBG

Population	Description
Intent-to-treat (ITT) Population	All ~~enrolled~~randomized/assigned patients. Patients will be analyzed according to the treatment to which they were assigned
Modified Intent-to-treat (mITT) Population	~~All enrolled patients who received at least 1 dose of study treatment, does not receive the correct treatment, or otherwise does not follow the protocol.~~All randomized/assigned patients who received at least 1 dose of study treatment, regardless of whether correct treatment was administered or whether protocol was followed,~~.~~ ~~Patients~~ will be analyzed according to the treatment to which they were assigned

10.3.1. General Statistical Considerations

For assessments of the primary endpoint and other categorical efficacy endpoints among induced ~~remitters~~responders, the ~~Cochran-Mantel-Haenszel (~~CMH~~)~~ chi-square test will be used to compare mirikizumab and placebo with stratification factors: (a) previous biologic therapy failure (yes or no), (b) baseline corticosteroid use (yes or no), ~~and~~(c) region (North America/Europe/Other)~~,~~ ~~-~~and (d) induction remission status (yes/no). ~~For other major secondary endpoints and categorical efficacy endpoints among induced responders, similar CHM chi-square test will be used. Another stratification factor of induction remission status will be added in the analysis.~~

Treatment comparisons of continuous efficacy and health outcome variables with a single post-baseline time point will be made using analysis of covariance with: (a) treatment group, (b) previous biologic therapy failure (yes or no), (c) corticosteroid use (yes or no), (d) region (North America/Europe/Other), (e) baseline value in the model, and (f) induction remission status ~~(if analysis is among induced responders)~~. Type III sums of squares for LS means will be used for statistical comparison between treatment groups. The LS mean difference, standard error, p-value, and 95% CI, unless otherwise specified, will also be reported.

10.3.1.1. Missing Data Imputation:

- 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 dosing with mirikizumab prior to the time point of interest. ~~In addition, the patients who require UC surgery, take rescue dosing with mirikizumab, increase UC medication dose from baseline, or initiate new UC medications will be considered as nonresponders.~~

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. Medications started prior to randomization and medications started on study after randomization ~~Previous concomitant therapy (reported before randomization) and current concomitant therapy (reported after randomization)~~ will be presented separately in frequency tables by drug name and by cohort for all enrolled patients.

10.3.3.1. Primary Analyses

The primary endpoint is the proportion of patients with ~~durable~~ clinical remission at Week 40 (Week 52 of continuous therapy) among the patients who are ~~remitters~~responders to 300 mg mirikizumab IV at 12 weeks of induction dosing.

Rates of clinical remission at Week 40 among induction responders ~~remitters~~ will be analyzed. Patients who do not achieve clinical remission or who do not reach the Week 40 assessment will be considered to be nonremitters. In addition, patients who ~~undergo UC surgery,~~ take rescue dosing with mirikizumab~~, increase their concomitant UC medication, or initiate new UC medications~~ will be considered nonremitters.

10.3.7.1. Subgroup Analyses

~~The major subgroup analysis is for the primary and major secondary endpoints for biologic-failed patients described in Section 9.1.2.1. Multiplicity adjustment described in Section 10.3.1.2. will be used to control type I error.~~

~~Additional s~~Subgroup analyses will be conducted for the primary endpoint and selected major secondary endpoints.

11. References

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Ikeya K, Hanai H, Sugimoto K, Osawa S, Kawasaki S, Iida T, Maruyama Y, Watanabe F. The ulcerative colitis endoscopic index of severity more accurately reflects clinical outcomes and long-term prognosis than the Mayo endoscopic score. *J Crohns Colitis*. 2016;10:286-295.

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Appendix 1. Abbreviations and Definitions

UCEIS Ulcerative Colitis Endoscopic Index of Severity

Appendix 2. Clinical Laboratory Tests

Other tests[a]

Tryptase[h]
Complement (C3/C4)[h]
Cytokine panel[h]
Abbreviations: ADA = anti-drug antibody
[h] Performed only in the event of systemic allergic/hypersensitivity events, along with ADA and PK.

Appendix 3.1.7. Final Report Signature

The ~~investigator with the most enrolled patients will serve as the~~ CSR coordinating investigator will be selected by the study team. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

Appendix 6. Mayo Scoring System for the Assessment of Ulcerative Colitis Activity

Stool frequency reports the number of stools in a 24-hour period, relative to the normal number of stools for that patient. The reference "normal" stool frequency for that patient will be recorded electronically at the screening visit in Study AMAN. The Normal SF refers to when the patient was in remission or, if the patient has never achieved remission, the reported SF before initial onset of signs and symptoms of ulcerative colitis. Remission refers to a period of time since being diagnosed with ulcerative colitis when the patient is not experiencing any signs or symptoms relating to ulcerative colitis. This period of time may last a few weeks or a few months or may even last several years. The patient will record this electronically as source data in the tablet device at the screening study visit in Study AMAN.

Appendix 7. Patient-Reported Outcome Instruments

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~~worst possible pain).

Fatigue NRS: The Fatigue NRS is a single item that measures the "worst fatigue (weariness, tiredness) in the past 24 hours" using an 11-point NRS ranging from 0 (no fatigue) to 10 (fatigue as bad as you can imagine).

Appendix 8. Prohibited Medications

Drug Class	Comments
Rectally administered investigational preparations for UC such as arsenic preparations	Prohibited throughout treatment period
Intravenous corticosteroids for UC	A course of IV corticosteroids for UC is prohibited
Systemic corticosteroids for non-UC indications (oral or IV)	Patients requiring systemic corticosteroids for non-UC conditions are excluded. Exceptions ~~(except~~include corticosteroids to treat adrenal insufficiency, premedication for IP infusion, or l~~are excluded. L~~ocally administered corticosteroids (e.g., inhaled, intranasal, intra-articular, topical) (see Appendix 10).~~are allowed.~~

Appendix 9. Permitted Medications with Dose Stabilization

Drug Class	Comments
Oral 5-ASAs (for example, mesalamine, balsalazide, olsalazide) and sulfasalazine for UC ~~(for example, mesalamine, balsalazide, olsalazide)~~	May continue during study with stable doses encouraged
Oral corticosteroids for UC (prednisone ≤20 mg/day or equivalent~~, or~~ budesonide MMX 9 mg/day, or beclomethasone dipropionate [gastro-resistant prolonged-release tablet] 5 mg/day)	Responder patients who are receiving oral corticosteroids at the start of Study AMBG will start corticosteroid taper at the beginning of the study. Clinical nonresponders who undergo extended IV induction with mirikizumab will begin corticosteroid tapering if symptomatic response or symptomatic improvement based on investigator discretion is achieved at any time after starting extended induction (see *Corticosteroid Taper* in Section 7.7).
Corticosteroids for non-UC indications: corticosteroids to treat adrenal insufficiency, as premedication for IP infusion, or locally administered corticosteroids (e.g. inhaled, intranasal, intra-articular, topical).	May continue corticosteroids to treat adrenal insufficiency or locally administered corticosteroids during study with stable dose encouraged. Single doses of oral or IV corticosteroids as premedication to IP administration are allowed in patients with prior IP or other previous biologic injection reactions.

Abbreviations: IP = investigational product; UC = ulcerative colitis

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