

Protocol I6T-MC-AMAN(a)

A Phase 3, Multicenter, Randomized, Double-Blind, Parallel, Placebo-Controlled Induction Study of Mirikizumab in Conventional-Failed and Biologic-Failed Patients with Moderately to Severely Active Ulcerative Colitis LUCENT 1

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LUCENT 1**

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Mirikizumab (LY3074828)

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Table of Contents

Section	Page
Protocol I6T-MC-AMAN(a) A Phase 3, Multicenter, Randomized, Double-Blind, Parallel, Placebo-Controlled Induction Study of Mirikizumab in Conventional-Failed and Biologic-Failed Patients with Moderately to Severely Active Ulcerative Colitis LUCENT 1	1
Table of Contents	2
1. Synopsis	9
2. Schedule of Activities	16
3. Introduction	22
3.1. Study Rationale	22
3.2. Background	22
3.2.1. Disease State and Treatment Goals	22
3.2.2. Currently Available Treatments and Unmet Need	22
3.2.3. Interleukin-23 as a Therapeutic Target in Ulcerative Colitis	23
3.2.4. Preclinical and Clinical Studies of Mirikizumab	23
3.2.5. Other Interleukin-23 Targeted Therapies in Humans	25
3.3. Benefit/Risk Assessment	25
4. Objectives and Endpoints	27
5. Study Design	31
5.1. Overall Design	31
5.2. Number of Participants	32
5.3. Definition of Baseline	32
5.4. Definition of Enrollment	32
5.5. End of Study Definition	32
5.6. Scientific Rationale for Study Design	33
5.7. Justification for Dose	33
6. Study Population	35
6.1. Inclusion Criteria	35
6.2. Exclusion Criteria	40
6.2.1. Rationale for Exclusion of Certain Study Candidates	44
6.3. Lifestyle Restrictions	45
6.4. Screen Failures	45
7. Treatments	47
7.1. Treatments Administered	47
7.1.1. Packaging and Labeling	47

7.2.	Method of Treatment Assignment	48
7.2.1.	Selection and Timing of Doses	48
7.3.	Blinding	48
7.4.	Dosage Modification	49
7.5.	Preparation/Handling/Storage/Accountability	49
7.6.	Treatment Compliance	49
7.7.	Concomitant Therapy	49
7.8.	Treatment after the End of the Study	50
7.8.1.	Study Extensions	50
7.8.2.	Treatment after Study Completion	50
7.8.3.	Special Treatment Considerations	50
7.8.3.1.	Premedication for Infusions	50
7.8.3.2.	Management of Hypersensitivity, Infusion Related Events, and Infusion Site Reactions	51
8.	Discontinuation Criteria	53
8.1.	Discontinuation from Study Treatment	53
8.1.1.	Permanent Discontinuation from Study Treatment	53
8.1.2.	Temporary Interruption (Withholding) of Study Treatment	55
8.1.3.	Discontinuation of Inadvertently Enrolled Patients	55
8.2.	Discontinuation from the Study	56
8.3.	Lost to Follow-Up	56
9.	Study Assessments and Procedures	57
9.1.	Efficacy Assessments	57
9.1.1.	Primary Efficacy Assessment	57
9.1.1.1.	Primary Endpoint	57
9.1.1.2.	Mayo Score	57
9.1.1.3.	Endoscopy	59
9.1.1.4.	Endoscopic Biopsies	60
9.1.2.	Secondary Efficacy Assessments	61
9.1.2.1.	Major Secondary Endpoints	61
9.1.2.1.1.	Patient Reported Outcome Instruments	61
9.1.2.2.	Other Secondary Endpoints	61
9.1.2.2.1.	Physician Reported Instrument	61
9.1.2.2.2.	Patient Reported Outcome Instruments	61
9.1.2.2.3.	Histopathology Scoring Instrument	62
9.1.2.2.4.	Inflammatory Biomarkers	62
9.1.3.	Exploratory Efficacy Assessments	62
9.1.3.1.	Exploratory Endpoints	62

9.1.3.1.1. Patient Reported Outcome Instruments 62

9.1.3.2. Extraintestinal Manifestations 62

9.1.4. Appropriateness of Assessments 63

9.2. Adverse Events 63

9.2.1. Serious Adverse Events 64

9.2.1.1. Suspected Unexpected Serious Adverse Reactions 64

9.2.2. Adverse Events of Special Interest 65

9.2.3. Complaint Handling 66

9.3. Treatment of Overdose 66

9.4. Safety 66

9.4.1. Vital Signs 66

9.4.2. Electrocardiograms 66

9.4.3. Laboratory Tests 66

9.4.3.1. Pregnancy Testing 67

9.4.4. Immunogenicity Assessments 67

9.4.5. Other Tests 68

9.4.5.1. Physical Examination 68

9.4.5.2. Chest Radiography 68

9.4.5.3. Tuberculosis Screening 69

9.4.5.4. Hepatitis B Testing 71

9.4.5.5. Hepatitis C Testing 72

9.4.5.6. Depression and Suicidality 72

9.4.5.7. Stool Testing 73

9.4.6. Safety Monitoring 74

9.4.6.1. Hepatic Safety Monitoring 74

9.5. Pharmacokinetics 75

9.6. Pharmacodynamics 76

CCI [REDACTED]

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9.8. Biomarkers 76

9.9. Medical Resource Utilization and Health Economics 77

10. Statistical Considerations 78

10.1. Sample Size Determination 78

10.2. Populations for Analyses 79

10.3. Statistical Analyses 79

10.3.1. General Statistical Considerations 79

10.3.1.1. Missing Data Imputation 81

10.3.1.2. Adjustment for Multiple Comparisons 81

10.3.2. Treatment Group Comparability..... 81

 10.3.2.1. Patient Disposition..... 81

 10.3.2.2. Patient Characteristics 82

 10.3.2.3. Concomitant Therapy 82

 10.3.2.4. Treatment Compliance..... 82

10.3.3. Efficacy Analyses 82

 10.3.3.1. Primary Analyses 82

 10.3.3.2. Secondary Analyses..... 83

10.3.4. Safety Analyses..... 83

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses 83

10.3.6. Evaluation of Immunogenicity 84

10.3.7. Other Analyses..... 84

 10.3.7.1. Subgroup Analyses..... 84

10.3.8. Interim Analyses 84

11. References 86

12. Appendices 92

List of Tables

Table	Page
Table AMAN.1. Schedule of Activities.....	17
Table AMAN.2. Objectives and Endpoints.....	27
Table AMAN.3. Treatment Regimens.....	47
Table AMAN.4. Endpoint Definitions.....	57

List of Figures

Figure

Page

Figure AMAN.1. Illustration of study design for Clinical Protocol I6T-MC-AMAN.32

List of Appendices

Appendix		Page
Appendix 1.	Abbreviations and Definitions.....	93
Appendix 2.	Clinical Laboratory Tests.....	98
Appendix 3.	Study Governance Considerations.....	101
Appendix 4.	Risk Factors for Latent Tuberculosis Infection.....	106
Appendix 5.	Hepatic Monitoring Tests for Treatment-Emergent Abnormality.....	108
Appendix 6.	Mayo Scoring System for the Assessment of Ulcerative Colitis Activity.....	110
Appendix 7.	Patient Reported Outcome Instruments	112
Appendix 8.	Examples of Infections that May Be Considered Opportunistic in the Setting of Biologic Therapy	116
Appendix 9.	Prohibited Medications	118
Appendix 10.	Permitted Medications with Dose Stabilization	122
Appendix 11.	Additional Information on Systemic Drug Administration Reactions	124
Appendix 12.	Additional Information on the Columbia Suicide Severity Rating Scale, and Quick Inventory of Depressive Symptomatology (self report)	126
Appendix 13.	Protocol Amendment I6T-MC-AMAN(a) Summary A Phase 3, Multicenter, Randomized, Double-Blind, Parallel, Placebo-Controlled Induction Study of Mirikizumab in Conventional-Failed and Biologic- Failed Patients with Moderately to Severely Active Ulcerative Colitis LUCENT 1	128

1. Synopsis

Title of Study:

A Phase 3, Multicenter, Randomized, Double-Blind, Parallel, Placebo-Controlled Induction Study of Mirikizumab in Conventional-Failed and Biologic-Failed Patients with Moderately to Severely Active Ulcerative Colitis

Rationale:

Interleukin-23 (IL-23) has been implicated as a pro-inflammatory factor in mucosal inflammation in ulcerative colitis (UC). Study I6T-MC-AMAN (AMAN) is designed to evaluate, over a 12-week induction period, the safety and efficacy of mirikizumab in patients with moderately to severely active UC who have an inadequate response to, loss of response to, or are intolerant to corticosteroid or immunomodulator therapy for UC (termed “conventional-failed”), and those who have an inadequate response to, loss of response to, or are intolerant to biologic therapy for UC (termed “biologic-failed”). Patients who complete Study AMAN, irrespective of clinical response status, may be eligible to participate in the maintenance study, Study I6T-MC-AMBG (AMBG), provided the eligibility criteria for Study AMBG are met.

Objectives/Endpoints:

Objectives	Endpoints
Primary^a	
<ul style="list-style-type: none"> To test the hypothesis that mirikizumab is superior to placebo in inducing clinical remission at Week 12 in patients with moderately to severely active ulcerative colitis (UC) 	<ul style="list-style-type: none"> The proportion of patients in clinical remission at Week 12. Clinical remission is based on the modified Mayo score (MMS) and is defined as: <ul style="list-style-type: none"> Stool frequency (SF) subscore = 0, or SF = 1 with a ≥ 1-point decrease from baseline, and Rectal bleeding (RB) subscore = 0, and Endoscopic subscore (ES) = 0 or 1 (excluding friability)
Major Secondary^a	
<ul style="list-style-type: none"> To evaluate the efficacy of treatment with mirikizumab compared to placebo in inducing a clinical response at Week 12 	<ul style="list-style-type: none"> The proportion of patients in clinical response at Week 12. Clinical response is based on the MMS and is defined as: <ul style="list-style-type: none"> A decrease in the MMS of ≥ 2 points and $\geq 30\%$ decrease from baseline, and A decrease of ≥ 1 point in the RB subscore from baseline or a RB score of 0 or 1
<ul style="list-style-type: none"> To evaluate the efficacy of treatment with mirikizumab compared to placebo in inducing endoscopic remission at Week 12 	<ul style="list-style-type: none"> The proportion of patients with endoscopic remission at Week 12, defined as: <ul style="list-style-type: none"> ES = 0 or 1 (excluding friability)
<ul style="list-style-type: none"> To evaluate the efficacy of treatment with mirikizumab compared to placebo in inducing symptomatic remission at Week 4 	<ul style="list-style-type: none"> The proportion of patients in symptomatic remission at Week 4, defined as: <ul style="list-style-type: none"> SF = 0, or SF = 1 with a ≥ 1-point decrease from baseline, and RB = 0
<ul style="list-style-type: none"> To evaluate the efficacy of treatment with mirikizumab compared to placebo in inducing symptomatic remission at Week 12 	<ul style="list-style-type: none"> The proportion of patients in symptomatic remission at Week 12, defined as: <ul style="list-style-type: none"> SF = 0, or SF = 1 with a ≥ 1-point decrease from baseline and

Objectives	Endpoints
<ul style="list-style-type: none"> To evaluate the efficacy of treatment with mirikizumab compared to placebo in inducing clinical response in the biologic-failed population at Week 12 	<ul style="list-style-type: none"> ○ RB = 0 The proportion of patients in the biologic-failed population in clinical response at Week 12. Clinical response is based on the MMS and is defined as: <ul style="list-style-type: none"> ○ A decrease in the MMS of ≥ 2 points and $\geq 30\%$ decrease from baseline, and ○ A decrease of ≥ 1 point in the RB subscore from baseline or a RB score of 0 or 1
<ul style="list-style-type: none"> To evaluate the efficacy of treatment with mirikizumab compared to placebo in inducing bowel movement urgency improvement at Week 12 in patients with bowel urgency symptoms at baseline 	<ul style="list-style-type: none"> The proportion of patients with bowel movement urgency improvement at Week 12 as defined in the study statistical analysis plan (SAP)
Other Secondary	
<ul style="list-style-type: none"> To evaluate the numerical value and change from baseline of individual MMS subscores of SF, RB, and ES at various times during the 12-week induction, in patients receiving mirikizumab compared with patients receiving placebo 	<ul style="list-style-type: none"> The numerical value and change from baseline in each of the following items: <ul style="list-style-type: none"> ○ SF (Weeks 2, 4, 6, 8, and 12) ○ RB (Weeks 2, 4, 6, 8, and 12) ○ The composite clinical endpoint of the sum of the SF and RB subscores (Weeks 2, 4, 6, 8, and 12) ○ ES (Week 12)
<ul style="list-style-type: none"> To evaluate the efficacy of mirikizumab compared to placebo on achieving an endoscopic subscore of 0 at Week 12 	<ul style="list-style-type: none"> The proportion of patients achieving an endoscopic subscore of 0 at Week 12
<ul style="list-style-type: none"> To evaluate the efficacy of treatment with mirikizumab compared to placebo in inducing an endoscopic response at Week 12 	<ul style="list-style-type: none"> The proportion of patients in endoscopic response at Week 12, defined as: A decrease in the ES of ≥ 1 point compared to baseline
<ul style="list-style-type: none"> To evaluate the efficacy of treatment with mirikizumab compared to placebo in inducing symptomatic response at Weeks 2, 4, 6, 8, and 12 	<ul style="list-style-type: none"> The proportion of patients achieving symptomatic response, defined as: <ul style="list-style-type: none"> ○ $\geq 30\%$ decrease from baseline in the composite clinical endpoint of the sum of SF and RB subscores at Weeks 2, 4, 6, 8, and 12
<ul style="list-style-type: none"> To evaluate the efficacy of treatment with mirikizumab compared to placebo in inducing symptomatic remission at Weeks 2, 6, and 8 	<ul style="list-style-type: none"> The proportion of patients achieving symptomatic remission at Weeks 2, 6, and 8, defined as: <ul style="list-style-type: none"> ○ SF = 0, or SF = 1 with a ≥ 1-point decrease from baseline, and ○ RB = 0
<ul style="list-style-type: none"> To evaluate the efficacy of treatment with mirikizumab compared to placebo in achieving the SF component of clinical remission definition at Weeks 2, 6, and 8 	<ul style="list-style-type: none"> The proportion of patients achieving the following at Weeks 2, 6, and 8: <ul style="list-style-type: none"> ○ SF = 0, or SF = 1 with a ≥ 1-point decrease from baseline
<ul style="list-style-type: none"> To evaluate the efficacy of treatment with mirikizumab compared to placebo in achieving the RB component of clinical remission at Weeks 2, 6, and 8 	<ul style="list-style-type: none"> The proportion of patients achieving the following at Weeks 2, 6, and 8: <ul style="list-style-type: none"> ○ RB = 0

Objectives	Endpoints
Other Secondary (continued)	
<ul style="list-style-type: none"> To evaluate histologic remission between mirikizumab and placebo at Week 12 	<ul style="list-style-type: none"> Proportion of patients in histologic remission, as defined in the SAP
<ul style="list-style-type: none"> To evaluate the time to symptomatic response 	<ul style="list-style-type: none"> Time to symptomatic response, defined as at least a 30% decrease from baseline in the composite clinical endpoint of the sum of SF and RB subscores
<ul style="list-style-type: none"> To evaluate the time to symptomatic remission 	<ul style="list-style-type: none"> Time to symptomatic remission, defined as SF = 0, or SF = 1 with a ≥ 1-point decrease from baseline, and RB = 0
<ul style="list-style-type: none"> To evaluate the primary and major secondary objectives in the subgroup of patients who were on UC concomitant therapy at enrollment 	<ul style="list-style-type: none"> Primary and major secondary endpoints in the subgroup of patients who were on concomitant UC therapy at enrollment (that is, receiving corticosteroids only at baseline, receiving immunomodulators only at baseline, receiving both corticosteroids and immunomodulators at baseline, and not receiving either at baseline)
<ul style="list-style-type: none"> To evaluate the primary and major secondary objectives in the conventional-failed and biologic-failed subgroups of patients 	<ul style="list-style-type: none"> Primary and major secondary endpoints in the conventional-failed and biologic-failed subgroup of patients. Please note that clinical response in the biologic-failed population is a major secondary endpoint and will not be re-tested here.
<ul style="list-style-type: none"> To evaluate the efficacy of treatment with mirikizumab compared to placebo in improving abdominal pain at Week 12 	<ul style="list-style-type: none"> The proportion of patients with a NRS pain score ≥ 3 at baseline who achieve an improvement of $\geq 30\%$ from baseline in 7-day average abdominal pain NRS score at Week 12
<ul style="list-style-type: none"> To evaluate the effect of mirikizumab compared to placebo on changes in health outcome endpoints at Week 12 	<ul style="list-style-type: none"> Change from baseline in: <ul style="list-style-type: none"> Inflammatory Bowel Disease Questionnaire (IBDQ) score at Week 12 European Quality of Life 5 Dimensions 5 Level (EQ-5D 5L) index at Week 12 Work Productivity and Activity Impairment Questionnaire Ulcerative Colitis (WPAI:UC) score at Week 12 Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), Version 2 physical and mental component and domain scores at Week 12

Objectives	Endpoints
Other Secondary (continued)	
<ul style="list-style-type: none"> To evaluate the effect of mirikizumab compared to placebo on changes in inflammatory biomarkers 	<ul style="list-style-type: none"> Change from baseline in biomarkers such as: <ul style="list-style-type: none"> C-reactive protein Fecal calprotectin (at Weeks 4 and 12)
<ul style="list-style-type: none"> To evaluate the pharmacokinetic and pharmacokinetic/pharmacodynamic relationships of mirikizumab 	<ul style="list-style-type: none"> Clearance and volume of distribution of mirikizumab Relationship between LY3074828 exposure and efficacy
<ul style="list-style-type: none"> To evaluate the potential development of anti-mirikizumab antibodies and their potential relationship with efficacy, safety and mirikizumab exposure 	<ul style="list-style-type: none"> Relationship between treatment emergent anti-drug antibodies (TEADA) and efficacy Relationship between TEADA and safety Relationship between TEADA and mirikizumab pharmacokinetics.
<ul style="list-style-type: none"> To evaluate the efficacy of mirikizumab compared to placebo in Ulcerative Colitis Endoscopic Index of Severity (UCEIS) endoscopic remission at Week 12 	<ul style="list-style-type: none"> The proportion of patients with a UCEIS score of ≤ 1 at Week 12
<ul style="list-style-type: none"> To evaluate the efficacy of mirikizumab compared to placebo in mucosal healing at Week 12 	<ul style="list-style-type: none"> The proportion of patients with mucosal healing at Week 12, defined as achieving both: <ul style="list-style-type: none"> Histologic remission, as described in the SAP, and Endoscopic remission, defined as ES = 0 or 1 (excluding friability)
<ul style="list-style-type: none"> To evaluate the efficacy of mirikizumab compared to placebo on changes in fatigue at Week 12 	<ul style="list-style-type: none"> Change from baseline in Fatigue NRS scores at Week 12

^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 0.00125. 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 AMAN is a multicenter, randomized, double-blind, parallel-arm, placebo-controlled study designed to evaluate the safety and efficacy of mirikizumab, compared with placebo, over a 12-week induction period. The study population includes patients with moderately 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).

Treatment Groups and Duration:

Patients will be randomized with a 3:1 ratio to receive blinded intravenous administration of 300 mg mirikizumab or placebo every 4 weeks at Weeks 0, 4, and 8. Randomization will be stratified by (a) biologic-failed status (yes/no), (b) baseline corticosteroid use (yes/no), (c) baseline disease activity (modified Mayo score [MMS]: [4-6] or [7-9]), and (d) region (North America/Europe/Other). Duration of treatment with the investigational product is 12 weeks. The total duration of participation in this study may be up to approximately 32 weeks, as detailed below.

Screening Period: up to 28 days.

Treatment Period: 12 weeks.

Post-Treatment Follow-Up Period: 16 weeks after last visit for those who discontinue treatment prior to the Week 12 assessment, or those who are unable or are not willing to participate in the maintenance study.

Number of Planned Patients:

Screened: approximately 2230

Randomized: approximately 1160

Completed: approximately 1044

Statistical Analysis:

The study will randomize approximately 1160 patients with a 3:1 ratio of 300 mg mirikizumab to placebo, with an assumption that approximately 1044 patients will complete the study. Patients will be stratified by (a) biologic-failed status (yes/no), (b) baseline corticosteroid use (yes/no), (c) baseline disease activity (MMS: [4-6] or [7-9]), and (d) region (North America/Europe/Other).

The power calculations for this study assume the following:

- (1) The randomized study population will include approximately 50% biologic-failed patients and approximately 50% conventional-failed patients.
- (2) The predicted clinical remission rates at Week 12 for mirikizumab versus placebo are expected to be 23% versus 7.8% (biologic-failed patients: 16% versus 3.5%; conventional-failed patients: 30% versus 12%).

The primary endpoint of this study is to test the hypothesis that mirikizumab is superior to placebo in inducing **clinical remission** at Week 12 in patients with moderately to severely active UC. Given the assumptions described above, a sample size of 1160 patients are expected to provide >90% power to demonstrate that mirikizumab is superior to placebo in achieving this endpoint, based on a chi-square test with a 2-sided significance level of 0.00125.

Patients who complete Study AMAN may be eligible to participate in Study AMBG, a 40-week maintenance study. The primary objective of Study AMBG is to test the hypothesis that

mirikizumab is superior to placebo in achieving clinical remission at Week 40 of Study AMBG (Week 52 of continuous therapy) amongst patients induced into clinical response with mirikizumab at Week 12 of Study AMAN. A sample size of 1160 patients in Study AMAN is predicted to ensure that there will be a sufficient number of biologic-failed patients in clinical remission at Week 12 of Study AMAN who will enter Study AMBG. This is expected to provide >90% power to demonstrate that mirikizumab is superior to placebo in achieving the primary endpoint in Study AMBG, based on a chi-square test with a 2-sided significance level of 0.05.

Summary statistics for continuous variables may include mean, standard deviation (SD), 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 will be 2-sided, and the family-wise type I error rate (FWER) will be controlled at an α level of 0.00125 for primary and major secondary endpoints using a pre-specified graphical procedure. Weights and alpha propagations will be finalized and included in the Statistical Analysis Plan (SAP) prior to first unblinding of efficacy data.

For assessments of the primary endpoint and other categorical efficacy endpoints, the Cochran–Mantel–Haenszel (CMH) chi-square test will be used to compare the 2 treatment groups with the following stratification factors: (a) previous biologic therapy failure status (yes/no), (b) baseline corticosteroid use (yes/no), (c) baseline disease activity (MMS: [4-6] or [7-9]), and (d) region (North America/Europe/Other).

The 2-sided CMH chi-square p-value and the relative risk along with its 99.875% 2-sided confidence interval (CI) will be provided for the primary and major secondary endpoints. Patients who have missing data for the endpoint will be assumed to have not responded (referred to as nonresponder imputation).

Unless otherwise specified, analysis of hypotheses will be tested under multiplicity control at a family wise significance level of 0.00125. A 2-sided 99.875% CI will be provided along with the p-value. For other analyses, statistical tests without multiplicity control will be conducted using a 2-sided significance level of 0.05. The corresponding p-value along with its 95% 2-sided CI will be provided. These analyses will also include subgroup analyses for the primary and the major secondary endpoints, except for the subgroup which is included in the scope of multiplicity control.

Treatment comparisons of continuous efficacy and health outcome variables with multiple postbaseline time points will be made using the mixed-effects model for repeated measures (MMRM). The MMRM will include the following effects and covariates: (a) treatment group, (b) previous biologic therapy failure status (yes/no), (c) corticosteroid use (yes/no), (d) disease activity (MMS: [4-6] or [7-9] at baseline), (e) region (North America/Europe/Other), (f) baseline value in the model, (g) visit, and (h) the interactions of treatment-by-visit and baseline-by-visit as fixed factors. Treatment comparisons of continuous efficacy and health outcome variables with a single postbaseline time point will be made using analysis of covariance (ANCOVA) with the following in the model: (a) treatment group, (b) previous biologic therapy failure status (yes/no),

(c) corticosteroid use (yes/no), (d) disease activity (MMS: [4-6] or [7-9]) at baseline), (e) region (North America/Europe/Other), and (f) baseline value.

Multiplicity controlled analyses will be performed to test the primary and major secondary hypotheses in order to control the overall FWER at 0.00125. A prespecified graphical multiple testing approach will be used. The graphical approach is a closed testing procedure. Hence, it strongly controls the FWER across all endpoints. Details of the specific graphical testing scheme (including testing order, interrelationships, type I error allocation for the major secondary endpoints, and the associated propagation of alpha) will be prespecified in the SAP prior to first unblinding of efficacy data.

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 visit and by treatment. The change from baseline to last observation value will be analyzed with 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 test results) will also be produced.

2. Schedule of Activities

Table AMAN.1. Schedule of Activities

Procedure	Treatment Period							V997 (UV) ^c	Post-Treatment Follow-Up Period		Notes:
	V0	V1	V2 ^a	V3	V4	V5	ETV ^b		V801	V802	
Visit											
Week		0	2	4	8	12			LV + 4	LV + 16	
Day and/or Visit Interval Tolerance	≤28 from V1	1	15 ± 3	29 ± 3	57 ± 3	85 ± 7			± 4	± 4	
<i>All activities should be completed prior to any study drug administration unless otherwise stated below. Post-treatment Follow-up visits should only occur if the patient is not proceeding to Study AMBG.</i>											
Informed consent	X										
Explain UC remission stool frequency question to patient	X										Investigator or site staff should explain the purpose of UC remission question in the TrialSlate (tablet) device before the patient answers the question to ensure accurate data capture. Errors in response cannot be corrected once response is saved and confirmed by the patient.
Inclusion and exclusion criteria	X	X									
Demographic information	X										
Medical history and pre-existing conditions	X										Includes relevant surgical history
Concomitant medication	X	X	X	X	X	X	X	X	X	X	
Review AEs	X	X	X	X	X	X	X	X	X	X	
Tobacco/nicotine use	X					X	X				
Alcohol/caffeine use	X										
IP Administration											
Randomization		X									
IP administration		X		X	X						
Physical Examination											
Vital signs (T, BP, PR)	X	X		X	X	X	X	X	X	X	

Procedure	Treatment Period							V997 (UV) ^c	Post-Treatment Follow-Up Period		Notes:
	Visit	V0	V1	V2 ^a	V3	V4	V5		ETV ^b	V801	
Week		0	2	4	8	12			LV + 4	LV + 16	
Day and/or Visit Interval Tolerance	≤28 from V1	1	15 ± 3	29 ± 3	57 ± 3	85 ± 7			± 4	± 4	
<i>All activities should be completed prior to any study drug administration unless otherwise stated below. Post-treatment Follow-up visits should only occur if the patient is not proceeding to Study AMBG.</i>											
Weight		X				X	X				
Height		X									
Physical examination	X	X				X	X				
Evaluate for EIMs	X	X		X	X	X	X	X			
12-lead ECG (locally read)	X					X	X				
Laboratory Investigations											
Urinalysis	X										
Urine pregnancy test		X		X	X			X	X	X	Only in women of childbearing potential. Done locally and prior to dosing.
HIV testing	X										
HBV, HCV testing	X										
HBV DNA ^d	X					X	X			X	For patients with the following HBV serology at screening: HBsAg-, anti-HBc+, HBV DNA not detected.
Hematology	X	X		X	X	X	X	X	X	X	
Chemistry	X	X		X	X	X	X	X	X	X	
Fasting lipid profile ^e		X				X	X				
hsCRP ^e		X				X	X				
FSH (optional in women to confirm nonchild-bearing potential) ^e	X	X		X	X	X	X	X			Optional, to confirm post-menopausal status in women ≥50 with amenorrhea >1 year.
Serum pregnancy test ^e	X										Only in women of childbearing potential.
Serum and plasma for cytokines		X		X		X	X				
PK assessment											Serum for PK assessment and

Procedure	Treatment Period							V997 (UV) ^c	Post-Treatment Follow-Up Period		Notes:
	V0	V1	V2 ^a	V3	V4	V5	ETV ^b		V801	V802	
Week		0	2	4	8	12			LV + 4	LV + 16	
Day and/or Visit Interval Tolerance	≤28 from V1	1	15 ± 3	29 ± 3	57 ± 3	85 ± 7			± 4	± 4	
<i>All activities should be completed prior to any study drug administration unless otherwise stated below. Post-treatment Follow-up visits should only occur if the patient is not proceeding to Study AMBG.</i>											
Pre-dose PK sample		X		X	X						mirikizumab assay development. 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.
Post-dose PK sample		X		X							
PK sample						X	X	X		X	
ADA assessment		X		X	X	X	X	X		X	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.
CCI [REDACTED]		CCI [REDACTED]									CCI [REDACTED]
Serum, plasma and whole blood for exploratory biomarkers		X		X		X	X				
Interferon-γ release assay (or tuberculin skin test)	X										
Additional Screening Tests											
CXR	X										
C-SSRS, Self-Harm Supplement Form, Self-Harm “Follow-Up” Form	X										
QIDS-SR16		X				X	X				
Stool Samples											
Stool culture	X										Additional local stool testing (for

Procedure	Treatment Period							V997 (UV) ^c	Post-Treatment Follow-Up Period		Notes:
	V0	V1	V2 ^a	V3	V4	V5	ETV ^b		V801	V802	
Visit											
Week		0	2	4	8	12			LV + 4	LV + 16	
Day and/or Visit Interval Tolerance	≤28 from V1	1	15 ± 3	29 ± 3	57 ± 3	85 ± 7			± 4	± 4	
<i>All activities should be completed prior to any study drug administration unless otherwise stated below. Post-treatment Follow-up visits should only occur if the patient is not proceeding to Study AMBG.</i>											
<i>C. difficile</i> testing	X					X ^f	X ^f	X ^g			example, ova & parasites) is allowed at the investigator's discretion
Fecal calprotectin and exploratory fecal biomarkers		X		X		X	X				
Endoscopic Procedure											
Endoscopy with biopsies	X					X	X				Screening endoscopy within 14 days of V1. Please refer to Section 9.1.1.3 for procedure clarification.
UC Activity Assessments											
Patient diary dispensed	X										
Patient diary compliance review		X	X	X	X	X	X	X			
PGA		X		X	X	X	X				
Review Modified Mayo Score		X				X	X				
Patient diary collected						X	X				
Health Outcome Assessments											
IBDQ		X				X	X				
EQ-5D 5L		X				X	X				
SF-36		X				X	X				
WPAI:UC		X				X	X				
PGRC				X	X	X	X				

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; CXR = chest x-ray; 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; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; IBDQ = Inflammatory Bowel Disease Questionnaire; IP = investigational product; LV = last visit; 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); RB = rectal bleeding; SF = stool frequency; 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.

- a Visit 2 (Week 2) is a telephone visit. These assessments will be made by a telephone call to the patient.
- b ETV may occur on any day without regard to visit interval.
- c Additional study procedures can be performed at an unscheduled visit at the discretion of the investigator.
- d This test will be performed on a sub-set of study patients, as described in the Notes column of the applicable row.
- e These tests will be run from the “chemistry” sample.
- f *Clostridium difficile* tests at V5 and ETV may be performed for patients who do not move into Study AMBG.
- g *Clostridium difficile* test at UV may be performed if visit is due to worsening SF and/or RB.

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-AMAN (AMAN) is a Phase 3 clinical trial that is designed to evaluate the safety and efficacy of mirikizumab in inducing remission at Week 12 in patients with moderately to severely active ulcerative colitis (UC). The study population includes patients with moderately to severely active UC who have an inadequate response to, loss of response to, or are intolerant to conventional therapy for UC (defined as corticosteroids, azathioprine [AZA] or 6-mercaptopurine [6-MP] for this study; “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 in 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, 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 AZA and 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 medications, and as a first-line treatment for UC in selected patients. However, in the pivotal ACT1 and ACT2 studies of infliximab therapy in patients with moderately to severely active UC and in the pivotal PURSUIT studies of golimumab in the same patient population, only approximately 50% to 65% of the patients achieved clinical response (as defined by complete Mayo score) at the induction time point (Weeks 6 to 8), with approximately 50% of the patients maintaining clinical response to Week 54 (Rutgeerts et al. 2005; Sandborn et al. 2014a, 2014b). In the pivotal ULTRA studies of adalimumab in the same patient population, 16.5% of patients achieved clinical remission at Week 8 (Sandborn et al. 2012a). Similarly, in the pivotal GEMINI 1 study of vedolizumab in patients with moderately to severely active disease, 47% achieved a clinical response at Week 6 and up to 45% of these patients were in clinical remission at Week 52 (Feagan et al. 2013). These data illustrate the unmet need for new medications in UC.

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

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

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

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

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

3.2.4. Preclinical and Clinical Studies of Mirikizumab

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

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

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

Study 16T-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, 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. 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 $\geq 90\%$ improvement in PASI ("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) IV at Weeks 0, 4 and 8. Exposure-based dose adjustments was applied in two 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 of Study AMAC 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 Interleukin-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 AMAN 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 every 4 weeks (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 (CD) 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 AMAN were chosen based on nonclinical safety data and based on analyses of safety, efficacy, and pharmacokinetic (PK) data from the primary analysis of Study AMAC (Section 5.7).

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 AMAN.2 shows the objectives and endpoints of the study.

Table AMAN.2. Objectives and Endpoints

Objectives	Endpoints
Primary^a	
<ul style="list-style-type: none"> To test the hypothesis that mirikizumab is superior to placebo in inducing clinical remission at Week 12 in patients with moderately to severely active ulcerative colitis (UC) 	<ul style="list-style-type: none"> The proportion of patients in clinical remission at Week 12. Clinical remission is based on the modified Mayo score (MMS) and is defined as: <ul style="list-style-type: none"> Stool frequency (SF) subscore = 0, or SF = 1 with a ≥ 1-point decrease from baseline, and Rectal bleeding (RB) subscore = 0, and Endoscopic subscore (ES) = 0 or 1 (excluding friability)
Major Secondary^a	
<ul style="list-style-type: none"> To evaluate the efficacy of treatment with mirikizumab compared to placebo in inducing a clinical response at Week 12 	<ul style="list-style-type: none"> The proportion of patients in clinical response at Week 12. Clinical response is based on the MMS and is defined as: <ul style="list-style-type: none"> A decrease in the MMS of ≥ 2 points and $\geq 30\%$ decrease from baseline, and A decrease of ≥ 1 point in the RB subscore from baseline or a RB score of 0 or 1
<ul style="list-style-type: none"> To evaluate the efficacy of treatment with mirikizumab compared to placebo in inducing endoscopic remission at Week 12 	<ul style="list-style-type: none"> The proportion of patients with endoscopic remission at Week 12, defined as: <ul style="list-style-type: none"> ES = 0 or 1 (excluding friability)
<ul style="list-style-type: none"> To evaluate the efficacy of treatment with mirikizumab compared to placebo in inducing symptomatic remission at Week 4 	<ul style="list-style-type: none"> The proportion of patients in symptomatic remission at Week 4, defined as: <ul style="list-style-type: none"> SF = 0, or SF = 1 with a ≥ 1-point decrease from baseline, and RB = 0
<ul style="list-style-type: none"> To evaluate the efficacy of treatment with mirikizumab compared to placebo in inducing symptomatic remission at Week 12 	<ul style="list-style-type: none"> The proportion of patients in symptomatic remission at Week 12, defined as: <ul style="list-style-type: none"> SF = 0, or SF = 1 with a ≥ 1-point decrease from baseline and RB = 0
<ul style="list-style-type: none"> To evaluate the efficacy of treatment with mirikizumab compared to placebo in inducing clinical response in the biologic-failed population at Week 12 	<ul style="list-style-type: none"> The proportion of patients in the biologic-failed population in clinical response at Week 12. Clinical response is based on the MMS and is defined as: <ul style="list-style-type: none"> A decrease in the MMS of ≥ 2 points and $\geq 30\%$ decrease from baseline, and A decrease of ≥ 1 point in the RB subscore from baseline or a RB score of 0 or 1
<ul style="list-style-type: none"> To evaluate the efficacy of treatment with mirikizumab compared to placebo in inducing bowel movement urgency improvement at Week 12 in patients with bowel urgency symptoms at baseline 	<ul style="list-style-type: none"> The proportion of patients with bowel movement urgency improvement at Week 12 as defined in the study statistical analysis plan (SAP)

Objectives	Endpoints
Other Secondary	
<ul style="list-style-type: none"> To evaluate the numerical value and change from baseline of individual MMS subscores of SF, RB, and ES at various times during the 12-week induction, in patients receiving mirikizumab compared with patients receiving placebo 	<ul style="list-style-type: none"> The numerical value and change from baseline in each of the following items: <ul style="list-style-type: none"> SF (Weeks 2, 4, 6, 8, and 12) RB (Weeks 2, 4, 6, 8, and 12) The composite clinical endpoint of the sum of the SF and RB subscores (Weeks 2, 4, 6, 8, and 12) ES (Week 12)
<ul style="list-style-type: none"> To evaluate the efficacy of mirikizumab compared to placebo on achieving an endoscopic subscore of 0 at Week 12 	<ul style="list-style-type: none"> The proportion of patients achieving an endoscopic subscore of 0 at Week 12
<ul style="list-style-type: none"> To evaluate the efficacy of treatment with mirikizumab compared to placebo in inducing an endoscopic response at Week 12 	<ul style="list-style-type: none"> The proportion of patients in endoscopic response at Week 12, defined as: <ul style="list-style-type: none"> A decrease in the ES of ≥ 1 point compared to baseline
<ul style="list-style-type: none"> To evaluate the efficacy of treatment with mirikizumab compared to placebo in inducing symptomatic response at Weeks 2, 4, 6, 8, and 12 	<ul style="list-style-type: none"> The proportion of patients achieving symptomatic response, defined as: <ul style="list-style-type: none"> $\geq 30\%$ decrease from baseline in the composite clinical endpoint of the sum of SF and RB subscores at Weeks 2, 4, 6, 8, and 12
<ul style="list-style-type: none"> To evaluate the efficacy of treatment with mirikizumab compared to placebo in inducing symptomatic remission at Weeks 2, 6, and 8 	<ul style="list-style-type: none"> The proportion of patients achieving symptomatic remission at Weeks 2, 6, and 8, defined as: <ul style="list-style-type: none"> SF = 0, or SF = 1 with a ≥ 1-point decrease from baseline, and RB = 0
<ul style="list-style-type: none"> To evaluate the efficacy of treatment with mirikizumab compared to placebo in achieving the SF component of clinical remission definition at Weeks 2, 6, and 8 	<ul style="list-style-type: none"> The proportion of patients achieving the following at Weeks 2, 6, and 8: <ul style="list-style-type: none"> SF = 0, or SF = 1 with a ≥ 1-point decrease from baseline
<ul style="list-style-type: none"> To evaluate the efficacy of treatment with mirikizumab compared to placebo in achieving the RB component of clinical remission at Weeks 2, 6, and 8 	<ul style="list-style-type: none"> The proportion of patients achieving the following at Weeks 2, 6, and 8: <ul style="list-style-type: none"> RB = 0
<ul style="list-style-type: none"> To evaluate histologic remission between mirikizumab and placebo at Week 12 	<ul style="list-style-type: none"> Proportion of patients in histologic remission, as defined in the SAP
<ul style="list-style-type: none"> To evaluate the time to symptomatic response 	<ul style="list-style-type: none"> Time to symptomatic response, defined as at least a 30% decrease from baseline in the composite clinical endpoint of the sum of SF and RB subscores
<ul style="list-style-type: none"> To evaluate the time to symptomatic remission 	<ul style="list-style-type: none"> Time to symptomatic remission, defined as SF = 0, or SF = 1 with a ≥ 1-point decrease from baseline, and RB = 0

Objectives	Endpoints
Other Secondary (continued)	
<ul style="list-style-type: none"> To evaluate the primary and major secondary objectives in the subgroup of patients who were on UC concomitant therapy at enrollment 	<ul style="list-style-type: none"> Primary and major secondary endpoints in the subgroup of patients who were on concomitant UC therapy at enrollment (that is, receiving corticosteroids only at baseline, receiving immunomodulators only at baseline, receiving both corticosteroids and immunomodulators at baseline, and not receiving either at baseline)
<ul style="list-style-type: none"> To evaluate the primary and major secondary objectives in the conventional-failed and biologic-failed subgroups of patients 	<ul style="list-style-type: none"> Primary and major secondary endpoints in the conventional-failed and biologic-failed subgroup of patients. Please note that clinical response in the biologic-failed population is a major secondary endpoint and will not be re-tested here.
<ul style="list-style-type: none"> To evaluate the efficacy of treatment with mirikizumab compared to placebo in improving abdominal pain at Week 12 	<ul style="list-style-type: none"> The proportion of patients with a NRS pain score ≥ 3 at baseline who achieve an improvement of $\geq 30\%$ from baseline in 7-day average abdominal pain NRS score at Week 12
<ul style="list-style-type: none"> To evaluate the effect of mirikizumab compared to placebo on changes in health outcome endpoints at Week 12 	<ul style="list-style-type: none"> Change from baseline in: <ul style="list-style-type: none"> Inflammatory Bowel Disease Questionnaire (IBDQ) score at Week 12 European Quality of Life 5 Dimensions 5 Level (EQ-5D 5L) index at Week 12 Work Productivity and Activity Impairment Questionnaire Ulcerative Colitis (WPAI:UC) score at Week 12 Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), Version 2 physical and mental component and domain scores at Week 12
<ul style="list-style-type: none"> To evaluate the effect of mirikizumab compared to placebo on changes in inflammatory biomarkers 	<ul style="list-style-type: none"> Change from baseline in biomarkers such as: <ul style="list-style-type: none"> C-reactive protein Fecal calprotectin (at Weeks 4 and 12)
<ul style="list-style-type: none"> To evaluate the pharmacokinetic and pharmacokinetic/pharmacodynamic relationships of mirikizumab 	<ul style="list-style-type: none"> Clearance and volume of distribution of mirikizumab Relationship between LY3074828 exposure and efficacy
<ul style="list-style-type: none"> To evaluate the potential development of anti-mirikizumab antibodies and their potential relationship with efficacy, safety and mirikizumab exposure 	<ul style="list-style-type: none"> Relationship between treatment emergent anti-drug antibodies (TEADA) and efficacy Relationship between TEADA and safety Relationship between TEADA and mirikizumab pharmacokinetics.
<ul style="list-style-type: none"> To evaluate the efficacy of mirikizumab compared to placebo in Ulcerative Colitis Endoscopic Index of Severity (UCEIS) endoscopic remission at Week 12 	<ul style="list-style-type: none"> The proportion of patients with a UCEIS score of ≤ 1 at Week 12.

Objectives	Endpoints
<ul style="list-style-type: none"> • To evaluate the efficacy of mirikizumab compared to placebo in mucosal healing at Week 12 	<ul style="list-style-type: none"> • The proportion of patients with mucosal healing at Week 12, defined as achieving both: <ul style="list-style-type: none"> ○ Histologic remission, as described in the SAP, and ○ Endoscopic remission, defined as ES = 0 or 1 (excluding friability)
<ul style="list-style-type: none"> • To evaluate the efficacy of mirikizumab compared to placebo on changes in fatigue at Week 12 	<ul style="list-style-type: none"> • Change from baseline in Fatigue NRS scores at Week 12

- ^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 0.00125. 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.

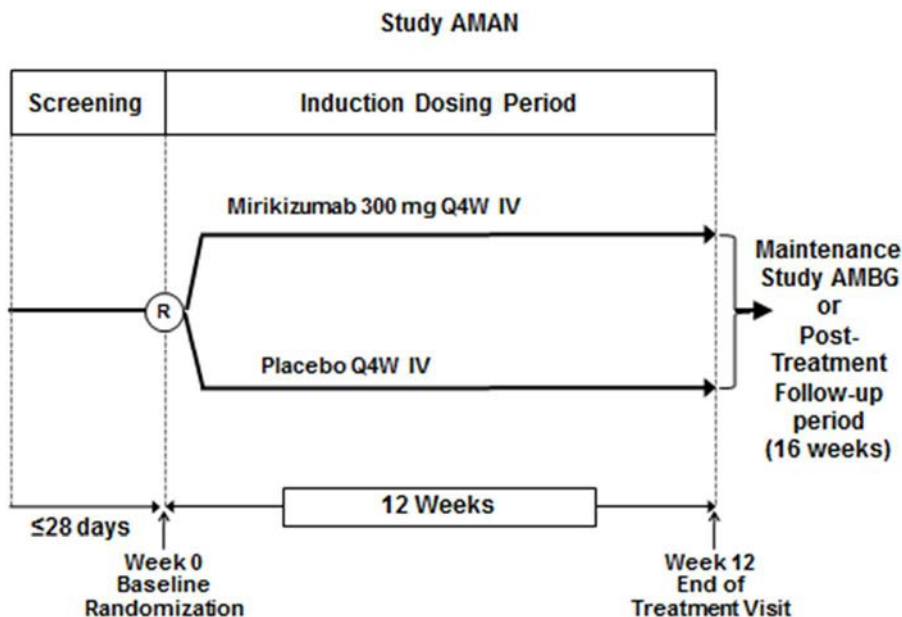
5. Study Design

5.1. Overall Design

Study AMAN is a multicenter, randomized, double-blind, parallel-arm, placebo-controlled study designed to evaluate the safety and efficacy of mirikizumab, compared with placebo, over a 12-week induction period. The study population includes patients with moderately to severely active UC who have an inadequate response to, loss of response to, or are intolerant to corticosteroid or immunomodulator therapy for UC (termed “conventional-failed” in this protocol), and those who have an inadequate response to, loss of response to, or are intolerant to biologic therapy for UC (termed “biologic-failed” in this protocol). Complete definitions of the “conventional-failed” and “biologic-failed” terms are given in Section 6.1, Inclusion Criterion [8]. Patients will be randomized with a 3:1 ratio allocation across the 2 treatment groups: 300 mg mirikizumab and placebo IV Q4W.

Patients who complete Study AMAN through Week 12 will either complete post-treatment follow-up within Study AMAN or be eligible to participate in the maintenance Study AMBG. Patients who discontinue treatment prior to the Week 12 assessment, or those who are unable or are not willing to participate in the maintenance Study AMBG will complete post-treatment follow-up 16 weeks after their last visit. [Figure AMAN.1](#) illustrates the study design.

Study governance considerations are described in detail in [Appendix 3](#).



Abbreviations: IV = intravenous; R = randomization.

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

5.2. Number of Participants

Approximately 2230 patients will be screened to achieve approximately 1160 randomized patients.

5.3. Definition of Baseline

Visit 1 (Week 0) is the baseline randomization visit. The baseline modified Mayo score is calculated from valid daily diary entries obtained prior to endoscopy during the screening period and the endoscopic appearance of the mucosa at this screening endoscopy (Section 9.1.1.2). For other efficacy, health outcome and safety assessments, baseline is defined as the last non-missing assessment recorded on or prior to the date of Visit 1 (Week 0).

5.4. Definition of Enrollment

A patient is considered enrolled in the study once the patient is randomized and assigned to treatment.

5.5. End of Study Definition

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

5.6. 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: This 12-week induction study, including both conventional-failed and biologic-failed patients.
- Study I6T-MC-AMBG (AMBG): A maintenance study with a 40-week treatment duration.
- Study I6T-MC-AMAP (AMAP): A long-term extension study.

Study AMAN is designed to evaluate the safety and efficacy of mirikizumab in inducing clinical remission at Week 12 of treatment. Nonbiologic background therapy (for example, 5-ASA, corticosteroids, AZA or 6-MP) is allowed in Study AMAN, subject to concomitant medication and dose stabilization criteria. The use of a placebo comparator is justified in this study, as mirikizumab can be added to pre-existing background therapy (EMA/CHMP [WWW]; FDA 2001 [WWW]).

The timing of the primary endpoint was based on characterization of the safety and efficacy of mirikizumab at Week 12 of continuous treatment in Study AMAC, the Phase 2, placebo-controlled, double-blind clinical trial of mirikizumab in moderately to severely active UC.

As detailed in Section 10, the study is powered to the primary endpoint of demonstrating a statistically significant difference in clinical remission between mirikizumab therapy and placebo at Week 12. The 3:1 randomization scheme to 300 mg mirikizumab or placebo arms IV Q4W is designed to maximize the chance that a patient will receive mirikizumab in this study (3:1 chance).

Patients who complete Study AMAN through Week 12 will either complete post-treatment follow-up within Study AMAN or be eligible to participate in the maintenance Study AMBG. There is no rescue arm in Study AMAN. However, patients who complete Study AMAN through Week 12 (with an acceptable safety profile) who did not achieve a clinical response to mirikizumab at Week 12 may be eligible to receive an induction dose of mirikizumab in Study AMBG. Patients who complete Study AMBG through Week 40 (with an acceptable safety profile) may be eligible to participate in the long-term extension Study AMAP.

5.7. Justification for Dose

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

Safety Considerations

The safety data collected in completed and ongoing clinical studies and in nonclinical toxicology studies support the proposed dose regimen. In particular, there were no dose-related safety or

tolerability issues observed in Study AMAC in ulcerative colitis subjects for a period of up to 92 weeks with doses up to 200 mg SC Q4W .

Single intravenous (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 CD, 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 CD (Study AMAG) has not revealed a safety concern that differs from the safety findings noted above 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 for the 300 mg Q4W (IV) 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.

Considerations of Efficacy and Exposure–Response Relationship

Significant efficacy relative to placebo was observed at Week 12 in the 50 mg and 200 mg IV Q4W cohorts in the Phase 2 study AMAC. 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 at Week 12 indicated that doses below 300 mg may lead to decreased efficacy, while doses above 300 mg 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 supports the selection of 300 mg IV Q4W for this study.

6. Study Population

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

6.1. Inclusion Criteria

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

Informed Consent

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

Patient Characteristics

- [2.] are male or female patients ≥ 18 and ≤ 80 years of age at the time of initial screening.

- [2a.] male patients:

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

- [2b.] female patients:

women of childbearing potential:

- A. must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to exposure.

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. two effective methods of contraception (such as male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges) will be used. The subject may choose to use a double barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide. It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable because of 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) level >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.
- [3.] venous access sufficient to allow blood sampling and IV administration as per the protocol.

Disease-Specific Inclusion Criteria

- [4.] have had an established diagnosis of UC of ≥ 3 months in duration before baseline (Week 0), which includes endoscopic evidence of UC and a histopathology report that supports a diagnosis of UC (see Section 9.1.1.3). Supportive endoscopy and histopathology reports must be available in the source documents. Patients with rectal sparing on baseline endoscopy must have documentation of rectal involvement on a prior endoscopy and histopathology report to confirm UC diagnosis.

- [5.] have moderately to severely active UC as defined by a modified Mayo score (MMS) of 4 to 9 with an endoscopic subscore (ES) ≥ 2 , with endoscopy performed within 14 days before baseline.
- [6.] have evidence of UC extending beyond the rectum (more proximal to the rectosigmoid junction). The rectosigmoid junction lies approximately 10 to 15 cm from the anal margin.
- [7.] have documentation of:
 - [7a.] 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

- [7b.] in patients for whom Inclusion Criterion [7a] does not apply, up-to-date colorectal cancer surveillance (performed according to local standard).

At the discretion of the investigator, a colonoscopy (instead of a flexible sigmoidoscopy) can be performed as the screening endoscopy for this study. Patients who do not have a colonoscopy report available in source documentation will have a colonoscopy at screening.

Prior Medication Failure Criteria

- [8.] patients must have an inadequate response to, loss of response to, or intolerance to at least 1 of the medications described in Inclusion Criteria [8a] OR [8b].

Documentation of dose, frequency, route of administration and duration of the prior failed treatment is required.

- [8a.] **Conventional-failed patients:** Patients who have an inadequate response to, loss of response to, or are intolerant to at least one of the following medications:
 - corticosteroids
 - corticosteroid-refractory colitis, defined as signs and/or symptoms of active UC despite oral prednisone (or equivalent oral corticosteroid excluding budesonide MMX and beclomethasone dipropionate gastro-resistant prolonged-release tablet) at doses of at least 30 mg/day for a minimum of 2 weeks; or
 - corticosteroid-dependent colitis, defined as:
 - a. an inability to reduce corticosteroids below the equivalent of prednisone 10 mg/day within 3 months of starting corticosteroids without a return of signs and/or symptoms of active UC; or

- b. a relapse within 3 months of completing a course of corticosteroids; or
 - history of intolerance of corticosteroids (including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, or neuropsychiatric side-effects, including insomnia, associated with corticosteroid treatment).
- immunomodulators:
 - signs and/or symptoms of persistently active disease despite at least 3 months' treatment with one of the following:
 - oral AZA (≥ 1.5 mg/kg/day) or 6-MP (≥ 0.75 mg/kg/day), or
 - oral AZA or 6-MP within a therapeutic range as judged by thioguanine metabolite testing, or
 - a combination of a thiopurine and allopurinol within a therapeutic range as judged by thioguanine metabolite testing
 - history of intolerance to at least 1 immunomodulator (including but not limited to nausea/vomiting, abdominal pain, pancreatitis, liver function test abnormalities, and lymphopenia)

AND

- have neither failed nor demonstrated an intolerance to a biologic medication (anti-TNF antibody or anti-integrin antibody) that is indicated for the treatment of UC

[8b.] **Biologic-failed patients:** Patients who have an inadequate response to, loss of response to, or are intolerant to biologic therapy for UC (such as anti-TNF antibodies or anti-integrin antibodies) or to janus kinase (JAK) inhibitors (such as tofacitinib). The medication used to qualify the patient for entry into this category must be approved for the treatment of UC.

Investigators must be able to document an adequate clinical trial of the medication. Patients should fulfill 1 of the following criteria:

- Inadequate response: Signs and symptoms of persistently active disease despite induction treatment at the approved induction dosing that was indicated in the product label, or
- Loss of response: Recurrence of signs and symptoms of active disease during approved maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify as having failed or being intolerant to UC biologic therapy), or
- Intolerance: History of intolerance to infliximab, adalimumab, golimumab, vedolizumab, tofacitinib or other approved biologics or JAK inhibitors (including but not limited to infusion-related event, demyelination, congestive heart failure, or any other drug-related AE that led to a reduction in dose or discontinuation of the medication).

Patients previously exposed to biologic therapy who do not meet Inclusion Criterion [8b] must still meet Inclusion Criterion [8a] in order to be eligible to participate in the study.

Patients previously exposed to investigational therapies for the treatment of UC must still meet Inclusion Criteria [8a] OR [8b].

Patients who meet both Inclusion Criteria [8a] and [8b] will be considered to be “biologic-failed”, for the purpose of this study.

UC Medication Dose Stabilization Criteria

[9.] stable doses of the following drugs are permitted (see [Appendix 10](#)):

[9a.] oral 5-ASA therapy: if the prescribed dose has been stable for at least 2 weeks prior to the screening endoscopy.

[9b.] oral corticosteroid therapy (prednisone ≤ 20 mg/day or equivalent, or budesonide extended release tablets 9 mg/day [budesonide MMX]); if the prescribed dose has been stable for at least 2 weeks before the screening endoscopy

[9c.] AZA, 6-MP, and methotrexate: if these immunomodulators have been prescribed at a stable dose for at least 8 weeks before the screening endoscopy.

Study Procedure Inclusion Criteria

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

[11.] have clinically acceptable central laboratory test results at screening (retesting is allowed for hematology and chemistry), including:

[11a.] hematology: absolute neutrophil count ≥ 1.5 times (\times) $10^9/L$ ($\geq 1.5 \times 10^3/\mu L$ or ≥ 1.5 GI/L), platelet count $\geq 100 \times 10^9/L$ ($\geq 100 \times 10^3/\mu L$ or ≥ 100 GI/L), hemoglobin ≥ 8.5 g/dL (≥ 85 g/L) for males and > 8.0 g/dL (> 80 g/L) for females, lymphocyte count ≥ 500 cells/ μL ($> 0.50 \times 10^3/\mu L$ or > 0.50 GI/L), and total white blood cell count $\geq 3.0 \times 10^9/L$ ($\geq 3.0 \times 10^3/\mu L$ or ≥ 3.0 GI/L)

[11b.] chemistry:

- serum creatinine $\leq 2 \times$ upper limit of normal (ULN).
- total bilirubin level (TBL) $\leq 1.5 \times$ ULN.
- alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 2 \times$ ULN.
- alkaline phosphatase (ALP) $\leq 1.5 \times$ ULN.
- patients with an established diagnosis of Gilbert’s syndrome (requires source documentation showing unconjugated hyperbilirubinemia, with no evidence of hemolysis) can be included with bilirubin levels $\leq 3 \times$ ULN.

6.2. Exclusion Criteria

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

Gastrointestinal Exclusion Criteria:

- [12.] have a current diagnosis of Crohn's disease, inflammatory bowel disease-unclassified (IBD-U) (formerly known as indeterminate colitis), or UC proctitis (disease limited to the rectum, that is, distal to the recto-sigmoid junction, which lies approximately 10-15 cm from anal margin).
- [13.] have an inherited immunodeficiency syndrome or a known monogenic cause of UC-like colonic inflammation.
- [14.] previous bowel resection or intestinal or intra-abdominal surgery:
 - have had extensive colonic surgery for UC or for other reasons (for example, subtotal colectomy), or are likely to require surgery for the treatment of UC during the study. Patients who have had limited colonic surgery (for example, segmental colonic resection) may be allowed in the study, if this does not affect the assessment of efficacy. Discussion with the sponsor should occur prior to screening of such patients.
 - have had any small bowel or colonic surgery within 6 months prior to baseline.
 - have had any nonintestinal intra-abdominal surgery within 3 months of baseline.
- [15.] have evidence of toxic megacolon, intra-abdominal abscess, or stricture/stenosis within the small bowel or colon.

Adenoma, Dysplasia, and Gastrointestinal Cancer Exclusion Criteria:

- [16.] any history or current evidence of cancer of the gastrointestinal tract.
- [17.] any current sporadic adenoma without dysplasia (adenomatous polyps occurring proximal to known areas of colitis) that has not been removed. Once completely removed, the patient is eligible for study.
- [18.] dysplasia occurring in flat mucosa, sporadic adenomas containing dysplasia, and dysplasia-associated lesions or masses (DALMs) will be managed as follows:
 - [18a.] any history or current evidence of high-grade dysplasia is exclusionary.
 - [18b.] any history or current evidence of dysplasia occurring in flat mucosa is exclusionary. This includes histopathology reporting "indefinite for dysplasia," low-grade dysplasia, and high-grade dysplasia.
 - [18c.] any history or current evidence of a nonadenoma-like DALM, with or without evidence of dysplasia, is exclusionary.

[18d.] any current sporadic adenoma containing dysplasia or any current adenoma-like DALM that has not been removed is exclusionary. Once completely removed the patient is eligible for the study.

Criteria for Prohibited Medications

- [19.] have received any of the following for treatment of UC within the time frames specified below:
- [19a.] corticosteroid enemas, corticosteroid suppositories, oral budesonide standard formulation, or a course of IV corticosteroids within 2 weeks prior to screening endoscopy.
- [19b.] 5-ASA enemas or 5-ASA suppositories within 2 weeks prior to screening endoscopy.
- [19c.] immunomodulatory medications, including oral cyclosporine, IV cyclosporine, tacrolimus, mycophenolate mofetil, thalidomide or Janus kinase inhibitors (for example, tofacitinib) within 4 weeks prior to the screening endoscopy.
- AZA, 6-MP, and methotrexate are allowed (see Inclusion Criterion [9b]).
 - other immunomodulatory medications should be discussed with the sponsor prior to screening.
- [19d.] anti-TNF antibodies (for example, infliximab, adalimumab, or golimumab) within 8 weeks prior to screening endoscopy.
- [19e.] anti-integrin antibodies (for example, vedolizumab) within 8 weeks prior to screening endoscopy.
- [19f.] agents that deplete B or T cells (for example, rituximab, alemtuzumab, or visilizumab) within 12 months of baseline. Patients remain excluded if there is evidence of persistent targeted lymphocyte depletion at the time of screening endoscopy.
- [19g.] any investigational nonbiologic therapy within 4 weeks prior to the screening endoscopy or within 5 half-lives prior to the screening endoscopy, whichever is longer.
- [19h.] any investigational biologic therapy within 8 weeks prior to the screening endoscopy or within 5 half-lives prior to the screening endoscopy, whichever is longer.
- [19i.] leukocyte apheresis (leukapheresis, for example, Adacolumn) within 3 weeks prior to screening endoscopy.
- [19j.] interferon therapy within 8 weeks prior to screening endoscopy.

- [20.] have ever received anti-IL12p40 antibodies (for example, ustekinumab [Stelara®]) or anti-IL-23p19 antibodies (for example, risankizumab [BI-655066], brazikumab [MEDI-2070], guselkumab [CNTO1959], or tildrakizumab [MK-3222]) for any indication, including investigational use.
- [21.] have failed 3 or more biologic therapies for UC.

Infectious Disease Exclusion Criteria:

- [22.] patients who:
- [22a.] have evidence of active tuberculosis (TB), or
 - [22b.] have a past history of active TB, regardless of treatment, or
 - [22c.] are diagnosed with latent tuberculosis infection (LTBI) at screening.

Patients diagnosed with LTBI at screening may be allowed to re-screen for the study, provided they fulfil the criteria described in Section 9.4.5.3. Patients who have a documented history of completing an appropriate TB prophylaxis regimen with no history of risk of reexposure since their treatments were completed and no evidence of active TB are eligible to participate in the study.

- [23.] have received a Bacillus Calmette-Guerin (BCG) vaccination within 12 months or received live attenuated vaccine(s) within 3 months of baseline or intend to receive such during the study.
- [24.] have human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) or test positive for HIV antibodies at screening.
- [25.] have acute or chronic hepatitis B infection; or test positive for hepatitis B virus (HBV) at screening, which is defined as:
- [25a.] positive for hepatitis B surface antigen (HBsAg+)
- OR**
- [25b.] negative for hepatitis B surface antigen (HBsAg-) and positive for anti-hepatitis B core antibody (anti-HBc+) in conjunction with detectable HBV DNA (see Section 9.4.5.4).
- OR**
- [25c.] detectable HBV DNA (see Section 9.4.5.4).
- [26.] have current hepatitis C infection; or test positive for hepatitis C virus (HCV) at screening, defined as:
- positive for hepatitis C antibody and detectable HCV RNA (see Section 9.4.5.5).

- [27.] had *Clostridium difficile* or other intestinal infection within 30 days of screening endoscopy, or test positive at screening for *C. difficile* or for other intestinal pathogens. Patients with a confirmed diagnosis of cytomegalovirus-associated colitis should have adequate treatment and resolution of symptoms at least 3 months prior to screening endoscopy.
- [28.] patients with serious, opportunistic or chronic/recurring extraintestinal infections should be adequately treated and off antibiotics for 30 days without recurrence of symptoms prior to screening, including but not limited to the following:
- [28a.] infections requiring IV antibiotics.
 - [28b.] infections requiring hospitalization.
 - [28c.] infections that are considered “opportunistic” (examples are listed in [Appendix 8](#))
 - [28d.] chronic, recurrent infections (e.g. osteomyelitis, recurring cellulitis).

Patients with an opportunistic infection or chronic, recurrent infection (within the last 60 days) should be discussed on a case-by-case basis with the medical monitor.

- [29.] Patients with nonserious extraintestinal infections not adequately treated prior to screening.
- [30.] have evidence of active/infectious herpes zoster infection ≤ 8 weeks prior to screening. Herpes zoster infections remain active until all vesicles are crusted over.

General Exclusion Criteria:

- [31.] have had lymphoma, leukemia, or any malignancy within the past 10 years. Exceptions: the following conditions are not exclusionary: a) basal cell or squamous epithelial carcinoma of the skin that has been adequately treated with no evidence of metastatic disease for 1 year, or b) cervical carcinoma in situ that has been adequately treated with no evidence of recurrence within the 3 years prior to baseline.
- [32.] are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
- [33.] are Lilly employees or employees of third-party organizations involved with the study.
- [34.] 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.
- [35.] have previously completed or discontinued from this study or any other study investigating mirikizumab. This criterion does not apply to patients undergoing rescreening procedures.

- [36.] have had extra-abdominal surgery and have not recovered fully following surgery, including complete wound healing, before screening.
- [37.] 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 during the screening period prior to dosing at Visit 1;

OR

marked yes to C-SSRS suicide behaviors questions during the screening period prior to dosing at Visit 1;

AND

the ideation or behavior occurred within the past month.

- [38.] have an unstable or uncontrolled illness, including but not limited to cerebrocardiovascular, respiratory, gastrointestinal (excluding UC), hepatic, renal, endocrine, hematologic, or neurological disorders that would potentially affect patient safety within the study or confound efficacy assessment. Patients requiring systemic corticosteroids for non-UC conditions (except corticosteroids to treat adrenal insufficiency) are excluded.
- [39.] have a known hypersensitivity to any component of this investigational product.
- [40.] have a solid organ transplant or hematopoietic stem cell transplantation.
- [41.] 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 AMAN, or unable to complete other study procedures.
- [42.] are unsuitable for inclusion in the study in the opinion of the investigator or sponsor for any reason that may compromise the subject’s safety or confound data interpretation.
- [43.] unable to complete study procedures.
- [44.] are pregnant, breastfeeding, or planning pregnancy (women only) while enrolled in the study, or within 20 weeks after receiving the last dose of study agent.
- [45.] current or history of alcohol dependence and/or drug abuse within the last year.

6.2.1. Rationale for Exclusion of Certain Study Candidates

Both male and female patients are allowed to participate in this study. Patients will not be excluded on the basis of gender.

Patients aged between 18 and 80 years of age at screening will be included in this study. Patients >80 years of age at screening will not be allowed in the study for the following reasons. Elderly patients are at increased risk of ischemic colitis and segmental colitis associated with diverticula,

which may confound efficacy assessment. Elderly patients are also at increased risk of hospitalization and poorer outcomes following hospitalization for UC, which include an increased risk of venous thromboembolism and mortality. Elderly patients who require surgery for UC also have increased rates of postoperative complications and increased length of hospital stay compared with younger patients (Ananthakrishnan and Binion 2009). These factors may increase the risk to patients >80 years of age in participating in a clinical trial of an investigational product.

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. In order to participate in the study, patients must agree to the contraception, reproduction, and breastfeeding criteria detailed in Inclusion Criterion [2] and Exclusion Criterion [44].

6.4. Screen Failures

Patients who have failed screening because of the following Inclusion/Exclusion Criteria may be rescreened when the reason for screen failure has resolved: [4] to [11], [14], [17 (once polyps are removed)], [18d (once all of the following have been removed: sporadic adenoma[s] containing dysplasia, or adenoma like-DALM[s] containing an area diagnosed as “indefinite for dysplasia” or low grade dysplasia)], [19], [22c (if treated for latent tuberculosis infection [LTBI] for at least 4 weeks and compliant with LTBI therapy while on study, see Section 9.4.5.3)], [23], [28] to [31], [34], [36], [38], and [44] to [45]. Individuals may be rescreened up to 2 times, for a maximum total of 3 screens. The interval between rescreenings should be at least 4 weeks, unless a shorter interval has been agreed with the study’s medical monitor. Each time rescreening is performed the individual must sign a new informed consent form (ICF) and will be assigned a new identification number.

Patients who have failed screening because of Exclusion Criterion [27] may be rescreened once when the reason for screen failure has resolved. It is recommended that the investigator confirms the patient has a negative stool for *C. difficile* stool culture/stool ova and parasites (as applicable) before performing additional rescreening investigations (see Section 9.4.5.7).

Patients who have failed screening because of the following Exclusion Criteria may not be rescreened: [12], [13], [15], [16], [18a] to [18c], [20], [21], [22a and 22b (if current or past history of active TB)], [24] to [26], [32], [33], [35], [37], and [39] to [43].

Retesting of screening investigations (without a requirement for screen failure and rescreening) is allowed at the discretion of the medical monitor. The screening investigations specified below may be retested once at the discretion of the investigator.

- **Screening hematology and chemistry blood tests:** where 1 or more results are outside the acceptable range for inclusion in the study but may be within the acceptable range for inclusion on retesting, due to test-retest variability.
- **Stool testing:** if there is a technical difficulty in performing or reporting the *C. difficile* or stool culture assays.

- **Retesting or confirmatory testing with an interferon- γ release assay (IGRA):** for example, QuantiFERON[®]-TB Gold or T-SPOT[®] assay) in selected patients as part of screening for LTBI (see Section [9.4.5.3](#) for details).
- **Endoscopy:** where the endoscopist is unable to adequately visualize the mucosa (e.g. due to poor bowel preparation, technical issues with equipment) or where the central reader is unable to determine the centrally read Mayo ES (e.g. failure of the recording equipment).

Retesting of all other screening investigations should be discussed with the medical monitor prior to retesting.

7. Treatments

7.1. Treatments Administered

This study involves a comparison of IV administration of mirikizumab versus placebo during a 12-week induction period. [Table AMAN.3](#) shows the treatment regimens.

Table AMAN.3. Treatment Regimens

Treatment Group	Description
Induction Period	
Mirikizumab Dose Arm 1	300 mg given as an intravenous infusion (Weeks 0, 4, 8)
Control	Placebo given as an intravenous infusion (Weeks, 0, 4, 8)

Intravenous infusion of mirikizumab or placebo will occur over at least 30 minutes. All subjects should be monitored for 1 hour or longer after dosing, 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 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 a single-use solution vial containing mirikizumab or placebo with study-specific labels. The 15-mL vial of mirikizumab is manufactured to deliver 300 mg (20 mg/mL). Mirikizumab cannot be distinguished visually from placebo. Vials will be supplied

in cartons, with the appropriate quantity specific to the planned dispensing schedule of the investigational product.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized to double-blind treatment at Visit 1. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). To achieve between-group comparability, patients will be stratified to these arms based upon (a) biologic-failed status (yes/no) (see Inclusion Criterion [8b]), (b) baseline corticosteroid use (yes/no), (c) baseline disease activity (MMS: [4-6] or [7-9]), and (d) region (North America/Europe/Other); this stratification will be controlled by IWRS.

7.2.1. Selection and Timing of Doses

Patients will be assigned to treatment groups and are planned to receive their assigned treatment as outlined in Section 7.1. The actual time of all dose administrations will be recorded in the patient's electronic case report form (eCRF).

7.3. Blinding

This is a double-blind study. To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete. 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 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 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 study drug and must complete the early termination visit (ETV) and posttreatment follow-up as per protocol. 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.

7.4. Dosage Modification

Dose adjustments are not permitted in this study.

7.5. Preparation/Handling/Storage/Accountability

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

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

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

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 drug 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. Overall compliance with therapy is defined in the statistical analysis plan (SAP). If, in consultation with Lilly or its designee, the noncompliance is deemed to be significant or if further noncompliance occurs, the patient may be discontinued from the study.

7.7. Concomitant Therapy

All concomitant medications taken during the study must be recorded on the Concomitant Medication eCRF. All patients are encouraged to maintain their usual medication regimens for

concomitant conditions or diseases throughout the study unless those medications are specifically excluded ([Appendix 9](#)).

Patients taking permitted UC concomitant medications are to keep doses stable unless modifications are needed due to AEs and follow the instructions regarding dose stabilization as detailed in [Appendix 10](#). Use of such medications should not be withheld if, in the opinion of the investigator, failure to prescribe them would compromise patient safety. Patients who require a prohibited medication to treat their UC (see [Appendix 9](#)) need to be discontinued from study drug and complete an ETV and posttreatment follow-up visits.

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

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

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

7.8. Treatment after the End of the Study

7.8.1. Study Extensions

Patients who complete the 12-week treatment period, irrespective of clinical response status, may be eligible to participate in the maintenance study, Study AMBG, provided the eligibility criteria for Study AMBG are met.

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 infusions is not planned. Any premedication for infusions 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, and Infusion 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 site reactions.

Hypersensitivity Events

If a patient experiences a systemic hypersensitivity reaction involving the skin or mucous membranes, respiratory, cardiovascular, gastrointestinal or urinary systems, during or up to 6 hours after an infusion of study drug, the following guidance should be followed (see [Appendix 11](#) for additional information):

- Study drug infusion should be stopped immediately and appropriate supportive care provided according to local standard practice (for example, administration of epinephrine, anti-histamine, systemic steroids and/or bronchodilators).
- After patient's stabilization, an ADA and PK sample should be collected; additional samples should be obtained 4 and 12 to 16 weeks after the event. 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 $>38^{\circ}\text{C}$ (in the absence of other 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 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 to 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 investigator discretion, and considering the risk/benefit of readministration.
- 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 patients symptoms.

- Premedication prior to subsequent study drug administration may be considered as judged by the investigator to be 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 posttreatment follow-up visits.

The investigator will also complete any AE reporting and follow-up that may be required (if applicable, see Section 9.2).

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

Patient Decision

- The patient requests to discontinue investigational product.

Discontinuation due to a Hepatic Event or Liver Test Abnormality

- Patients who are discontinued from investigational product because of 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 1 of the following conditions after consultation with the Lilly designated medical monitor:

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

Safety Criteria for Study Drug Discontinuation

- The patient requires treatment for exacerbation of UC with medication(s) at doses higher than those specified in the “dose stabilization” inclusion criterion (for example, prednisone >20 mg/day; Inclusion Criterion [9]), or with prohibited medications specified in the “prohibited medications” exclusion criterion (for example, a course of IV corticosteroids, or a single dose of infliximab or IV cyclosporine; Exclusion Criterion [19]) (see also [Appendix 9](#)).
- 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 [9.4.5.4](#)).
- A diagnosis of hepatitis C during the study or development of detectable HCV RNA during the study (see Section [9.4.5.5](#)).
- The patient becomes pregnant. Pregnant patients **will not** undergo an endoscopy at the ETV.
- The patient experiences an AE or SAE that, in the opinion of the investigator or sponsor, would preclude him/her 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 suicidal 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 posttreatment 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 LTBI), see Exclusion Criteria [27] and [28].
- Patient requires major surgery (administration of the investigational product may be restarted only after adequate wound healing).
- Patient develops a confirmed absolute neutrophil count $<1 \times 10^9/L$ ($<1 \times 10^3/\mu L$ or <1 GI/L) (2 assessments below this threshold).
- Patient develops absolute lymphocyte count <500 cells/ μL ($<0.5 \times 10^3/\mu L$ or <0.50 GI/L). AZA, 6-MP or MTX must be discontinued, if applicable, for a confirmed absolute lymphocyte count $<0.5 \times 10^3/\mu L$ (2 assessments below this threshold). The hematology must be repeated in 2 weeks. If the absolute lymphocyte count remains $<0.5 \times 10^3/\mu L$, 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 $<0.5 \times 10^3/\mu L$, 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 $<0.5 \times 10^3/\mu L$, 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 should 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 identifies 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 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 are 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 AMAN.4. Endpoint Definitions

Endpoint	Definition
Clinical remission	<ul style="list-style-type: none"> Stool frequency (SF) subscore = 0, or SF = 1 with a ≥ 1-point decrease from baseline, and Rectal bleeding (RB) subscore = 0, and Endoscopic subscore (ES) = 0 or 1 (excluding friability)
Clinical response	<ul style="list-style-type: none"> A decrease in the modified Mayo score (MMS) of ≥ 2 points and $\geq 30\%$ decrease from baseline, and A decrease of ≥ 1 point in the RB subscore from baseline or a RB score of 0 or 1
Endoscopic remission	<ul style="list-style-type: none"> ES = 0 or 1 (excluding friability)
Endoscopic response	<ul style="list-style-type: none"> A decrease in the ES of ≥ 1 point compared to baseline
Symptomatic remission	<ul style="list-style-type: none"> SF = 0, or SF = 1 with a ≥ 1-point decrease from baseline, and RB = 0
Symptomatic response	<ul style="list-style-type: none"> $\geq 30\%$ decrease from baseline in the composite clinical endpoint of the sum of SF and RB subscores
Histologic remission	<ul style="list-style-type: none"> This definition will be specified in the statistical analysis plan (SAP)
Mucosal healing	<ul style="list-style-type: none"> Histologic remission as described in the SAP, and Endoscopic remission defined as ES = 0 or 1 (excluding friability)
Bowel movement urgency improvement	<ul style="list-style-type: none"> This definition will be specified in the SAP

9.1.1. Primary Efficacy Assessment

9.1.1.1. Primary Endpoint

The primary endpoint is clinical remission at Week 12 (mirikizumab versus placebo). **Clinical remission** is based on the MMS and is defined in [Table AMAN.4](#).

9.1.1.2. Mayo Score

This study utilizes components and permutations 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 daily 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:

Stool Frequency (SF): 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 total 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 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 daily diary items are contained in the 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.

Rectal Bleeding (RB): The RB subscore is a patient-reported measure. This item reports the most severe amount of blood passed *per rectum* for a given day, on a 4-point scale (see [Appendix 6](#)). The patient will record this in a daily electronic diary ([Appendix 7](#)).

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 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, to give a maximum Mayo score of 12. The modified Mayo score (MMS) is a sum of the Mayo SF, RB and ES, giving a maximum MMS of 9. Additional permutations of the Mayo score have been described, and may be used in analyzing data from this study.

9.1.1.3. Endoscopy

Endoscopy will be used to determine the Mayo ES at screening and Week 12 (or ETV). Site and blinded central reading of endoscopies will be used to determine ES.

A flexible sigmoidoscopy or colonoscopy will be performed on all patients during screening, within 14 days prior to randomization. The endoscopy report and histopathology report (if biopsies sent to the local histopathology laboratory) must be available in the source documents. Prior to performing the screening endoscopy, investigators should ensure that patients have clinically acceptable central laboratory test results, including stool tests that are “negative” for *C. difficile* and other intestinal pathogens (see Inclusion Criterion [11] and Exclusion Criteria [22] and [24] to [27]).

Flexible sigmoidoscopy is recommended for all patients, except the following patients for whom colonoscopy is the required endoscopic procedure at screening:

1. Patients who require surveillance for UC-associated dysplasia and malignancy, who have not had a surveillance colonoscopy, including random and targeted biopsies, within 12 months of baseline. These include:
 - a. Patients with pancolitis of >8 years’ duration.
 - b. Patients with left-sided colitis of >12 years’ duration.
 - c. Patients with primary sclerosing cholangitis.

In these patients, the investigator can obtain additional biopsies to surveil for dysplasia at the screening colonoscopy. This screening colonoscopy will be performed according to local guidelines and biopsies will be sent to the local histopathology laboratory. Chromoendoscopy may be an acceptable method of targeting biopsies, if allowed according to local guidelines.

2. Patients who require screening for colorectal cancer, who do not have a current screening colonoscopy according to local guidelines. This may include:
 - a. Patients with family history of colorectal cancer.
 - b. Personal history indicating increased colorectal cancer risk, for example, previous adenomatous polyps.
 - c. Patients ≥ 50 years, or with other known risk factor.
3. Patients who do not have the report of a completed, full colonoscopy available in source documents to establish extent of the disease. Patients with rectal sparing on baseline endoscopy must have documentation of rectal involvement on a prior endoscopy.
4. Where, in the opinion of the investigator, a colonoscopy is indicated at screening, for example, to confirm that a recent removal of an adenomatous polyp is complete prior to randomization.

If a patient already has up-to-date surveillance for dysplasia and/or up-to-date screening for colorectal cancer, the endoscopy report and histopathology report (if applicable) used to support this must be available in the source documents, in order to satisfy Inclusion Criterion [7].

Patients who undergo colonoscopy at screening do not require a separate flexible sigmoidoscopy in the same screening period.

At Week 12 (or ETV), a flexible sigmoidoscopy is recommended for all patients. Colonoscopy can be performed instead of flexible sigmoidoscopy at Week 12 for clinically indicated reasons in the judgement of the investigator and after discussion with the medical monitor as appropriate. The endoscopy report and histopathology report (if biopsies are sent to the local histopathology laboratory) must be available in the source documents. Patients who undergo a flexible sigmoidoscopy at an ETV will not undergo additional endoscopies within the study. Patients who discontinue the study drug because of pregnancy **will not** undergo a flexible sigmoidoscopy at their ETV.

If a patient undergoes early termination soon after screening endoscopy, the need for ETV endoscopy should be discussed with the medical monitor.

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 site-read Mayo ES at each endoscopy and record this in the eCRF.

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

The central reader will determine the centrally-read Mayo ES at each colonoscopy in a blinded manner, as detailed in the image review charter.

Disagreement between the site and 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 site prior to randomization at Visit 1 to enable determination of the MMS for eligibility.

9.1.1.4. Endoscopic Biopsies

A histopathology report supporting the diagnosis of UC must be available in the source documents prior to randomization, in order to satisfy Inclusion Criterion [4]. If a histopathology report is not available, the investigator can obtain additional biopsies for this purpose at the screening endoscopy (sent to the local histopathology laboratory).

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 secure specimen transfer, processing, slide preparation

and digitization of slides for histopathologic scoring. These results will not be made available to study sites.

9.1.2. Secondary Efficacy Assessments

9.1.2.1. Major Secondary Endpoints

The MMS and the composite SF and RB score, derived from assessment of the Mayo score (see Section 9.1.1.2), will be used to determine the major secondary endpoints (see [Table AMAN.4](#) for definitions). The major secondary endpoints are as follows:

- Clinical response at Week 12.
- Endoscopic remission at Week 12.
- Symptomatic remission at Week 4.
- Symptomatic remission at Week 12.
- Clinical response at Week 12 in the biologic-failed population.
- Bowel movement urgency improvement at Week 12.

9.1.2.1.1. Patient Reported Outcome Instruments

The Urgency Numeric Rating Scale (NRS) (see [Appendix 7](#) for description) is a patient-reported outcome (PRO) instrument collected using a patient eDiary. The Urgency NRS will be used to determine the secondary endpoint for bowel movement urgency improvement.

9.1.2.2. Other Secondary Endpoints

Other secondary endpoints are found in [Table AMAN.2](#).

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. Patient Reported Outcome Instruments

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

- Abdominal Pain NRS
- Fatigue NRS

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)

9.1.2.2.3. Histopathology Scoring Instrument

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

9.1.2.2.4. Inflammatory Biomarkers

C-reactive protein (CRP): CRP is an acute phase protein expressed by hepatocytes in response to inflammatory cytokines, particularly IL-6, TNF, and IL-1 β (Sands 2015). CRP will be obtained at 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. Exploratory Efficacy Assessments

9.1.3.1. Exploratory Endpoints

Exploratory endpoints are defined in the SAP.

9.1.3.1.1. Patient Reported Outcome Instruments

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 stool frequency and rectal bleeding discussed in Section 9.1.1.2, and abdominal pain and urgency discussed in Section 9.1.2.2.1, fatigue is measured using an 11-point NRS, where ‘0’ = “No Symptom” and ‘10’ = “Symptom as bad as I could imagine”. The diary also includes items that asks the patient to report stool consistency, the frequency of night-time stools, fatigue, and overall disease severity.

The following exploratory endpoints will be assessed daily via the electronic diary tool:

- Nocturnal Stool
- Bristol Stool Scale
- Patient’s Global Rating of Severity (PGRS)

In addition to those exploratory endpoints assessed by the Symptom Diary, the Patient’s Global Rating of Change (PGRC) will be administered at applicable study visits using the tablet device. Additional descriptions of these PRO instruments can be found in [Appendix 7](#).

9.1.3.2. Extraintestinal Manifestations

Review of extraintestinal manifestations (EIMs) will be performed at the time points described in the Schedule of Activities (Section 2). EIMs present at screening will be documented as preexisting conditions. EIMs that occur after baseline or existing EIMs that change in severity will be documented as AEs. EIMs 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.

9.1.4. 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 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 1 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 Investigator's Brochure and that the investigator identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive

2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Adverse Events of Special Interest

Adverse events of special interest (AESIs) are AEs which the Sponsor specifies as being of special interest based on standard drug registration topics, safety findings from previous studies in development program, potential risks associated with biologic immunomodulators as noted in product labels and published literature, and comorbidities and risk factors prevalent in the studied populations. The AESIs for this study are defined in the 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 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).

ECGs should be completed prior to any blood draw. Patients should be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

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

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 during the screening period (see Section 6.4). Except where otherwise stated, laboratory tests should be obtained prior to dosing.

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, unless they meet the criteria describing women not of childbearing potential, outlined in Inclusion Criterion [2b].

Serum pregnancy test will be done at screening only and results will be confirmed by the central laboratory. Patients determined to be pregnant will be discontinued from the study.

Urine pregnancy testing will be performed locally during designated scheduled visits through Week 12. 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 [2b]. FSH can be optionally obtained during screening, at the discretion of the investigator. FSH can also be optionally obtained during the study, as indicated in the Schedule of Activities (Section 2), to determine postmenopausal status.

9.4.4. Immunogenicity Assessments

Venous blood samples will be collected prior to dosing 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.

In the event of a drug hypersensitivity event (immediate or nonimmediate), additional samples for ADA and PK will be collected as close to the onset of the event as possible and at 4 and 12 to 16 weeks after the event. 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 should 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 ethical review boards (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. The physical examination at screening will assist the investigator in determining whether the subject meets criteria required to participate in the study and will also serve as a monitor for preexisting conditions and as a baseline for treatment-emergent AE assessment. Physical examination is mandated at screening and Week 12 (or ETV). Physical exam 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. Chest Radiography

A posterior-anterior (PA) chest x-ray (CXR) will be obtained at screening (Visit 0). A lateral CXR can also be obtained, if in the opinion of the investigator, a lateral view is indicated. Patients with documentation of a CXR, read by a qualified radiologist, that is sufficient for TB evaluation according to local standard of care, performed within 3 months before initial screening, may not need to repeat CXR at screening, based on the judgement of the investigator. In either case, the CXR film(s)/image(s) or a radiology report must be available to the investigator for review.

Patients with CXR findings consistent with active TB or a past history of TB are excluded from the study (Exclusion Criterion 22). In addition, patients with CXR findings consistent with untreated infection (Exclusion Criteria 28 and 29), or unstable or uncontrolled illness (Exclusion Criterion 38) are excluded from the study.

9.4.5.3. Tuberculosis Screening

Initial Screening

All patients will be screened for active and LTBI. Screening for LTBI (Visit 0) will include the following:

- Medical history, and physical examination as described in Section 9.4.5.1,
- CXR, as described in Section 9.4.5.2 above, and
- A test to assess immune response to mycobacterial antigens:
 - Interferon- γ release assay (IGRA, eg, QuantiFERON-TB Gold or T-SPOT.TB), or
 - Tuberculin skin test (TST, also called a purified protein derivative [PPD] or Mantoux test).

Tests for Immune Response to Mycobacterial Antigens

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

Patients with documentation of a “negative” IGRA or TST within 3 months before initial screening may not need to repeat TB testing at screening, based on judgment of the investigator. Source documentation must include the original laboratory report (for IGRA) or a record of the size in millimeters of the induration response (for TST). A TST recorded as “negative” without documenting the size of induration in millimeters will not be acceptable and will require a retest.

Interpretation of Screening Tests for LTBI

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

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

Patients with a diagnosis of LTBI, based on a positive IGRA test result or a positive TST response, and no evidence of active TB on medical history, physical examination and chest x-ray, may be rescreened once and enrolled if they are treated for LTBI and meet the following requirements (as well as all other study entry criteria):

- have received at least 4 weeks of appropriate ongoing prophylactic 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 (WHO LTBI [WWW])
- have no evidence of hepatotoxicity (ALT and AST levels must remain ≤ 2 xULN) upon retesting of serum ALT and AST levels before randomization)

Such patients must meet all other inclusion and exclusion criteria for participation, and also continue and complete appropriate LTBI therapy during the course of the study to remain eligible for participation in the study.

Retesting and Confirmatory Testing

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

Confirmatory testing with an IGRA is allowed for selected patients who have a positive QuantiFERON-TB Gold assay, positive T-SPOT.TB assay, or positive TST who meet all of the following criteria, and are assessed by the investigator as likely having a false-positive test result: no risk factors for LTBI, no risk factors for increased likelihood of progressing from LTBI to active TB, and have never resided in a high-burden country (detailed in [Appendix 4](#)). If the confirmatory test is positive, the patient will be excluded from the study unless they complete at least 4 weeks of appropriate therapy for LTBI, based on national or international guidelines (as defined above) and have no evidence of hepatotoxicity (ALT and AST levels must remain $\leq 2 \times \text{ULN}$) upon retesting of serum ALT and AST levels after at least 4 weeks of LTBI treatment. Such patients must continue and complete appropriate full course of LTBI therapy during the course of the study to remain eligible to participate. If the confirmatory test is negative, these results will be discussed with the medical monitor in order to determine eligibility for the study.

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

Diagnosis of LTBI during Study

Patients diagnosed with LTBI during the study must have study drug interrupted. If treatment for LTBI is considered to be appropriate, the patient must complete at least 4 weeks of appropriate therapy for LTBI, based on national or international guidelines (as defined above), and have no evidence of hepatotoxicity (ALT and AST levels must remain $\leq 2 \times \text{ULN}$) 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.

Prior Treatment for LTBI

Patients who have a documented history of completing an appropriate TB prophylaxis regimen with no history of risk of reexposure since their treatments were completed and no evidence of active TB are eligible to participate in the study. These patients should not undergo TST or IGRA testing unless advised to do so based on local guidelines.

Active TB

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

Patients diagnosed with active TB at screening will be excluded and should be referred by the investigator for appropriate TB treatment and follow-up.

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..

9.4.5.4. Hepatitis B Testing**HBV Screening and Interpretation**

Patients with acute or chronic hepatitis B infection are excluded from the study.

Screening for HBV in this study is performed as follows: an initial test for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc), followed by a test for HBV DNA in patients who are HBsAg-, anti-HBc+.

Exclusion Based on HBV Serology and HBV DNA Testing

Patients with the following screening test results will be excluded from the study:

- HBsAg+, irrespective of anti-HBc result, *or*
- HBsAg-, anti-HBc+ with detectable HBV DNA.
- Detectable HBV DNA, irrespective of HBsAg or anti-HBc result.

Patients Potentially Allowed into the Study, Based on HBV Serology and HBV DNA Testing

Patients with the following screening test results may be eligible for inclusion, provided they meet the other inclusion/exclusion criteria:

- HBsAg-, anti-HBc-.
- HBsAg-, anti-HBc+ with no HBV DNA detected.

Management of patients with the following HBV serology at baseline: HBsAg-, anti-HBc+, HBV DNA not detected

Randomized patients with this serological pattern at screening will undergo HBV DNA monitoring at Week 12 and, if applicable, at the “Last Visit +16 Weeks” visit in the post-treatment follow-up period.

In addition, if such patients experience an elevated ALT or AST level $>3\times$ ULN during the study, they must have a HBV DNA test and be managed appropriately based on the results of that test.

Management of Patients with Detectable HBV DNA During the Study

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

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

- “Detectable HBV DNA”, if HBV DNA is detected without an increase in aminotransferase levels.
- “Reactivation of hepatitis B”, if HBV DNA is detected, in concert with an increase in aminotransferase levels and/or symptoms and signs of liver disease.

9.4.5.5. Hepatitis C Testing

Patients with current hepatitis C infection are excluded from the study.

Screening for HCV in this study is performed as follows: an initial test for HCV antibody, followed by a test for HCV RNA if the HCV antibody test is positive. Patients with a positive HCV antibody test and detectable HCV RNA, will be excluded from the study.

Patients who test negative for HCV antibody will not be tested for HCV RNA and may be eligible for inclusion in the study.

Patients who have spontaneously cleared hepatitis C infection, defined as (i) a positive HCV antibody test and (ii) a negative HCV RNA test, with no history of anti-HCV treatment, may be eligible for inclusion in the study, provided they have no detectable HCV RNA on screening for this study. Any patient with a history of hepatitis C infection who develops elevated ALT $>3\times$ ULN within the study will be tested for HCV RNA.

Patients with a previous diagnosis of hepatitis C who have been treated with antiviral therapy and achieved a sustained virologic response (SVR) may be eligible for inclusion in the study, provided they have no detectable HCV RNA at screening. Sustained virologic response is defined as an undetectable HCV RNA level 12 weeks after completion of a full, documented course of an approved, potentially curative antiviral therapy for HCV.

If a patient is diagnosed with hepatitis C during the study (detectable HCV RNA), 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 and should receive appropriate follow-up medical care.

9.4.5.6. Depression and Suicidality

Suicide-related events (behavior and/or ideations) will be assessed at screening (Visit 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, and Week 12 or ETV. These assessments are described below, and further information is provided in [Appendix 12](#).

Columbia Suicide Severity Rating Scale: The C-SSRS (Columbia University Medical Center [WWW]) is a scale that captures the occurrence, severity and frequency of suicide-related ideations and behaviors during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine if suicidal ideation and/or behavior occurred. The C-SSRS is administered by an appropriately trained health care professional with at least 1 year of patient care/clinical experience. Patient data for the C-SSRS will be 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-SR16. If a suicide-related event is discovered during the C-SSRS but was not captured during the spontaneous AE collection, 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.

9.4.5.7. Stool Testing

Stool Culture

A stool sample for culture will be obtained at screening. The stool culture assay will screen for the following pathogens: *Campylobacter*, *Salmonella*, *Shigella*, *Escherichia coli* 0157:H7 and *Yersinia enterocolitica*.

Patients must have a “negative” stool culture result in order to be randomized (Exclusion Criterion [27]). Re-testing is allowed within the same screening period if there is a technical difficulty in performing or reporting the stool culture assay.

Patients who have a “positive” stool culture result are excluded from the study (Exclusion Criterion [27]). These patients can be re-screened once, provided they have been adequately treated and are off antibiotics for 30 days. If antibiotics were not prescribed, these patients can

be re-screened once, provided that 30 days or more has elapsed since resolution of acute symptoms and signs associated with the underlying intestinal infection. A stool culture should be repeated prior to rescreening, as a “negative” result will be required prior to randomization.

C. difficile

A stool sample for *C. difficile* toxin will be obtained at screening. 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.

Patients should test negative for *C. difficile* in order to be randomized (Exclusion Criterion 27). Re-testing is allowed within the same screening period if there is a technical difficulty in performing or reporting the *C. difficile* assays, or if in the judgement of the investigator, the patient’s symptoms or signs are not consistent with *C. difficile* infection.

Patients who test positive at screening for *C. difficile* can be re-screened once for the study, provided that they have been adequately treated and off antibiotics for 30 days. Patients who have been adequately treated for *C. difficile* with fecal microbial transplantation or IV immunoglobulin therapy can be re-screened once for the study, 30 days after completing their therapy. Testing for *C. difficile* should be repeated prior to re-screening, as a “negative” result is required prior to randomization.

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 individual or group level, additional analyses of the safety data can be performed by members of the external data monitoring committee (DMC) (see Section 10.3.8) or by the sponsor, through its internal review committee process.

9.4.6.1. Hepatic Safety Monitoring

If a study patient experiences elevated ALT $\geq 3 \times \text{ULN}$, ALP $\geq 2 \times \text{ULN}$, or elevated TBL $\geq 2 \times \text{ULN}$, liver testing (Appendix 5) 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.

If a study patient experiences an ALT or AST $> 3 \times \text{ULN}$ and TBL $> 2 \times \text{ULN}$ or international normalized ratio > 1.5 , the study medical monitor should be consulted as soon as possible for further guidance on evaluation of the laboratory abnormalities.

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 $\geq 5xULN$ on 2 or more consecutive blood tests
- elevated serum TBL to $\geq 2xULN$ (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to $\geq 2xULN$ on 2 or more consecutive blood tests
- patient discontinued from treatment because of 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.

Pre-dose samples will be obtained at Weeks 0, 4 and 8. Additional PK samples will be taken at Week 12, ETV or UV, and post-treatment follow-up Visit 802. Post dose samples will be obtained at Weeks 0 and 4. These can be taken up to 2 hours after dosing. The time of dosing and time of sample collection should be noted.

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.

CCI



CCI [Redacted]

9.6. Pharmacodynamics

See Section 9.8.

CCI [Redacted]

CCI [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

CCI [Redacted]

CCI [REDACTED]

[REDACTED]

[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

The study will randomize approximately 1160 patients with a 3:1 ratio of 300 mg mirikizumab to placebo, with an assumption that approximately 1044 patients will complete the study. Patients will be stratified by (a) biologic-failed status (yes/no), (b) baseline corticosteroid use (yes/no), (c) baseline disease activity (MMS: [4-6] or [7-9]), and (d) region (North America/Europe/Other).

The power calculations for this study assume the following:

- (1) The randomized study population will include approximately 50% biologic-failed patients and approximately 50% conventional-failed patients.
- (2) The predicted clinical remission rates at Week 12 for mirikizumab versus placebo are expected to be 23% versus 7.8% (biologic-failed patients: 16% versus 3.5%; conventional-failed patients: 30% versus 12%).

The primary endpoint of this study is a test the hypothesis that mirikizumab is superior to placebo in inducing **clinical remission** at Week 12 in patients with moderately to severely active UC. Given the assumptions described above, a sample size of 1160 patients are expected to provide >90% power to demonstrate that mirikizumab is superior to placebo in achieving this endpoint, based on a chi-square test with a 2-sided significance level of 0.00125.

Patients who complete Study AMAN may be eligible to participate in Study AMBG, a 40-week maintenance study. The primary objective of Study AMBG is to test the hypothesis that mirikizumab is superior to placebo in achieving clinical remission at Week 40 of Study AMBG (Week 52 of continuous therapy) amongst patients induced into clinical response with mirikizumab at Week 12 of Study AMAN. A sample size of 1160 patients in Study AMAN is predicted to provide a sufficient number of biologic-failed patients in clinical remission at Week 12 of Study AMAN who will enter Study AMBG. This is expected to provide >90% power to demonstrate that mirikizumab is superior to placebo in achieving the primary endpoint in Study AMBG, based on a chi-square test with a 2-sided significance level of 0.05.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Intent-to-Treat (ITT) Population	All randomized patients. Patients will be analyzed according to the treatment to which they were assigned
Modified Intent-to-Treat (mITT) Population	All randomized patients who receive at least 1 dose of study treatment (regardless if the patient does not receive the correct treatment, or otherwise does not follow the protocol). Patients will be analyzed according to the treatment to which they were assigned
Safety Population	Same as mITT 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 receive 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.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

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

Efficacy analyses will be conducted on the modified intent-to-treat population. Safety analyses will be conducted on the modified intent-to-treat population (Safety 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. Additional safety analyses may be performed as deemed appropriate.

The baseline modified Mayo score is calculated from valid daily diary entries obtained prior to endoscopy during the screening period and the endoscopic appearance of the mucosa at this screening endoscopy (Section 9.1.1.2). For other efficacy, health outcome and safety assessments, baseline is defined as the last non-missing assessment recorded on or prior to the date of Visit 1 (Week 0).

Summary statistics for continuous variables may include mean, SD, 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 will be conducted as deemed appropriate. All hypothesis tests will be 2-sided, and the family-wise type I error rate (FWER) will be controlled at an α level of 0.00125 for primary and major secondary endpoints using a pre-specified

graphical procedure (see Section 10.3.1.2). Weights and alpha propagations will be finalized and included in the SAP prior to first unblinding of efficacy data

Unless otherwise specified, analysis of hypotheses will be tested under multiplicity control at a family wise significance level of 0.00125. A 2-sided 99.875% CI will be provided along with the p-value. For other analyses, statistical tests without multiplicity control will be conducted using a 2-sided significance level of 0.05. The corresponding p-value along with its 95% 2-sided CI will be provided. These analyses will also include subgroup analyses for the primary and the major secondary endpoints, except for the subgroup which is included in the scope of multiplicity control.

For assessments of the primary endpoint and other categorical efficacy endpoints, the Cochran–Mantel–Haenszel (CMH) chi-square test will be used to compare the 2 treatment groups with the following stratification factors: (a) previous biologic therapy failure status (yes/no), (b) baseline corticosteroid use (yes/no), (c) baseline disease activity (MMS: [4-6] or [7-9]), and (d) region (North America/Europe/Other). The CMH chi-square p-value and the relative risk along with its 2-sided CI will be provided. In addition, the absolute treatment difference in proportions will be provided along with the 2-sided CI estimate. The differences between each treatment group and placebo will also be tested separately using a logistic regression model that controls for: (a) previous biologic therapy failure status (yes/no) and (b) corticosteroid use (yes/no). 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 with multiple postbaseline time points will be made using mixed-effects model for repeated measures (MMRM) analysis. The MMRM will include the following effects and covariates: (a) treatment group, (b) previous biologic therapy failure status (yes/no), (c) corticosteroid use (yes/no), (d) disease activity (MMS: [4-6] or [7-9]) at baseline), (e) region (North America/Europe/Other), (f) baseline value in the model, (g) visit, 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 postbaseline time point will be made using ANCOVA with the following in the model: (a) treatment group, (b) previous biologic therapy failure status (yes/no), (c) corticosteroid use (yes/no), (d) disease activity (MMS: [4-6] or [7-9]) at baseline), (e) region (North America/Europe/Other), and (f) baseline value. 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. Missing data imputation method for the ANCOVA model will be specified in the SAP.

Any change to the data analysis methods and/or imputation 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 and/or imputation methods described in the protocol, along with the rationale 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 minimize 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 nonresponders for the NRI analysis if they do not meet the categorical efficacy criteria or have missing clinical efficacy data at a time point of interest.
- MMRM: For continuous variables, the primary analysis will be MMRM with the missing at random assumption for handling missing data. This analysis takes into account both missingness of data and the correlation of the repeated measurements. No additional imputation methods will be applied to the MMRM analysis.

Additional missing data imputation methodologies, for example, modified baseline observation carried forward (mBOCF) may be considered as sensitivity analyses and will be fully detailed in the SAP. Using mBOCF imputation, patients who discontinue the investigational product due to an AE or lack of efficacy will have their baseline observation carried forward to the corresponding primary endpoint for evaluation. For patients discontinuing investigational product for any other reason, the last nonmissing postbaseline observation before discontinuation will be carried forward to the corresponding primary endpoint for evaluation. Those sensitivity analyses and other additional methods 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. Adjustment for Multiple Comparisons

Multiplicity controlled analyses will be performed to test the primary and major secondary hypotheses in order to control the overall FWER at 0.00125. A prespecified graphical multiple testing approach (Bretz et al. 2009, 2011) will be used. 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 of alpha) to be implemented will be prespecified in the SAP prior to first unblinding of efficacy data.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

The number of randomized patients will be summarized. Frequency counts and percentages of all patients who are randomized, complete the study, and those who discontinue the study drug

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

10.3.2.2. Patient Characteristics

Year of birth, sex, weight, height, tobacco/nicotine use, previous biologic therapy, corticosteroid use and other demographic characteristics will be recorded. Age and body mass index will be calculated. Demographic and baseline disease characteristics will be summarized for each treatment group. Certain characteristics, such as weight, that are collected after baseline, will be reported as a listing.

10.3.2.3. Concomitant Therapy

Concomitant therapy will be collected at each visit and the reported term will be classified by the WHO drug dictionary. Previous concomitant therapy (reported before randomization and after ICF) will be listed. The current concomitant therapy (reported after randomization) will be presented separately in frequency tables by drug name for all randomized patients.

10.3.2.4. Treatment Compliance

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

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary efficacy end point of clinical remission will be assessed using the MMS, a 9-point instrument that includes the SF, RB and ES subscores of the Mayo Score (see Section 9.1.1.1; [Table AMAN.4](#)).

At the screening visit, each patient will be asked to identify how many stools he or she had in a 24-hour period when in remission from UC. If the patient does not report that he or she has achieved remission, then he/she will be asked to identify the number of stools he/she had per day before initial onset of signs and symptoms of UC. The response to these questions will be used as the reference SF for the calculation of the Mayo SF subscore.

For the study visits that are associated with an endoscopy (eg, Week 0, Week 12, ETV and possibly unscheduled visits), the SF and RB subscores of the Mayo Score will be calculated from daily electronic diary data by separately averaging the most recent 3 days out of the 7 days prior to commencing bowel preparation for endoscopy. The 3 days of patient diary data used for SF and RB calculation will exclude data from the following days: (i) days when patients receive bowel preparation, (ii) the day of an endoscopy, and (iii) the day after an endoscopy.

At other visits without endoscopy, the SF and RB subscores of the Mayo Score will be calculated from daily electronic diary data by separately averaging the most recent 3 days (possibly nonconsecutive) out of 7 days prior to that visit.

If data are available for fewer than 3 days in the 7-day window, the subscores will be considered missing.

To calculate the SF subscore, the reference stool frequency will be subtracted from the 3-day averaged stool frequency. The subtracted stool frequency value will then be rounded to the nearest integer and then mapped to obtain Mayo SF subscore.

Rectal bleeding subscore will be rounded to the nearest integer value of the 3-day averaged RB. Rates of clinical remission at Week 12, as defined in Section 9.1.1.1, will be analyzed. Patients who do not achieve clinical remission or who do not reach the Week 12 assessment will be considered to be 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 details will be provided in the SAP.

10.3.3.2. Secondary Analyses

The secondary efficacy and health outcome endpoints of the trial are presented in Table AMAN.2 and details of the analysis methods that will be utilized are provided in Section 10.3.1.

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

10.3.4. Safety Analyses

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 visit and by treatment. The change from baseline to last observation value will be analyzed with 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 test 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, ADA, etc.) and extrinsic factors (such as comedications) 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 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 that achieve clinical response, clinical remission, and endoscopic normalization at different percentiles (for example, quartiles) of exposure of

mirikizumab at Week 12. Measures of exposure may include population PK estimated average concentrations (C_{avg}) between Week 0 and Week 12, or estimated or observed trough concentrations at Week 12. 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 normalization. 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 postbaseline, and with treatment-emergent anti-drug antibody (TEADA) to mirikizumab will be tabulated. If no ADA are detected at baseline, TEADA are defined as those with a titer 2 fold (1 dilution) greater than the minimum required dilution (MRD) of the assay. For samples with ADA detected at baseline, TEADA are defined as those with a 4-fold (2 dilutions) increase in titer compared to baseline. For patients who have TEADA, the distribution of maximum titers will be described. The frequency of neutralizing antibodies will also be tabulated.

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

10.3.7. Other Analyses

10.3.7.1. Subgroup Analyses

Additional subgroup analyses will be conducted for the primary endpoint and select secondary endpoints. Subgroups to be evaluated include sex, age category, body weight, race, geographic region, baseline disease severity and activity, duration and location of disease, previous systemic therapy, previous biologic therapy, and concomitant therapy for UC. If any group within the subgroup is less than 10% of the total population, only summaries of the efficacy data will be provided (that is, no inferential testing). Additional 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.

The DMC is authorized to evaluate unblinded interim efficacy and safety analyses. 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 it is required for the safety of their patients.

In addition to the DMC, SAC and potential IRC if needed, a limited number of pre-identified individuals may gain access to 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 with 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
ACT1 and ACT2	Active Ulcerative Colitis Trials 1 and 2
ADA	anti-drug antibody
ADR	adverse drug reactions
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse event of special interest
AIDS	acquired immune deficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
anti-HBc	hepatitis B core antibody
5-ASA	5-aminosalicylic acid
AST	aspartate aminotransferase
AZA	azathioprine
BCG	Bacillus Calmette-Guerin
blinding	A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received.
clinical research physician	Individual responsible for the medical conduct of the study. Responsibilities of the clinical research physician may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CMH	Cochran–Mantel–Haenszel
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice, and applicable regulatory requirements.
CRP	C-reactive protein

CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTA	clinical trial application
CXR	chest x-ray
DALM	dysplasia-associated lesion or mass
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
eCRF	electronic case report form
EIM	extraintestinal manifestation
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
GCP	good clinical practice
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
GMP	Good Manufacturing Practices
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus

HIV	human immunodeficiency virus
IB	Investigator's Brochure
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	informed consent form
ICH	International Council for Harmonisation
IGRA	interferon- γ release assay
IL-23	Interleukin-23
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's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
ITT	intent to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intent to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
LS	least squares
LTBI	latent tuberculosis infection
MMRM	mixed-effects model for repeated measures
MMS	modified Mayo score
6-MP	6-mercaptopurine
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)
PURSUIT	Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment–Subcutaneous
Q4W	every 4 weeks
QIDS-SR16	Quick Inventory of Depressive Symptomatology –Self-Report (16 items)
RB	rectal bleeding
SAE	serious adverse event
SAP	statistical analysis plan
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
SVR	sustained virologic response
TB	tuberculosis
TBL	total bilirubin level
TEADA	treatment-emergent anti-drug antibody
TNF	tumor necrosis factor
TST	tuberculin skin test
UC	ulcerative colitis
UCEIS	Ulcerative Colitis Endoscopic Index of Severity
ULN	upper limit of normal
ULTRA	Ulcerative Colitis Long-Term Remission and Maintenance with Adalimumab
WPAI:UC	Work Productivity and Activity Impairment Questionnaire: Ulcerative Colitis

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology^{a,b}

Hemoglobin
 Hematocrit
 Erythrocyte count (RBCs)
 Mean cell volume
 Mean cell hemoglobin
 Mean cell hemoglobin concentration
 Leukocytes (WBCs)
 Cell morphology
 Neutrophils, segmented
 Lymphocytes
 Monocytes
 Eosinophils
 Basophils
 Platelets

Urinalysis^{a,b}

Specific gravity
 pH
 Protein
 Glucose
 Ketones
 Bilirubin
 Urobilinogen
 Blood
 Nitrite
 Urine leukocyte esterase
 Microscopic examination of sediment

Clinical Chemistry^{a,b}

Serum Concentrations of:

Sodium
 Chloride
 Bicarbonate
 Potassium
 Total bilirubin
 Total protein
 Direct bilirubin
 Alkaline phosphatase (ALP)
 Alanine aminotransferase (ALT)
 Aspartate aminotransferase (AST)
 Gamma-glutamyl transferase (GGT)
 Blood urea nitrogen (BUN)
 Creatinine
 Uric acid
 Calcium
 Glucose
 Albumin
 Cholesterol (total)
 Triglycerides
 Lipid Panel (fasting)^c
 High-density lipoprotein
 Low-density lipoprotein
 Creatine kinase (CK)

Other Tests^a

Hepatitis B core antibody ^{b,d}
 Hepatitis B surface antigen^{b,d}
 HBV DNA^{b,e}
 Hepatitis C antibody^{b,d,f}
 HIV^{b,d}
 Pregnancy test (serum^{b,d} and urine.^g)
 FSH^b
 QuantiFERON-TB Gold test^d or T-SPOT or TST

CCI [REDACTED]

CCI [REDACTED]

Anti-mirikizumab antibodies (immunogenicity)
 Serum mirikizumab concentration (PK)
 C-reactive protein, high-sensitivity
Clostridium difficile^{b,h} and Stool Culture^{b,h}
 Fecal calprotectin
 Tryptaseⁱ
 Complement (C3/C4)ⁱ
 Cytokine panelⁱ

Footnotes on next page.

Abbreviations: ADA = anti-drug antibody; ETV = early termination visit; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HIV = human immunodeficiency virus; PK = pharmacokinetics; RB = rectal bleeding; RBC = red blood cell; SF = stool frequency; TST – tuberculin skin test; UV = unscheduled visit; V = visit; 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 Performed at screening only.
- e Hepatitis B DNA testing will be performed in patients who test positive for anti-hepatitis B core antibody (at protocol-specified intervals).
- f A positive hepatitis C antibody laboratory assessment will be confirmed with an additional test method.
- g Urine pregnancy test will be evaluated locally.
- h *Clostridium difficile* tests at V5 and ETV may be performed for patients who do not move into Study AMBG. *Clostridium difficile* test at UV may be performed if visit is due to worsening SF and/or RB.
- i Test 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 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 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

Lilly and its designee are 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's Brochure, and updates during the course of the study
- ICF

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

Appendix 3.1.4. Regulatory Considerations

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

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

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

Appendix 3.1.5. Investigator Information

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

Appendix 3.1.6. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Appendix 3.1.7. Final Report Signature

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

The 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 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 assessment (eCOA) measures (for example, 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 endoscopic data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Data from compliant forms submitted to Lilly will be encoded and stored in the global product compliant 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-AMAN is described in the letters of agreement between the sponsor and the investigators and institutions.

Appendix 4. 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 $\geq 10\%$ 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.

World Health Organization List of High Burden Countries		
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: WHO TB [WWW].

**Appendix 5. 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, or clinical research physician. These tests will be performed at a Lilly-designated laboratory.

Hepatic Monitoring Tests

Hepatic Hematology

Hemoglobin
 Hematocrit
 RBCs
 WBCs
 Neutrophils, segmented
 Lymphocytes
 Monocytes
 Eosinophils
 Basophils
 Platelets

Hepatic Chemistry

Total bilirubin
 Direct bilirubin
 Alkaline phosphatase
 ALT
 AST
 GGT
 CPK

Haptoglobin

Hepatic Coagulation

Prothrombin time
 Prothrombin time, INR

Hepatic Serologies^a

Hepatitis A antibody, total
 Hepatitis A antibody, IgM
 Hepatitis B surface antigen
 Hepatitis B surface antibody
 Hepatitis B core antibody
 Hepatitis C antibody
 Hepatitis E antibody, IgG
 Hepatitis E antibody, IgM

Anti-nuclear antibody

Alkaline phosphatase isoenzymes

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

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

Note: The Mayo score ranges from 0 to 12, with higher scores indicating more severe disease. Modified Mayo score excludes the Physician's Global Assessment and ranges from 0 to 9. Composite stool frequency and rectal bleeding score ranges from 0 to 6. The original description of the Mayo score included friability in the definition of an endoscopic subscore of 1. Consistent with current clinical practice and regulatory guidance, this study excludes friability from the definition of an endoscopic subscore of 1.

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. The Normal SF (stool frequency) refers to when the patient was in remission or, if the patient has never achieved remission, the reported stool frequency 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.

Source: adapted from Schroeder et al. 1987, Scherl et al. 2009.

Appendix 7. Patient Reported Outcome Instruments

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

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

The following are descriptions of additional PRO instruments used in study AMAN using Patient eDiary or Tablet Device:

- **Urgency NRS:** A single item that measures the severity for 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 Numeric Rating Scale (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 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.
- **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.
- **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.

- **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 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; Irvine et al. 1996). Responses are graded on a 7-point Likert scale in which 7 denotes “not a problem at all” and 1 denotes “a very severe problem.” Scores range from 32 to 224; a higher score indicates a better quality of life. Patients will record their responses to the IBDQ 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. The second part of the questionnaire consists of a visual analog scale 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 two 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 (Reilly Associates [WWW]), i.e, worse outcomes. Patients will record their responses to the WPAI:UC electronically as source data in the tablet device at appropriate visits.

**Appendix 8. Examples of Infections that May Be
Considered Opportunistic in the Setting of Biologic
Therapy**

<i>Bacterial</i>	
	Bartonellosis (disseminated disease only)
	Campylobacteriosis (invasive disease only)
	Legionellosis
	Listeria monocytogenes (invasive disease only)
	Nocardiosis
	Tuberculosis
	Non-tuberculous mycobacterial disease (see Section 9.4.5.3)
	Salmonellosis (invasive disease only)
	Shigellosis (invasive disease only)
	Vibriosis (invasive disease due to <i>Vibrio vulnificus</i>)
<i>Viral</i>	
	BK virus disease including polyomavirus-associated nephropathy
	Cytomegalovirus disease
	Hepatitis B virus reactivation
	Hepatitis C virus progression
	Herpes simplex (invasive disease only)
	Herpes zoster (any form)
	Post-transplant lymphoproliferative disorder (Epstein-Barr virus)
	Progressive multifocal leukoencephalopathy (PML), John Cunningham (JC) virus [excluded from the study]
<i>Fungal</i>	
	Aspergillosis (invasive disease only)
	Blastomycosis
	Candidiasis (invasive disease or pharyngeal)
	Coccidioidomycosis
	Cryptococcosis
	Histoplasmosis
	Paracoccidioides infections
	Penicillium marneffeii
	Pneumocystis jirovecii (formerly Pneumocystis carinii)
	Sporothrix schenckii
	Other invasive fungi: Mucormycosis (zygomycosis) (<i>Rhizopus</i> , <i>Mucor</i> and <i>Lichtheimia</i>), <i>Scedosporium/Pseudallescheria boydii</i> , <i>Fusarium</i>
<i>Protozoan</i>	
	Leishmaniasis (visceral only)
	Microsporidiosis
	Toxoplasmosis
	<i>Trypanosoma cruzi</i> infection (Chagas' disease) (disseminated disease only)

Source: Adapted from Winthrop et al. 2015.

This table is provided to aid the investigator in recognizing infections that may be considered opportunistic in the context of biologic therapy, for the purposes of Exclusion Criterion [28c]. This list is not exhaustive. Investigators should use their own clinical judgement in determining if other infections may be considered opportunistic, for the purposes of Exclusion Criterion [28c].

Winthrop et al. (2015) consider tuberculosis (TB) and non-TB mycobacterial disease to be opportunistic infections in the context of biologic therapy. See Section 9.4.5.3 for the approach to screening for latent TB infection within the study. Patients with any history of **active** TB are excluded from the study, regardless of previous or current TB treatments.

Appendix 9. Prohibited Medications

This section outlines medications that are prohibited during the treatment phase of the study, including discontinuation windows for prohibited medications prior to the screening endoscopy, 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	Prohibited Medication Restrictions
Anti-TNF antibodies (for example, infliximab, adalimumab or golimumab)	Discontinue at least 8 weeks prior to screening endoscopy and prohibited throughout duration of study
Anti-integrin antibodies (for example, vedolizumab)	Discontinue at least 8 weeks prior to screening endoscopy and prohibited throughout duration of study
Agents depleting B or T cells (for example, rituximab, alemtuzumab, or visilizumab)	Discontinue at least 12 months prior to baseline; patients remain excluded if evidence of persistent targeted lymphocyte depletion at the time of screening endoscopy
Immunomodulatory medications, including oral cyclosporine, IV cyclosporine, tacrolimus, mycophenolate mofetil, thalidomide, or JAK inhibitors (for example, tofacitinib)	Discontinue at least 4 weeks prior to screening endoscopy and prohibited throughout duration of study
Rectally administered 5-ASA therapies (enemas or suppositories)	Discontinue at least 2 weeks prior to screening endoscopy and prohibited throughout duration of study
Rectally administered investigational preparations for UC such as arsenic preparations	Discontinue at least 4 weeks prior to screening endoscopy and prohibited throughout duration of study
Rectally administered corticosteroids (enemas or suppositories)	Discontinue at least 2 weeks prior to screening endoscopy and prohibited throughout duration of study
IV corticosteroids for UC	Discontinue at least 2 weeks prior to screening endoscopy. A course of IV corticosteroids for UC is prohibited throughout duration of study
Systemic corticosteroids for non-UC indications (oral or IV)	Patients requiring systemic corticosteroids for non-UC indications 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 <i>not the</i> oral budesonide extended release tablet formulation [budesonide MMX])	Discontinue at least 2 weeks prior to screening endoscopy and prohibited throughout duration of study.
Any investigational therapy (biologic or nonbiologic)	Discontinue at least 4 weeks, or 5 half-lives whichever is longer, prior to screening endoscopy and prohibited throughout duration of study
Interferon therapy	Discontinue at least 8 weeks prior to screening endoscopy and prohibited throughout duration of study
Leukocyte apheresis (leukapheresis, for example, Adacolumn)	Discontinue at least 3 weeks prior to screening endoscopy

Drug Class	Prohibited Medication Restrictions
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	Patients with any previous exposure not eligible to be enrolled
Bacillus Calmette-Guerin (BCG) vaccine	Last vaccination (if any) given at least 12 months prior to baseline. BCG vaccination prohibited throughout the duration of the study and for 12 months after discontinuation of study drug.
Live attenuated vaccines	Last vaccination (if any) given at least 3 months prior to baseline. Live attenuated vaccines are prohibited throughout the duration of the study and for 3 months after discontinuation of study drug.

Abbreviations: 5-ASA = 5-aminosalicylic acid; IV = intravenous; IP = investigational product; JAK = Janus Kinase; TNF= tumor necrosis factor; UC = ulcerative colitis.

Appendix 10. Permitted Medications with Dose Stabilization

Drug Class	Dose Stabilization Guidance
Oral 5-ASAs, for example, mesalamine, balsalazide, olsalazine and sulfasalazine (for UC)	May continue during study with stable dose 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)	Prescribed dose must have been stable for at least 2 weeks before screening endoscopy and to remain stable for duration of study.
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 methotrexate)	Prescribed at stable dose for at least 8 weeks before screening endoscopy; doses should remain stable throughout study unless medication is discontinued due to a toxicity related to the medication.
Antidiarrheals (for example, loperamide, diphenoxylate with atropine)	May continue during study with stable doses encouraged.
Low-dose or baby aspirin (75 to 162.5 mg)	Daily use for cardiovascular prophylaxis permitted.
Non-live (killed, inactivated or subunit) vaccines	Allowed during the study. The efficacy of non-live vaccinations with concomitant mirikizumab treatment is unknown.

Abbreviations: 5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; AZA = azathioprine; IV = intravenous; IP = investigational product; UC = ulcerative colitis.

**Appendix 11. Additional Information on Systemic Drug
Administration Reactions**

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

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

**Appendix 12. Additional Information on the Columbia
Suicide Severity Rating Scale, and Quick Inventory of
Depressive Symptomatology (self report)**

Columbia Suicide Severity Rating Scale

The 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 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 13. Protocol Amendment I6T-MC-AMAN(a) Summary A Phase 3, Multicenter, Randomized, Double- Blind, Parallel, Placebo-Controlled Induction Study of Mirikizumab in Conventional-Failed and Biologic-Failed Patients with Moderately to Severely Active Ulcerative Colitis LUCENT 1

Overview

Protocol I6T-MC-AMAN, A Phase 3, Multicenter, Randomized, Double-Blind, Parallel, Placebo-Controlled Induction Study of Mirikizumab in Conventional-Failed and Biologic-Failed Patients with Moderately to Severely Active Ulcerative Colitis LUCENT 1 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-AMAN Amendment (a)

Section # and Name	Description of Change	Brief Rationale
Section 1 Synopsis, Objectives/Endpoints:	Added, modified or deleted major secondary and other secondary objectives and endpoints	Match Section 4 Objectives and Endpoints
Section 1 Synopsis, Statistical Analysis	Updated power calculations	Match Section 10 Statistical Considerations
Section 2 Table AMAN.1. Schedule of Activities	Updated window for V5	Allow more time for V5
Section 2 Table AMAN.1. Schedule of Activities, Explain UC remission stool frequency question to patient	Added task to schedule of activities to explain UC remission stool frequency question to patient	Added this task to ensure patient's proper understanding of the UC remission question
Section 2 Table AMAN.1. Schedule of Activities, 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 AMAN.1. Schedule of Activities, PK Assessment samples 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 AMAN.1. Schedule of Activities, <i>C. difficile</i> testing	<i>C. difficile</i> testing added to V5, ETV and UV	Allow additional testing for detection
Section 2 Table AMAN.1. Schedule of Activities, Endoscopy with biopsies	Added clarification to refer to Section 9.1.1.3 of the protocol for specification of what endoscopic	Clarification of Table AMAN.1. Schedule of Activities comment for Endoscopy with biopsies

Section # and Name	Description of Change	Brief Rationale
	procedure can be performed when.	
Section 2 Table AMAN.1. Schedule of Activities, PGRC	Removed PGRC at V1	Corrected error in original protocol since this assessment is not applicable at baseline
Section 2 Table AMAN.1. Schedule of Activities	Added a description of “normal” SF	Clarification of definition of normal stool frequency for the modified Mayo score to patients entering the study
Section 2 Table AMAN.1. Schedule of Activities	Added footnotes and abbreviations	Clarification of acronyms and procedures
Section 4 Objectives and Endpoints, Table AMAN.2.	Added major secondary objective and endpoint of bowel movement urgency and removed from other secondary objective and endpoint list	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 AMAN.2.	Other secondary objectives and endpoints clarified	Histologic remission alone will no longer define mucosal healing. The objective has been modified to reflect the clarification of mucosal healing and location of definition clarified throughout the protocol amendment.
Section 4 Objectives and Endpoints, Table AMAN.2.	Other secondary objectives and endpoints clarified	Clarified the definition of symptomatic response
Section 4 Objectives and Endpoints, Table AMAN.2.	Other secondary objectives and endpoints added	Included UCEIS endoscopic remission; the UCEIS is considered to be an important endpoint assessing endoscopic disease activity. The central reading of endoscopies has included this assessment from the onset of the study. We are now adding it as an other secondary endpoint.
Section 4 Objectives and Endpoints, Table AMAN.2.	Other secondary objectives and endpoints added	Modified definition of the mucosal healing endpoint to align with current scientific literature, recent UC clinical trials, and regulatory guidance. New definition includes histologic remission plus endoscopic remission.
Section 4 Objectives and Endpoints, Table AMAN.2.	Other secondary objectives and endpoints added	Fatigue is a common symptom for patients with active disease. Added Fatigue endpoint to assess improvement in Fatigue. Published literature support fatigue as an

Section # and Name	Description of Change	Brief Rationale
		important symptom experienced by patients with UC. Therefore, this endpoint has been added as an other secondary endpoint
Section 6.1 Inclusion Criteria, Disease-Specific Inclusion Criteria	Added language that patients with rectal sparing on baseline endoscopy must have documentation of rectal involvement on a prior endoscopy and histopathology report to confirm UC diagnosis.	Additional clarification to confirm UC diagnosis.
Section 6.1 Inclusion Criteria, Disease-Specific Inclusion Criteria	Changed entry criteria requiring endoscopy to be performed within 14 rather than 10 days before baseline	To accommodate the time for central reading and scoring of endoscopy, the time from screening endoscopy to randomization was extended to 14 days. This change does not impact the baseline endoscopic evaluation.
Section 6.1 Inclusion Criteria, Disease-Specific Inclusion Criteria	Modified wording: “have evidence of UC extending beyond the rectum (more proximal to the rectosigmoid junction)...”	Editorial change
Section 6.1 Inclusion Criteria, Prior Medication Failure Criteria	Prednisone-equivalent language clarified in Inclusion Criterion 8(a): oral corticosteroid excluding budesonide MMX and beclomethasone dipropionate gastro-resistant prolonged-release tablet”	Clarification added to the corticosteroid conventional therapy failure inclusion criterion excluding budesonide MMX and beclomethasone dipropionate gastro-resistant prolonged-release tablet as these 2 medicines are orally available steroids with high first-pass metabolism, leading to limited systemic exposure. These preparations are approved or commonly used for the treatment of mild-moderate UC in some countries. Prior failure of these therapies does not qualify as conventional therapy failure.
Section 6.1 Inclusion Criteria, Biologic-failed patients	Clarified that the medication used to qualify the patient for entry into this category must be approved for the treatment of UC, deleting reference to the country of use at the time of use	Clarified language regarding approved therapies
Section 6.1 Inclusion Criteria, Study Procedure Inclusion Criteria	Removed assessment required by investigator due to the lab thresholds already described in Inclusion Criterion 11	Clarification of assessment
Section 6.2 Exclusion Criteria, Gastrointestinal Exclusion Criteria	Exclusion criteria clarified that patients who have had extensive colonic surgery for UC or for other reasons are excluded	Clarification of exclusion criteria
Section 6.2 Exclusion Criteria,	Criteria clarified from	Clarification of exclusion criteria

Section # and Name	Description of Change	Brief Rationale
Criteria for Prohibited Medications	‘Discontinuing Prohibited Medications’ to ‘Prohibited Medications’	
Section 6.2 Exclusion Criteria, Criteria for Prohibited Medications	Oral budesonide standard formulation added to Exclusion Criterion 19(a).	Clarification of exclusion criterion
Section 6.2 Exclusion Criteria, Infectious Disease Exclusion Criteria	Deleted ‘toxin’ from <i>C. difficile</i> in Exclusion Criterion 27	Clarification of what constitutes a <i>C. difficile</i> infection
Section 6.2 Exclusion Criteria, Infectious Disease Exclusion Criteria	Modified wording for extraintestinal infection criteria deleting redundant phrase	Editorial change
Section 6.2 Exclusion Criteria, Infectious Disease Exclusion Criteria	Changed: “patients with nonserious extraintestinal infections not adequately treated prior to screening” from “must have been adequately treated prior to screening”	Editorial change
Section 6.2 Exclusion Criteria, General Exclusion Criteria	Added C-SSRS to Exclusion Criterion 37	Editorial change
Section 6.4 Screen Failure	Changed to: “stool for <i>C. difficile</i> stool toxin/stool culture/stool ova and parasites”	Clarified screen failure criteria related to <i>C. difficile</i> infection
Section 7.7 Concomitant Therapy	Deleted text to align with other sections of the protocol.	Since all permitted UC concomitant medications have to remain at stable doses throughout the trial, deleted reference to corticosteroids since tapering of corticosteroids occurs in the maintenance study. In addition, removed discussion of treatment failure since treatment failure is defined in other sections of the protocol.
Section 7.8.3.2 Management of Hypersensitivity, Infusion Related Events, and Infusion 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 would be required for this sample collection.
Section 7.8.3.2 Management of Hypersensitivity, Infusion Related Events, and Infusion Site Reactions	Under “Other Infusion-Related Events and Infusion Site Reactions” clarified reaction consisting of headache, rigors and/or temperature >38°C	Clarification of criteria for other infusion related events
Section 7.8.3.2 Management of Hypersensitivity, Infusion Related	Added “These samples will also be used for tryptase, complement	Additional assessments added to better understand the possible

Section # and Name	Description of Change	Brief Rationale
Events, and Infusion Site Reactions	(C3/C4), and cytokine panel assays.”	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 would be required for this sample collection.
8.1.1. Permanent Discontinuation from Study Treatment, Safety Criteria for Study Drug Discontinuation	The patient requiring a proctocolectomy or partial colectomy during the study was added to safety criteria for drug discontinuation	Clarification of safety criteria for drug discontinuation
Table 9.1. Efficacy Assessments, Table AMAN.4.	Term “Mucosal Healing” deleted from Histologic remission endpoint definition	Clarification of term “histologic remission”
Table 9.1. Efficacy Assessments, Table AMAN.4.	“Mucosal Healing” endpoint definition added to table	Clarification to be consistent with Section 4 Objectives and Endpoints
Table 9.1. Efficacy Assessments, Table AMAN.4.	“Histologic Response” endpoint definition removed	Since there is no histologic response endpoint in Section 4, this definition is not needed and therefore was removed.
Table 9.1. Efficacy Assessments, Table AMAN.4.	Footnote under Table AMAN.4 has been deleted	Clarification to be consistent with Section 4 Objectives and Endpoints
Table 9.1. Efficacy Assessments, Table AMAN.4.	Term “bowel movement urgency improvement” added to endpoint definition table	Now included as a major secondary endpoint because of unmet patient needs and the symptom being one of the most meaningful and important symptoms from patient perspective
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	Window changed for a flexible sigmoidoscopy or colonoscopy to be performed from within 10 days to 14 days prior to randomization	This change was made to be consistent with changes in Section 6.1
Section 9.1.1.3. Endoscopy, 3.	Added extent of disease clarification. Added clarification that patients with rectal sparing on baseline endoscopy must have documentation of rectal involvement on a prior endoscopy	This change was made to be consistent with changes in Section 6.1
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	Clarification of when to discuss with medical monitor the need for colonoscopy vs. flexible sigmoidoscopy to assure appropriate

Section # and Name	Description of Change	Brief Rationale
	and after discussion with the medical monitor as appropriate.	consideration for patient safety.
Section 9.1.1.3. Endoscopy	Added that if a patient undergoes early termination soon after screening endoscopy, the need for ETV endoscopy should be discussed with the medical monitor.	Clarification of when to discuss with medical monitor the need for additional endoscopy to assure appropriate consideration for patient safety
9.1.2.1 Major Secondary Endpoints	Added “Bowel movement urgency improvement at Week 12”	Change reflecting Bowel movement urgency improvement at Week 12 moved from other secondary objective/endpoint to major secondary objective/endpoint.
9.1.2.1.1. Patient Reported Outcome Instruments	Description of Urgency NRS added to major secondary endpoints and deleted from other secondary endpoints	Change reflecting move of endpoint to major secondary endpoint category.
9.1.2.2.1 Physician Reported Instrument	Added description of UCEIS	Due to the addition of the objective/endpoint, added description of the instrument
9.1.2.2.2 Patient Reported Outcome Instruments	Moved Fatigue NRS to this section	Change made to reflect move of Fatigue NRS from exploratory to other secondary endpoint.
9.1.3.1.1. Patient Reported Outcome Instruments	Added fatigue in diary patient reporting items	Editorial correction of omission from this section.
Section 9.4.4. Immunogenicity Assessments	Added that ADA and PK will be collected for other infusion-related events and infusion site reactions. 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	Added ADA and PK assessments to be consistent with Section 7.8.3.2. 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 would be required for this sample collection.
Section 9.4.5.3. Tuberculosis Screening, Interpretation of Screening Tests for LTBI	For the treatment of LTBI, added that CDC guidelines are to be used for the US and the WHO guidelines are to be followed for countries outside of the US	Clarification of guidance for LTBI treatment
Section 9.4.5.7. Stool Testing, <i>C. difficile</i>	Reference to “stool toxin assay” removed	Editorial change
Section 9.5 Pharmacokinetics	CCI [REDACTED]	Clarification of what vendor is performing assay development activities

Section # and Name	Description of Change	Brief Rationale
10.1. Sample Size Determination	Power calculations in study population updated to be consistent with current population. Rates for clinical remission changed from “maintaining” to “achieving”.	Power calculations in study updated to reflect changes in the assumed proportion of biologic- and conventional-failed patients. Editorial changes made
Section 10.3.1.1.Missing Data Imputation	Deleted “or take rescue medication prior to the time point of interest”	Modifications made to align with other recent UC clinical trials and to clarify that patients who require treatment with rescue medication should be discontinued from the trial as described in Section 8.1.1 of the protocol. Therefore, imputing such patients as nonresponders will be performed because the data will be missing.
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 footnotes added; one footnote deleted	Clarification of procedures. Updates made to align with Section 7.8.3.2 Management of Hypersensitivity, Infusion Related Events, and Infusion Site Reactions of the protocol
Appendix 3. Section 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 for the Assessment of Ulcerative Colitis Activity	Note added to table for stool frequency	Definition of normal stool 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 9 Prohibited Medications	Term “washout periods” has been replaced with “discontinuation windows for prohibited medications”	Clarification of discontinuation windows for prohibited medications
Appendix 9. Prohibited Medications	Replaced table heading category “Conditions for Washout” with “Prohibited Medication Restrictions”	Clarification of discontinuation windows for prohibited medications
Appendix 9. 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 9. Prohibited Medications	Added “for UC” to IV corticosteroids category	Clarification of restrictions for IV corticosteroid use for UC vs. non

Section # and Name	Description of Change	Brief Rationale
		UC indication.
Appendix 9. 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 10. Permitted Medications with Dose Stabilization	Added sulfasalazine as another oral 5-ASA example	Clarification of drug class
Appendix 10. 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 10. 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 a permitted medication during the study along with prednisone or equivalent or budesonide MMX.
Appendix 10. 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 underscores.

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

Objectives/Endpoints

Objectives	Endpoints
Major Secondary^a	
<ul style="list-style-type: none"> To evaluate the efficacy of treatment with <u>mirikizumab compared to placebo in inducing bowel movement urgency improvement at Week 12 in patients with bowel urgency symptoms at baseline</u> 	<ul style="list-style-type: none"> The proportion of patients with bowel movement urgency improvement at Week 12 as defined in the <u>study statistical analysis plan (SAP)</u>
Other Secondary (continued)	
<ul style="list-style-type: none"> To evaluate histologic remission (mucosal healing) between mirikizumab and placebo at Week 12 	<ul style="list-style-type: none"> Proportion of patients in histologic remission, as defined in the histopathology charter <u>SAP</u>
<ul style="list-style-type: none"> To evaluate the time to symptomatic response 	<ul style="list-style-type: none"> Time to symptomatic response, defined as at least a 30% decrease from baseline in <u>the composite clinical endpoint of the sum of SF and RB subscores</u>
<ul style="list-style-type: none"> To evaluate the effect of mirikizumab compared to placebo on changes in the urgency numeric rating scale (NRS) at Week 12 	Change from baseline in: <ul style="list-style-type: none"> Urgency NRS at Week 12
<ul style="list-style-type: none"> To evaluate the efficacy of mirikizumab compared to placebo in <u>Ulcerative Colitis Endoscopic Index of Severity (UCEIS) endoscopic remission at Week 12</u> 	<ul style="list-style-type: none"> The proportion of patients with a <u>UCEIS score of ≤1 at Week 12</u>
<ul style="list-style-type: none"> To evaluate the efficacy of mirikizumab compared to placebo in <u>mucosal healing at Week 12</u> 	<ul style="list-style-type: none"> The proportion of patients with <u>mucosal healing at Week 12</u>, defined as achieving both: <ul style="list-style-type: none"> Histologic remission, as described in the histopathology charter <u>SAP</u>, and Endoscopic remission, defined as <u>ES = 0 or 1 (excluding friability)</u>
<ul style="list-style-type: none"> To evaluate the efficacy of mirikizumab compared to placebo on changes in <u>fatigue at Week 12</u>. 	<ul style="list-style-type: none"> Change from baseline in <u>Fatigue NRS scores at Week 12</u>.

1. Synopsis

Statistical Analysis

(1) The randomized study population will include approximately ~~5060%~~ biologic-failed patients and approximately ~~5040%~~ conventional-failed patients.

(2) The predicted clinical remission rates at Week 12 for mirikizumab versus placebo are expected to be ~~21.6~~ 23% versus ~~6.9-7.8%~~ (biologic-failed patients: 16% versus 3.5%; conventional-failed patients: 30% versus 12%).

The primary endpoint of this study is ~~to~~ test the hypothesis that mirikizumab is superior to placebo in inducing **clinical remission** at Week 12 in patients with moderately to severely active UC. Given the assumptions described above, a sample size of 1160 patients are expected to provide >90% power to demonstrate that mirikizumab is superior to placebo in achieving this endpoint, ~~as assessed using~~ based on a chi-square test with a 2-sided significance level of 0.00125.

Patients who complete Study AMAN may be eligible to participate in Study AMBG, a 40-week maintenance study. ~~One endpoint of interest in~~ The primary objective of Study AMBG is to test the hypothesis that mirikizumab is superior to placebo in ~~maintaining~~ achieving clinical remission at Week 40 of Study AMBG (Week 52 of continuous therapy) amongst patients induced into clinical ~~remission~~ response with mirikizumab at Week 12 of Study AMAN. A sample size of 1160 patients in Study AMAN is predicted to ensure that there will be a sufficient number of biologic-failed patients in clinical remission at Week 12 of Study AMAN who will enter Study AMBG, ~~—This is expected to provide in order to achieve an approximately 980%~~ power to demonstrate that mirikizumab is superior to placebo in achieving this the primary endpoint in Study AMBG, as assessed based on using a chi-square test with a 2-sided significance level of 0.05.

2. Schedule of Activities

Table AMAN.1. Schedule of Activities

Visit 5: 85 ± 4-7

Procedure added to V0: Explain UC remission stool frequency question to patient; Notes: Investigator or site staff should explain the purpose of UC remission question in the TrialSlate (tablet) device before the patient answers the question to ensure accurate data capture. Errors in response cannot be corrected once response is saved and confirmed by the patient.

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

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

ADA Assessment: Patients with potential hypersensitivity or infusion-related event should have sample taken as soon as possible after event occurs

C. Difficile Testing: visits added to V5, ETV, and V997

Endoscopy with biopsies: Screening endoscopy within ~~10~~14 days of V1. Please refer to Section 9.1.1.3 for procedure clarification.

PGRC: V1 visit deleted

Abbreviations: DNA = deoxyribonucleic acid; RB = rectal bleeding; SF = stool frequency;

Footnotes:

f Clostridium difficile tests at V5 and ETV may be performed for patients who do not move into Study AMBG.

g Clostridium difficile test at UV may be performed if visit is due to worsening SF and/or RB.

4. Objectives and Endpoints

See Section 1 Synopsis Objective(s)/Endpoints above

6.1. Inclusion Criteria

Disease-Specific Inclusion Criteria

[4.] have had an established diagnosis of UC of ≥ 3 months in duration before baseline (Week 0), which includes endoscopic evidence of UC and a histopathology report that supports a diagnosis of UC (see Section 9.1.1.3). Supportive endoscopy and histopathology reports must be available in the source documents. Patients with rectal sparing on baseline endoscopy must have documentation of rectal involvement on a prior endoscopy and histopathology report to confirm UC diagnosis.

[5.] have moderately to severely active UC as defined by a modified Mayo score (MMS) of 4 to 9 with an endoscopic subscore (ES) ≥ 2 , with endoscopy performed within ~~10~~14 days before baseline.

[6.] ~~have evidence of UC extending proximal to the rectum (distal to the rectosigmoid junction, which lies approximately 10-15 cm from anal margin).~~ have evidence of UC extending beyond the rectum (more proximal to the rectosigmoid junction). The rectosigmoid junction lies approximately 10 to 15 cm from the anal margin.

6.1. Inclusion Criteria

Prior Medication Failure Criteria

[8a.] **Conventional-failed patients:** Patients who have an inadequate response to, loss of response to, or are intolerant to at least one of the following medications:

- corticosteroids
 - corticosteroid-refractory colitis, defined as signs and/or symptoms of active UC despite oral prednisone (or equivalent oral corticosteroid excluding budesonide MMX and beclomethasone dipropionate gastro-resistant prolonged-release tablet) at doses of at least 30 mg/day for a minimum of 2 weeks; or

[8b.] Biologic-failed patients: Patients who have an inadequate response to, loss of response to, or are intolerant to biologic therapy for UC (such as anti-TNF antibodies or anti-integrin antibodies) or to janus kinase (JAK) inhibitors (such as tofacitinib). The medication used to qualify the patient for entry into this category must be approved for the treatment of UC ~~in the country of use, at the time of use.~~ **Investigators must be able to document an adequate clinical trial of the medication.** Patients should fulfill 1 of the following criteria:

- Inadequate response: Signs and symptoms of persistently active disease despite induction treatment at the approved induction dosing that was indicated in the product label ~~at the time of use,~~ or

6.1. Inclusion Criteria

Study Procedure Inclusion Criteria

[11.] have clinically acceptable central laboratory test results at screening (retesting is allowed for hematology and chemistry), ~~as assessed by the investigator,~~ including:

6.2. Exclusion Criteria

Gastrointestinal Exclusion Criteria:

[14.] previous bowel resection or intestinal or intra-abdominal surgery:

- have had extensive colonic surgery for UC or for other reasons (for example, subtotal colectomy), or are likely to require surgery for the treatment of UC during the study. Patients who have had limited colonic surgery ~~for UC~~ (for example, segmental colonic resection) may be allowed in the study, if this does not affect the assessment of efficacy. Discussion with the sponsor should occur prior to screening of such patients.

6.2. Exclusion Criteria

Criteria for ~~Discontinuing~~ Prohibited Medications

[19a.] corticosteroid enemas, corticosteroid suppositories, oral budesonide standard formulation, or a course of IV corticosteroids within 2 weeks prior to screening endoscopy.

6.2. Exclusion Criteria

Infectious Disease Exclusion Criteria

[27.] had *Clostridium difficile* or other intestinal infection within 30 days of screening endoscopy, or test positive at screening for *C. difficile* ~~toxin~~ or for other intestinal pathogens.

[28.] patients with serious, opportunistic or chronic/recurring extraintestinal infections should be adequately treated and off antibiotics for 30 days without recurrence of symptoms prior to screening. ~~— Serious extraintestinal infections include but are including but~~ not limited to the following:

[29.] Patients with nonserious extraintestinal infections ~~must have been~~not adequately treated prior to screening.

6.2. Exclusion Criteria

General Exclusion Criteria:

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

OR

marked yes to C-SSRS suicide behaviors questions during the screening period prior to dosing at Visit 1;

6.4. Screen Failures

Patients who have failed screening because of Exclusion Criterion [27] may be rescreened once when the reason for screen failure has resolved. It is recommended that the investigator confirms the patient has a negative stool for *C. difficile* ~~stool toxin~~/stool culture/stool ova and parasites (as applicable) before performing additional rescreening investigations (see Section 9.4.5.7).

7.7. Concomitant Therapy

Patients taking permitted UC concomitant medications ~~other than oral corticosteroids~~, are to keep doses stable unless modifications are needed due to AEs and follow the instructions regarding dose stabilization as detailed in Appendix 10. ~~Administration of prohibited UC medications, approved or investigational, constitutes treatment failure.~~ Use of such medications should not be withheld if, in the opinion of the investigator, failure to prescribe them would compromise patient safety. Patients who require a prohibited medication to treat their UC (see Appendix 9) need to be discontinued from study drug and complete an ETV and posttreatment follow-up visits.

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

Hypersensitivity Events

- After patient's stabilization, an ADA and PK sample should be collected; additional samples should be obtained 4 and 12 to 16 weeks after the event. 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 $>38^{\circ}\text{C}$ (in the absence of other signs or symptoms of a systemic hypersensitivity reaction),

- 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 to 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.
- Systemic hypersensitivity event or anaphylaxis to ~~mirikizumab~~ study drug.

9.1. Efficacy Assessments

Table AMAN.4. Endpoint Definitions

Endpoint	Definition
Histologic remission (mucosal healing)	<ul style="list-style-type: none"> • This definition will be specified in the histopathology charter <u>statistical analysis plan (SAP)</u>
Mucosal healing	<ul style="list-style-type: none"> • <u>Histologic remission as described in the SAP, and</u> • <u>Endoscopic remission defined as ES = 0 or 1 (excluding friability)</u>
Histologic response	This definition will be specified in the histopathology charter
Bowel movement urgency improvement	<u>This definition will be specified in the SAP</u>

~~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 clinical study report~~

9.1.1.2. Mayo Score

Stool Frequency (SF): 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 total 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 screening visit. ~~Normal SF for that patient is on the reported SF 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.~~

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.

9.1.1.3. Endoscopy

Endoscopy will be used to determine the Mayo ES at screening and Week 12 (or ETV). Site and blinded central reading of endoscopies will be used to determine ES.

A flexible sigmoidoscopy or colonoscopy will be performed on all patients during screening, within ~~10~~14 days prior to randomization.

3. Patients who do not have the report of a completed, full colonoscopy available in source documents to establish extent of the disease. Patients with rectal sparing on baseline endoscopy must have documentation of rectal involvement on a prior endoscopy.

4. Where, in the opinion of the investigator, a colonoscopy is indicated at screening, for example, to confirm that a recent removal of an adenomatous polyp is complete prior to randomization.

If a patient already has up-to-date surveillance for dysplasia and/or up-to-date screening for colorectal cancer, the endoscopy report and histopathology report (if applicable) used to support this must be available in the source documents, in order to satisfy Inclusion Criterion [7].

Patients who undergo colonoscopy at screening do not require a separate flexible sigmoidoscopy in the same screening period.

At Week 12 (or ETV), ~~patients will undergo~~ a flexible sigmoidoscopy is recommended for all patients. Colonoscopy can be performed instead of flexible sigmoidoscopy at Week 12 for clinically indicated reasons in the judgement of the investigator and after discussion with the medical monitor as appropriate. The endoscopy report and histopathology report (if biopsies are sent to the local histopathology laboratory) must be available in the source documents. Patients who undergo a flexible sigmoidoscopy at an ETV will not undergo additional endoscopies within the study. Patients who discontinue the study drug because of pregnancy **will not** undergo a flexible sigmoidoscopy at their ETV.

If a patient undergoes early termination soon after screening endoscopy, the need for ETV endoscopy should be discussed with the medical monitor.

9.1.2.1. Major Secondary Endpoints

The major secondary endpoints are as follows:

- Clinical response at Week 12 in the biologic-failed population.
- Bowel movement urgency improvement at Week 12.

9.1.2.1.1. Patient Reported Outcome Instruments

The Urgency Numeric Rating Scale (NRS) (see Appendix 7 for description) is a patient-reported outcome (PRO) instrument collected using a patient eDiary. The Urgency NRS will be used to determine the secondary endpoint for bowel movement urgency improvement.

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. Patient Reported Outcome Instruments

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

- Abdominal Pain ~~Numeric Rating Scale (NRS)~~
- Fatigue NRS
- ~~Urgency NRS~~

9.1.3.1.1. Patient Reported Outcome Instruments

In addition to stool frequency and rectal bleeding discussed in Section 9.1.1.2, and abdominal pain and urgency discussed in Section 9.1.2.2.1, fatigue is measured using an 11-point NRS, where ‘0’ = “No Symptom” and ‘10’ = “Symptom as bad as I could imagine”. The diary also includes items that asks the patient to report stool consistency, the frequency of night-time stools, fatigue, and overall disease severity.

The following exploratory endpoints will be assessed daily via the electronic diary tool:

- Patient’s Global Rating of Severity (PGRS)
- ~~Fatigue NRS~~

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 to 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 should be recorded.

9.4.5.3. Tuberculosis Screening

Interpretation of Screening Tests for LTBI

Patients with a diagnosis of LTBI, based on a positive IGRA test result or a positive TST response, and no evidence of active TB on medical history, physical examination and chest x-ray, may be rescreened once and enrolled if they are treated for LTBI and meet the following requirements (as well as all other study entry criteria):

- have received at least 4 weeks of appropriate ongoing prophylactic 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 (WHO LTBI [WWW])

9.4.5.7. Stool Testing

C. difficile Toxin

- A stool sample for *C. difficile* toxin will be obtained at screening. 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.
- Patients should test negative ~~must have a “negative” test for *C. difficile* stool toxin (*C. difficile* EIA)~~ in order to be randomized (Exclusion Criterion 27). Re-testing is allowed within the same screening period if there is a technical difficulty in performing or reporting the *C. difficile* ~~toxin~~ assays, or if in the judgement of the investigator, the patient’s symptoms or signs are not consistent with *C. difficile* infection.
- Patients who test positive at screening for *C. difficile* can be re-screened once for the study, provided that they have been adequately treated and off antibiotics for 30 days. Patients who have been adequately treated for *C. difficile* with fecal microbial transplantation or IV immunoglobulin therapy can be re-screened once for the study, 30 days after completing their therapy. Testing for A *C. difficile* stool toxin assay should be repeated prior to re-screening, as a “negative” result is required prior to randomization.

9.5. Pharmacokinetics

CCI

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

10.1. Sample Size Determination

The power calculations for this study assume the following:

- (1) The randomized study population will include approximately ~~60~~50% biologic-failed patients and approximately ~~40~~50% conventional-failed patients.
- (2) The predicted clinical remission rates at Week 12 for mirikizumab versus placebo are expected to be ~~21.6~~23% versus ~~6.9~~7.8% (biologic-failed patients: 16% versus 3.5%; conventional-failed patients: 30% versus 12%).

The primary endpoint of this study is a test the hypothesis that mirikizumab is superior to placebo in inducing **clinical remission** at Week 12 in patients with moderately to severely active UC. Given the assumptions described above, a sample size of 1160 patients are expected to provide >90% power to demonstrate that mirikizumab is superior to placebo in achieving this

endpoint, based on ~~as assessed using~~ a chi-square test with a 2-sided significance level of 0.00125.

Patients who complete Study AMAN may be eligible to participate in Study AMBG, a 40-week maintenance study. ~~One~~ The primary objective of endpoint of interest in Study AMBG is to test the hypothesis that mirikizumab is superior to placebo in ~~maintaining~~ achieving clinical remission at Week 40 of Study AMBG (Week 52 of continuous therapy) amongst patients induced into clinical ~~remission response~~ with mirikizumab at Week 12 of Study AMAN. A sample size of 1160 patients in Study AMAN is predicted to ~~ensure that there will be~~ provide a sufficient number of biologic-failed patients in clinical remission at Week 12 of Study AMAN who will enter Study AMBG, ~~in order to achieve an approximately 80%~~ This is expected to provide >90% power to demonstrate that mirikizumab is superior to placebo in achieving ~~this the~~ primary endpoint in Study AMBG, ~~as assessed using~~ based on a chi-square test with a 2-sided significance level of 0.05.

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 nonresponders for the NRI analysis if they do not meet the categorical efficacy criteria or have missing clinical efficacy data at a time point of interest ~~or take rescue medication prior to the time point of interest.~~

11. References

- Arai M, Naganuma M, Sugimoto S, Kiyohara H, Ono K, Mori K, Saigusa K, Nanki K, Mutaguchi M, Mizuno S, Bessho R, Nakazato Y, Hosoe N, Matsuoka K, Inoue N, Ogata H, Iwao Y, Kanai T. The Ulcerative Colitis Endoscopic Index of Severity is useful to predict medium- to long-term prognosis in ulcerative colitis patients with clinical remission. *J Crohns Colitis*. 2016;10:1303-1309.
- 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.
- Tontini GE, Bisschops R, Neumann H. Endoscopic scoring systems for inflammatory bowel disease: Pros and cons. *Expert Rev Gastroenterol Hepatol*. 2014;8:543-554.

Appendix 1. Abbreviations

UCEIS Ulcerative Colitis Endoscopic Index of Severity

Appendix 2. Clinical Laboratory Tests

Other tests^a

Tryptaseⁱ

Complement (C3/C4)ⁱ

Cytokine panelⁱ

Abbreviations: ADA = anti-drug antibody; ETV = early termination visit; RB = rectal bleeding; SF = stool frequency; UV = unscheduled visit; V = visit.

- ~~h~~ Test required only at screening (Visit 0) to determine eligibility of patient for the study. Visit 0 stool sample will be used for *Clostridium difficile* and biomarker testing.
- h *Clostridium difficile* tests at V5 and ETV may be performed for patients who do not move into Study AMBG. *Clostridium difficile* test at UV may be performed if visit is due to to worsening SF and/or RB.
- i Test 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

Note:

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. The Normal SF (stool frequency) refers to when the patient was in remission or, if the patient has never achieved remission, the reported stool frequency 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.

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 9. Prohibited Medications

This section outlines medications that are prohibited during the treatment phase of the study, including discontinuation windows for prohibited medications ~~washout periods~~ prior to the screening endoscopy, 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	Prohibited Medication Restrictions Conditions for Washout
Anti-TNF antibodies (for example, infliximab, adalimumab or golimumab)	Discontinue at least 8 weeks prior to screening endoscopy and prohibited throughout duration of study
Anti-integrin antibodies (for example, vedolizumab)	Discontinue at least 8 weeks prior to screening endoscopy and prohibited throughout duration of study
Agents depleting B or T cells (for example, rituximab, alemtuzumab, or visilizumab)	Discontinue at least 12 months prior to baseline; patients remain excluded if evidence of persistent targeted lymphocyte depletion at the time of screening endoscopy
Immunomodulatory medications, including oral cyclosporine, IV cyclosporine, tacrolimus, mycophenolate mofetil, thalidomide, or JAK inhibitors (for example, tofacitinib)	Discontinue at least 4 weeks prior to screening endoscopy and prohibited throughout duration of study
Rectally administered 5-ASA therapies (enemas or suppositories)	Discontinue at least 2 weeks prior to screening endoscopy and prohibited throughout duration of study
<u>Rectally administered investigational preparations for UC such as arsenic preparations</u>	<u>Discontinue at least 4 weeks prior to screening endoscopy and prohibited throughout duration of study</u>
Rectally administered corticosteroids (enemas or suppositories)	Discontinue at least 2 weeks prior to screening endoscopy and prohibited throughout duration of study
IV corticosteroids <u>for UC</u>	Discontinue at least 2 weeks prior to screening endoscopy. A course of IV corticosteroids <u>for UC</u> is prohibited throughout duration of study
Systemic corticosteroids for non-UC indications (oral or IV)	Patients requiring systemic corticosteroids for non-UC indications <u>are excluded</u> . (except <u>Exceptions include</u> corticosteroids to treat adrenal insufficiency, <u>premedication for IP infusion, or</u> are excluded . <u>locally administered corticosteroids (e.g. inhaled, intranasal, intra-articular, topical)</u> are <u>allowed</u> (see Appendix 10).

Abbreviations: 5-ASA = 5-aminosalicylic acid; IV = intravenous; IP = investigational product; JAK = Janus Kinase; TNF= tumor necrosis factor; UC = ulcerative colitis.

Appendix 10. Permitted Medications with Dose Stabilization

Drug Class	Dose Stabilization Guidance
<u>Oral 5-ASAs, for example, mesalamine, balsalazide, olsalazine (and sulfasalazine for UC) (for example, mesalamine, balsalazide, olsalazine)</u>	May continue during study with stable dose encouraged.
<u>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)</u>	Prescribed dose must have been stable for at least 2 weeks before screening endoscopy and to remain stable for duration of study.
<u>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).</u>	<u>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.</u>

Abbreviations: 5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; AZA = azathioprine; IV = intravenous; IP = investigational product; UC = ulcerative colitis.

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