Protocol: I6T-MC-AMAM(e)

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo- and Active-Controlled, Treat-Through Study to Evaluate the Efficacy and Safety of Mirikizumab in Patients with Moderately to Severely Active Crohn's Disease

NCT03926130

Approval Date: 23 Feb 2022

Title Page

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Protocol Number: I6T-MC-AMAM

Amendment Number: e

Compound Number: LY3074828

Study Phase: 3

Acronym: VIVID-1

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

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Approval Date: Protocol Amendment (e) Electronically Signed and Approved by Lilly on date provided below.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment d	*07-Feb-2022*
Amendment c	*01-Apr-2021*
Amendment b	*18-Dec-2020*
Amendment a	*08-Apr-2020*
Original Protocol	*25-Mar-2019*

Amendment [e]

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The main purpose of this protocol amendment is to revise the co-primary and secondary objectives and endpoints in response to Food and Drug Administration (FDA) feedback.

Changes specific to certain protocol sections and a brief rationale are provided in the below table. Other minor typographical corrections not affecting content have also been made in the document.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Updated objectives and endpoints	Address FDA feedback and editorial consistency
1.3. Schedule of Activities	Removed 'mirikizumab assay development' from footnote 'n'	Clarification
1.3. Schedule of Activities	Revised footnote 'o' to indicate that results from the PK, immunogenicity (ADA) and exploratory hypersensitivity analyses in the event of a systemic allergic/hypersensitivity event will not be provided to the investigator	Clarification
1.3. Schedule of Activities	Revised footnote 'u' for diary compliance check to specify compliance percentage threshold	Clarification
1.3. Schedule of Activities	Added a footnote to allow Visit 2 assessments and dosing to be performed over 2 days after consultation with the medical monitor	Clarification

Section # and Name	Description of Change	Brief Rationale
2.2.1. Disease State and Treatment Goals	Replaced assessment by PRO to CDAI	Address FDA feedback
2.2.5. Preclinical and Clinical Studies of Mirikizumab	Updated the results of Studies 16T-MC-AMAN and 16T-MC-AMAG	Reflect most recent data
3. Objectives and Endpoints	Updated co-primary endpoints to include clinical response by PRO at Week 12, endoscopic response and clinical remission by CDAI at Week 52	Address FDA feedback
3. Objectives and Endpoints	Updated the following efficacy assessments in major and other secondary objectives and endpoints, • clinical remission by CDAI at Week 12 and 52, • clinical response by PRO at Week 12, • clinical remission by PRO at Week 52 • corticosteroid-free and either clinical remission by CDAI (removed by PRO) at Week 52 • stability of clinical remission by CDAI (removed by PRO)	Alignment to FDA feedback
3. Objectives and Endpoints	Added the following efficacy assessments in secondary objectives and endpoints • Urgency NRS at Week 12 and Week 52 • urgency remission at Week 52 • clinical response by CDAI (removed by PRO) at Week 4	Alignment to FDA feedback
3. Objectives and Endpoints	Added footnotes defining the mITT population and the efficacy endpoints (Clinical response by PRO, Endoscopic response, Clinical remission by CDAI, Clinical remission by PRO, Clinical response by CDAI, Urgency remission, Endoscopic remission, Endoscopic remission SES-CD ≤4)	Editorial consistency

Section # and Name	Description of Change	Brief Rationale
3. Objectives and Endpoints	Revised the section to remove duplicate objectives and endpoints	Editorial consistency
4.2. Scientific Rationale for Study Design	Added CDAI as an endpoint used for the primary objective	Alignment to FDA feedback
5.1. Inclusion Criteria Inclusion criterion 9d	Revised language for Crohn's disease treatment	Clarification
5.1. Inclusion Criteria Inclusion criterion 11b	Removed 'an established' from diagnosis of Gilbert's syndrome	Clarification
5.2. Exclusion Criteria Inclusion criterion 17	Removed adenoma without dysplasia and added colonic adenomatous polyp	Reflect most recent data
5.2. Exclusion Criteria Inclusion criterion 18	Removed colonic dysplasia and added any adenomatous polyp, any evidence of dysplasia in GI tract, or presence of any serrated lesion	Reflect most recent data
6.5.3. Corticosteroid Taper	Added oral corticosteroid dose initiation for participants not on corticosteroids at randomization	Clarification
6.5.4. Rescue Medicine	Removed "other than oral 5 ASA compounds or immunomodulators"	Correction
7.1.1. Criteria for Permanent Discontinuation of Study Drug	Removed intestinal dysplasia and added any colonic adenomatous polyp, any evidence of dysplasia in GI tract, or presence of any serrated lesion in safety considerations	Reflect most recent data
8.1.1. Primary Efficacy Assessments	Updated co-primary endpoints with the changes made in Section 3 (Objectives and Endpoints)	Alignment to FDA feedback
8.1.1. Primary Efficacy Assessments	Crohn's Disease Activity Index (CDAI) description added as part of Primary Efficacy Assessments Removed CDAI description	Alignment to co-primary objectives
8.2.5 Stool Testing	Updated *C. difficile* toxin testing	Clarified intended collection and testing

Section # and Name	Description of Change	Brief Rationale
8.2.6. Tuberculosis Testing	Updated retesting and confirmatory testing for participants who have been assessed by the PI to have a false positive TB test	Clarified intended collection and testing
8.5. Pharmacokinetics	Revised the additional samples to indicate that results from these samples in the event of a systemic allergic/hypersensitivity event will not be provided to the investigator	Clarification
8.5.1. Mirikizumab Assay Development	Removed this section with Corgenix samples collection and testing including sample use and retention	Clarification
9.1. Statistical Hypotheses	Revised primary hypothesis and major secondary hypotheses with the changes made in Section 3 (Objectives and Endpoints)	Address FDA feedback
9.2. Sample Size Determination	Revised estimated power for the co-primary endpoint	Address FDA feedback and editorial consistency
9.4.1. General Statistical Considerations	Replaced stratification factors with covariates and removed region and 95% confidence interval in Cochran-Mantel-Haenszel chi-square test Removed baseline corticosteroid use and region from restricted maximum-likelihood-based mixed effects model of repeated measures Added finalized graphical testing scheme to be provided in the SAP	Clarification and editorial consistency
9.4.1.3. Missing Data Imputation	Revised selected analysis for participants in placebo group	Clarification
9.4.1.4. Multiple Comparisons/Multiplicity	Added ‘mirikizumab’ to compare with placebo for Group 1 and to compare with ustekinumab for Group 2 Added pre-specified graphical scheme for comparisons in Group 1	Clarification and editorial consistency

Section # and Name	Description of Change	Brief Rationale
9.4.3.1. Primary Analyses	Updated primary analyses with the changes made in Section 3 (Objectives and Endpoints) and added definitions for clinical response by PRO and clinical remission by CDAI	Address FDA feedback
10.2. Appendix 2: Clinical Laboratory Tests	Updated *C. difficile* toxin testing	Clarified intended collection and testing
10.2. Appendix 2: Clinical Laboratory Tests	Removed 'serum for PK assessment and mirikizumab assay development' from exploratory biomarker samples	Clarified intended testing
10.7. Appendix 7: Permitted Medications	Revised language for Crohn's disease treatment	Clarification
10.12. Appendix 12: Provisions for Changes in Study Conduct During Exceptional Circumstances	Revised changes in study conduct during exceptional circumstances	Clarification for flexibility outlined for study conduct during exceptional circumstances
10.12. Appendix 12: Provisions for Changes in Study Conduct During Exceptional Circumstances	Added the following to 'Local laboratory testing option', "Local collection of screening laboratories for eligibility may be collected after approval by the sponsor and may not be allowed in all circumstances."	Clarification for local labs during exceptional circumstances

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1 Protocol Summary

1.1 Synopsis

Protocol Title: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo- and Active-Controlled, Treat-Through Study to Evaluate the Efficacy and Safety of Mirikizumab in Patients with Moderately to Severely Active Crohn's Disease

Acronym: VIVID-1

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-AMAM (AMAM) is a Phase 3 clinical trial designed to evaluate the safety and efficacy of mirikizumab in achieving endoscopic and clinical outcomes up to Week 52 in participants with moderately to severely active Crohn's disease (CD). Participants who have an inadequate response to, loss of response to, or are intolerant to corticosteroid or immunomodulator therapy for CD (termed "conventional-failed"), and those who have an inadequate response to, loss of response to, or are intolerant to biologic therapy for CD (termed "biologic-failed") will be included in the study.

Objectives and Endpoints

The study primary and secondary objectives will be assessed based on the Primary Analysis Set as defined in Section 9.3.

Objectives	Endpoints
Co-primary	
To evaluate the efficacy of mirikizumab is superior to placebo as assessed by • clinical response by PRO at Week 12 and endoscopic response at Week 52 • clinical response by PRO at Week 12 and clinical remission by CDAI at Week 52	• Proportion of participants achieving clinical response by PRO[c] at Week 12 and endoscopic response[d] at Week 52 • Proportion of participants achieving clinical response by PRO[c] at Week 12 and clinical remission by CDAI[e] at Week 52

Objectives	Endpoints
Major Secondary [a,b]	
To evaluate the efficacy of mirikizumab is superior to placebo at Week 52 as assessed by • endoscopic response • clinical remission by CDAI	• Proportion of participants achieving endoscopic response[d] at Week 52 • Proportion of participants achieving clinical remission by CDAI[e] at Week 52
To evaluate the efficacy of mirikizumab is superior to placebo at Week 12 as assessed by • endoscopic response • endoscopic remission • clinical remission by CDAI • Urgency NRS	• Proportion of participants achieving endoscopic response[d] at Week 12 • Proportion of participants achieving endoscopic remission SES-CD≤4[j] at Week 12 • Proportion of participants achieving clinical remission by CDAI[e] at Week 12 • Change from baseline in Urgency NRS at Week 12
To evaluate the efficacy of mirikizumab is superior to placebo as assessed by both clinical response by PRO at Week 12 and each below, individually: • clinical remission by PRO at Week 52 • endoscopic remission at Week 52 • corticosteroid-free and either clinical remission by CDAI or endoscopic remission at Week 52	Proportion of participants achieving clinical response by PRO[c] at Week 12 and each below, individually: • Clinical remission by PRO[f] at Week 52 • Endoscopic remission SES-CD≤4[j] at Week 52 • Corticosteroid-free from Week 40 to Week 52 and either clinical remission by CDAI[e] at Week 52 or endoscopic remission SES-CD≤4[j] at Week 52
To evaluate the efficacy of mirikizumab is superior to placebo at Week 52 as assessed by Urgency NRS	Change from baseline in Urgency NRS at Week 52

Objectives	Endpoints
To evaluate the efficacy of mirikizumab in comparison to ustekinumab at Week 52 as assessed by • endoscopic response (superior) • endoscopic remission (superior) • clinical remission by CDAI (non-inferior)	Proportion of participants achieving • Endoscopic response[d] at Week 52 • Endoscopic remission SES-CD≤4[j] at Week 52 • Clinical remission by CDAI[e] at Week 52

Abbreviations: AP = abdominal pain; CDAI = Crohn's Disease Activity Index; CS = corticosteroid; NRS = numeric rating scale; PRO = patient reported outcome; SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency.

[a] All primary and major secondary endpoint analyses will utilize the multiplicity control approach based on 'graphical multiple testing procedure' to control the overall family-wise type I error rate at a 2-sided alpha level of 0.05. The graphical multiple testing procedure described in Bretz et al. (2009, 2011) will be used.

[b] The order of testing of the major secondary endpoints will be detailed in the statistical analysis plan (SAP). Therefore, the order of the secondary endpoints does not reflect the order of the statistical testing.

[c] Clinical response by PRO is defined as at least a 30% decrease in SF and/or AP with neither score worse than baseline.

[d] Endoscopic response is defined as ≥50% reduction from baseline in SES CD Total Score.

[e] Clinical remission by CDAI is defined as CDAI total score <150.

[f] Clinical remission by PRO is defined as SF≤3 and not worse than baseline (as per Bristol Stool Scale Category 6 or 7) and AP ≤1 and no worse than baseline at Week 52.

[i] Endoscopic remission is defined as SES-CD Total Score ≤2

[j] Endoscopic remission SES-CD ≤4 is defined as SES-CD Total Score ≤4 and at least a 2-point reduction from baseline and no subscore >1

Overall Design:

Study AMAM is a Phase 3, multicenter, randomized, double-blind, double-dummy, parallel group, placebo and active controlled, treat-through study to evaluate the safety and efficacy of mirikizumab compared to placebo and ustekinumab. The study population includes participants with moderately to severely active CD who have an inadequate response to, loss of response to, or intolerance to conventional or biologic therapy for CD.

Disclosure Statement:

This is a parallel, double-blinded treatment study with three groups in Period 1 and four groups in Period 2.

Number of Participants:

Approximately 1100 participants will be randomly assigned to study intervention such that approximately 690 participants complete the study.

Intervention Groups and Duration:

Participants will be randomized in a 6:3:2 ratio to receive, respectively:

- Mirikizumab 900 mg intravenously (IV) every 4 weeks (Q4W) for 3 doses, then 300 mg subcutaneously (SC) Q4W
- Ustekinumab ~6 mg/kg IV for one dose, then 90 mg SC every 8 weeks
- Placebo
    - When Period 1 concludes (Week 12), responders continue receiving placebo, and
    - Nonresponders (NR) at Week 12 will receive mirikizumab as described above.

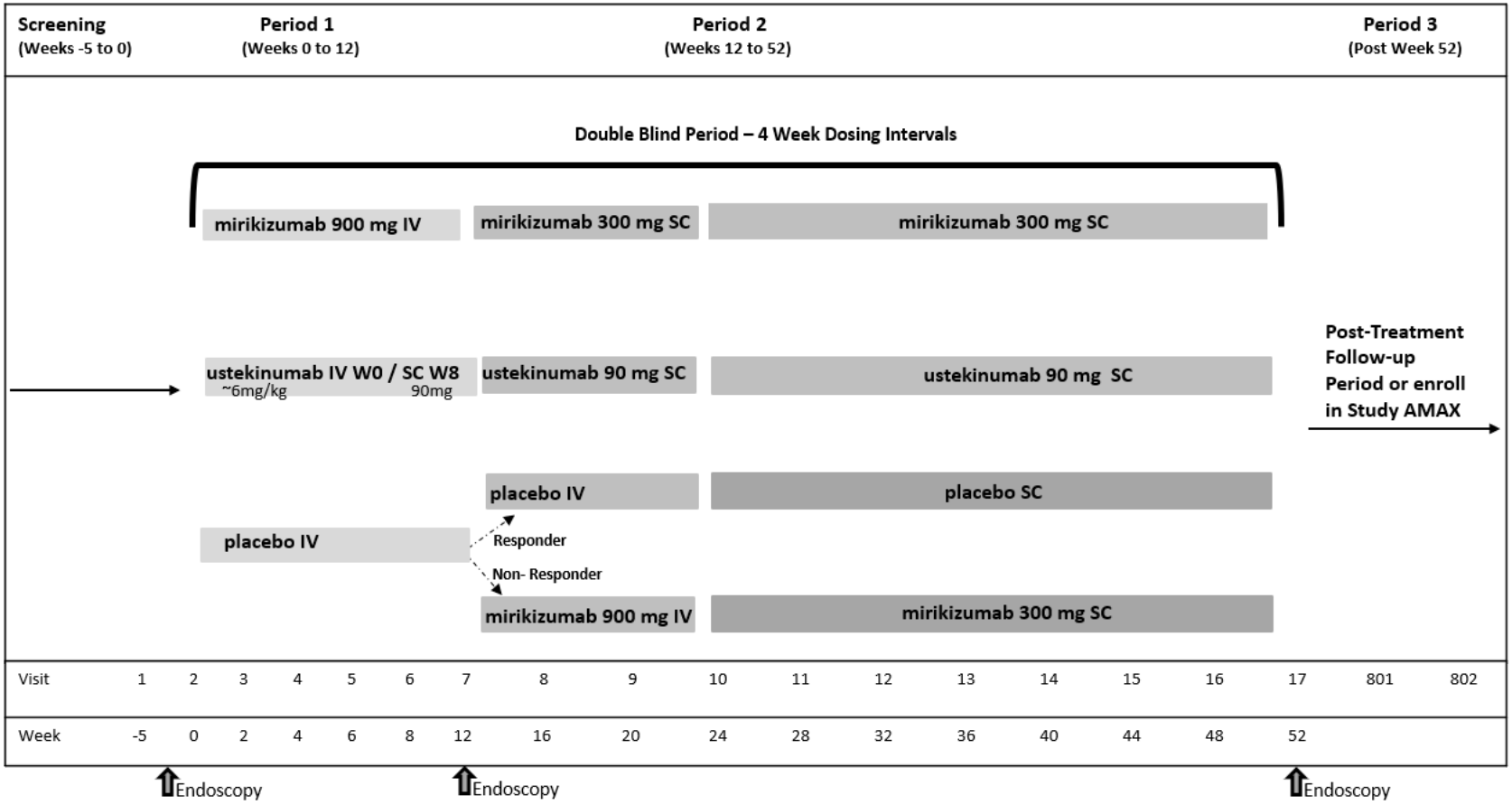
To maintain blinding, participants receive placebo in a double-dummy manner.

The maximum total duration of study participation for each participant is 73 weeks, across the following study periods:

- Screening: up to 5 weeks
- Intervention Period 1: 12 weeks
- Intervention Period 2: 40 weeks
- Post-Treatment Follow-Up: 12 to 16 weeks

Data Monitoring Committee: Yes

1.2 Schema



Abbreviations: IV = intravenous; mg = milligram; kg = kilogram; SC = subcutaneous

Note: From Week 8 through Week 20, all participants receive their assigned treatment and matching placebo via both IV and SC administration.

1.3 Schedule of Activities (SoA)

	Screening	Period 1						Period 2												UA/SV[ac]	Post-Treatment Follow-up	
Visit Number	**V1[a,b]**	**V2[b]**	**V3[c]**	**V4**	**V5[c]**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**ETV[w]**	**V997[x]**		**V801**	**V802**
Week Relative to Study Drug Start	**-5**	**0**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**N/A**	**N/A**		**LV/ETV + 4**	**LV/ETV +12/16**
Days Relative to Study Drug Start and Visit Interval Tolerance (Days)[ad]	**≤35 from V2**	**1**	**15 ± 3**	**29 ± 3**	**43 ± 3**	**57 ± 3**	**85 ± 6**	**113 ± 7**	**141 ± 7**	**169 ± 7**	**197 ± 7**	**225 ± 7**	**253 ± 7**	**281 ± 7**	**309 ± 7**	**337 ± 7**	**365 ± 7**	**N/A**	**N/A**		**± 10**	**± 10**
Informed consent	X																					
Preexisting conditions / Medical history / Relevant surgical history	X																					
Inflammatory bowel disease diagnosis forms	X																					
Inclusion/ Exclusion Criteria	X	X																				
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Alcohol use	X																					
Tobacco/ Nicotine use	X						X										X	X				
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Physical Evaluation																						
VS (T, PR, BP)[d]	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	Opt		X	X
Height	X																					
Weight	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	Opt	Opt		
Physical exam[e]	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	Opt		X	X
EIMs		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	Opt		X	X
Fistula evaluation		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	Opt		X	X
Clinician CDAI		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X				
12-lead ECG[f]	X																		Opt	Opt		
Chest x-ray[g]	X																		Opt	Opt		

	Screening	Period 1						Period 2												UA/SV[ac]	Post-Treatment Follow-up	
Visit Number	**V1[a,b]**	**V2[b]**	**V3[c]**	**V4**	**V5[c]**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**ETV[w]**	**V997[x]**		**V801**	**V802**
Week Relative to Study Drug Start	**-5**	**0**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**N/A**	**N/A**		**LV/ETV + 4**	**LV/ETV +12/16**
Days Relative to Study Drug Start and Visit Interval Tolerance (Days)[ad]	**≤35 from V2**	**1**	**15 ± 3**	**29 ± 3**	**43 ± 3**	**57 ± 3**	**85 ± 6**	**113 ± 7**	**141 ± 7**	**169 ± 7**	**197 ± 7**	**225 ± 7**	**253 ± 7**	**281 ± 7**	**309 ± 7**	**337 ± 7**	**365 ± 7**	**N/A**	**N/A**		**± 10**	**± 10**
TB Monitoring[ab]	X						X			X			X			X			Opt	Opt		
Laboratory Tests																						
Serum Chemistry / Hematology	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	Opt	Opt		
Fasting Lipid panel		X					X										X	X[y]	Opt	Opt		
FSH[h] (optional)	X																		Opt	Opt		
Urine pregnancy[i]		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	Opt		X	X
Serum pregnancy[j]	X																		Opt	Opt		
Urinalysis	X																		Opt	Opt		
Interferon-γ release assay (or tuberculin skin test[k])	X																		Opt	Opt		
HIV testing	X																		Opt	Opt		
HBV testing	X																		Opt	Opt		
HBV DNA[l]	X						X			X			X			X			Opt	Opt		
HCV testing[m]	X																		Opt	Opt		
Predose PK sample[n]		X		X		X	X	X		X			X							Opt		
Postdose PK sample[n,o]		X		X																Opt		
PK sample[n,o]																	X	X	Opt	Opt		X
Immunogenicity (ADA) samples[o]		X		X			X	X		X			X				X	X	Opt	Opt		X
Serum and plasma samples for cytokines		X		X		X	X	X			X						X	X	Opt	Opt		
hsCRP	X	X		X		X	X	X			X				X		X	X	Opt	Opt		
Serum and plasma for exploratory biomarkers		X		X		X	X				X						X	X	Opt	Opt		

	Screening	Period 1						Period 2												UA/SV[ac]	Post-Treatment Follow-up	
Visit Number	**V1[a,b]**	**V2[b]**	**V3[c]**	**V4**	**V5[c]**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**ETV[w]**	**V997[x]**		**V801**	**V802**
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Blood for RNA and DNA (epigenetic) exploratory biomarkers		X		X		X	X				X						X	X	Opt	Opt		
Blood for DNA pharmacogenetics[p]		X																	Opt	Opt		
Stool Samples[q]																						
Stool culture[s]	X																		Opt[r]	Opt		
C. Difficile testing[s]	X																		Opt	Opt		
Fecal calprotectin		X		X			X	X			X				X		X	X	Opt	Opt		
Exploratory fecal biomarkers		X		X			X	X			X				X		X	X	Opt	Opt		
Supply stool collection kit [t]						X										X			Opt	Opt		
Patient Diary																						
Patient diary dispensed	X																					
Diary compliance check[u]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Opt	Opt		
Diary collection																	X	X				
Questionnaires																						
IBDQ		X					X										X	X				
SF-36 v2 Acute		X					X										X	X				
EQ-5D-5L		X					X										X	X				
WPAI-CD		X					X										X	X				
PGIC				X		X	X										X	X				
FACIT-Fatigue		X					X										X	X				
IBD-DI	X																					
QIDS-SR16	X	X					X			X			X				X	X	Opt	Opt		
C-SSRS	X																					

	Screening	Period 1						Period 2												UA/SV[ac]	Post-Treatment Follow-up	
Visit Number	**V1[a,b]**	**V2[b]**	**V3[c]**	**V4**	**V5[c]**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**ETV[w]**	**V997[x]**		**V801**	**V802**
Week Relative to Study Drug Start	**-5**	**0**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**N/A**	**N/A**		**LV/ETV + 4**	**LV/ETV +12/16**
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DSI-CD	X																					
Endoscopy																						
Endoscopy / SES-CD with biopsies[v]	X						X										X	X	Opt	Opt		
Randomization and Dosing																						
Randomization[z]		X																				
Dosing[aa]		X		X		X	X	X	X	X	X	X	X	X	X	X						

Abbreviations: ADA = anti-drug antibodies (immunogenicity); AE = adverse event; anti-HBc+ = positive for anti-hepatitis B core antibody; AP = abdominal pain; BMC = bowel movement count; BP = blood pressure; CDAI = Crohn's Disease Activity Index; CDAI-SF= Crohn's Disease Activity Index – Stool Frequency; CRF = case report form; C-SSRS = Columbia-Suicide Severity Rating Scale; CXR = chest x-ray; DSI-CD= Disease Severity Index-Crohn's Disease; ECG = electrocardiogram; EIM = extraintestinal manifestation; EQ-5D-5L = European Quality of Life 5–Dimension 5 Level; ETV = early termination visit, FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; FSH = follicle-stimulating hormone; F/U=follow-up; 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; IBD-DI =Inflammatory Bowel Disease-Disability Index; IBDQ = Inflammatory Bowel Disease Questionnaire, IP = investigational product; LV = last visit; N/A = not applicable; NRS = numeric rating scale; Opt = optional procedure; PGIC = Patient Global Impression of Change; PGRS = Patient Global Rating of Severity; PK = pharmacokinetic; PR = pulse rate; QIDS-SR16 = Quick Inventory of Depressive Symptomatology-Self Report (16 items); SES-CD = Simple Endoscopic Score for Crohn's Disease; SF-36v2 Acute = Medical Outcomes Study 36-Item Short Form Health Survey; T = temperature; UA/SV = Unscheduled Assessments during a Scheduled Visit; V997 = unscheduled visit; V = visit; VS = vital signs; WPAI-CD = Work Productivity and Activity Impairment Questionnaire Crohn's Disease.

[a] Visit 1 procedures may be conducted over more than 1 day as long as all tasks are completed within the allowable visit tolerance. It is required that you have received and reviewed all of your screening laboratory test results, as well as screening endoscopy results, prior to randomization and dosing at V2. Please note at least 3 business days should be allowed for receipt of laboratory test results. Lab results can take up to 10 business days to obtain after the sample was received at the laboratory, and endoscopy results may take up to 5 business days after receipt of video.

[b] All screening/baseline activities should be completed prior to any study drug administration unless otherwise stated below.

[c] Telephone visit.

[d] Sitting blood pressure and pulse rate to be obtained at approximately the same time of day as ECG measurements and/or blood sampling. When multiple assessments are scheduled for the same visit, the preferred order of completion is: Vital signs, ECG (if applicable) then blood sampling.

[e] One complete physical examination (excluding pelvic, rectal, and breast examinations) will be performed at screening and will include peripheral lymph nodes. After screening, physical examinations include a symptom-directed evaluation as well as examination of eyes, heart, lungs, abdomen and visual examination of the skin.

[f] ECG should be completed prior to any blood draw. Participants should be supine for approximately 5 to 10 minutes before ECG collection and remain supine and awake during ECG collection.

[g] Chest radiography (CXR) (posterior-anterior view interpreted and reported by a radiologist or pulmonologist) will be performed at screening unless such radiography has been performed within 3 months before initial screening (provided the radiographs and/or formal report are available for the investigator's review). A computed tomography (CT) scan can be performed as an alternative to the CXR based on regional standard of practice.

[h] Optional, may be performed to confirm postmenopausal status.

[i] Urine pregnancy test to be performed only on women of childbearing potential. Done locally and **prior** to dosing.

[j] Serum pregnancy test to be performed only on women of childbearing potential.

[k] Participants who had a tuberculin skin test (TST) will return 48 to 72 hours after placement to have their test results read (See Section 8.2.6).

[l] Perform only if participant HBcAB+ with negative HBV DNA test at screening. Any enrolled participant who is HBcAB + will undergo monitoring of HBV DNA at specified intervals. Any participant with a positive HBV DNA test at any time must be discontinued from the study and receive appropriate follow-up medical care.

[m] Participants 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 24 weeks after completion of a full, documented course of an approved, potentially curative antiviral therapy for HCV.

[n] Serum for PK assessment.

[o] In the event of an systemic allergic/hypersensitivity event, blood samples will be collected for PK, immunogenicity (ADA) and exploratory hypersensitivity analyses at the following time points: as close as possible to: (1) the onset of the systemic allergic/hypersensitivity event, (2) the resolution of the systemic allergic/Hypersensitivity Event, and (3) 30 [±3] days following the systemic allergic/hypersensitivity events and (4)12 to 16 weeks after the event. Exploratory hypersensitivity samples may be analyzed for markers of basophil/mast cell activation (for example, tryptase), immune complex formation (for example, C3 levels) and cytokine release (for example, IL-6) as appropriate for the clinical presentation. The results will not be provided to the investigator.

[p] Sample can be obtained at any time at or after V2.

[q] Stool samples must be collected up to 3 days before endoscopy and prior to beginning bowel prep for endoscopy at Visits 7 and 17. For all other visits, samples may be collected on the day of visit. If stool collection is not possible on the day of the visit, the sample may be collected at home and returned to the site. Additional local stool testing (for example, ova and parasites) is allowed at the investigator's discretion.

[r] Optional per country requirements.

[s] Stool culture and *C. difficile* must be negative at screening prior to randomization.

[t] Instruct participants that the stool samples must be collected up to 3 days before endoscopy and prior to beginning bowel prep for endoscopy at Visits 7 and 17.

[u] Diary compliance check of >80% for each visit (BMC, CDAI-SF with Bristol Stool Scale, CDAI-AP, CDAI well-being, Abdominal Pain NRS, Urgency NRS, PGRS).

[v] Screening endoscopy must occur within 21 days (inclusive) of randomization. Allow 5 business days for receipt of endoscopy results prior to randomization (Visit 2). Biopsies will be taken during each endoscopy; instruction for collection will be provided in a laboratory manual. It is recommended that the collection of responses to study questionnaires, administration of IP, and endoscopy (with or without sedation) be performed on separate days within visit window with the endoscopy preceding the study questionnaires and IP administration. However, if logistical issues preclude this and all has to occur on same day, the following order of procedures must be followed: (1) Collection of responses to questionnaires; (2) Administration of IP with protocol-specific observation period (at least 1 hour); (3) Performance of endoscopy with or without sedation.

[w] Early Termination Visits (ETV) may occur on any day without regard to visit interval. An endoscopy should only be performed at the ETV if the visit occurs at least 16 weeks after the last endoscopy. An ETV endoscopy will not be performed during Period 1 or the post-treatment follow-up period.

[x] Unscheduled visits (V997) may be performed at the discretion of the investigator between protocol visits. During all unscheduled visits, concomitant medications and AEs must be completed. Other assessments are considered optional (defined as Opt), and if performed, require documentation via the appropriate standard (CRF, laboratory requisition, and/or source documentation).

[y] Fasting is not required for the lipid panel at an early termination visit.

[z] Randomization will be timed to begin no earlier than 14 days from the start of screening procedures.

[aa] Visit procedures and assessments must be completed prior to dosing, except as noted in the applicable footnotes above

[ab] Participants will be assessed for risk factors for TB (Appendix 10.4). If the participant has a risk factor(s), the investigator should conduct a thorough exam to evaluate for TB, including examination of peripheral lymph nodes and documentation of body temperature. If there are relevant physical findings, an IGRA and CXR should be performed. A CT scan can be performed as an alternative to the CXR based on regional standard of practice.

[ac] Unscheduled assessments may be performed during a scheduled visit at the discretion of the investigator and are considered part of that protocol scheduled visit. The optional assessments (defined as Opt), if performed, require documentation via the appropriate standard (CRF, laboratory requisition, and/or source documentation).

[ad] Visit 2 may be done over 2 days if needed, after consultation with medical monitor

2 Introduction

2.1 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-AMAM (AMAM) is a Phase 3 clinical trial designed to evaluate the safety and efficacy of mirikizumab in achieving endoscopic and clinical outcomes up to Week 52 in participants with moderately to severely active Crohn's disease (CD). Participants who have an inadequate response to, loss of response to, or are intolerant to corticosteroid or immunomodulator therapy for CD (termed "conventional-failed"), and those who have an inadequate response to, loss of response to, or are intolerant to biologic therapy for CD (termed "biologic-failed") will be included in the study.

2.2 Background

2.2.1 Disease State and Treatment Goals

Crohn's disease (CD) is a chronic disease of unknown etiology with environmental, genetic, and immunologic influences. Transmural inflammation affecting any part of the gastrointestinal tract from the mouth to the anus, usually appearing as discontinuous lesions, are normal characteristics for CD (Baumgart and Sandborn 2007). Symptoms include chronic diarrhea (often bloody and containing pus or mucus), abdominal pain (AP), weight loss, fever, fatigue, anemia, rectal bleeding, and a feeling of fullness in the abdomen. Symptoms depend on the severity of the disease and location of the disease, with most patients experiencing an abscess, fistula, stricture or an obstruction requiring surgical intervention. Relapsing–remitting symptoms, meaning that many patients have intermittent disease flares that are interspersed with periods of remission, is very common in CD (Lichtenstein et al. 2018).

Treatment goals in clinical practice are control of symptoms and healing of the intestinal mucosa. In clinical trials, these goals are reflected by assessing induction of response (typically within a 6-week to 12-week period) and maintenance of remission in the longer term (over 52 weeks of continuous treatment) as assessed by Crohn's Disease Activity Index (CDAI), including a reduction in stool frequency [SF] and AP). In both clinical practice and in clinical trials, assessment of the response to therapeutic interventions includes endoscopy to assess improvement in the endoscopic appearance of the mucosa and healing of ulcers.

2.2.2 Currently Available Treatments and Unmet Need

Medications used for the treatment of CD may include aminosalicylic acid (5-ASA)–containing medications (sulfasalazine, mesalazine, balsalazide, olsalazine), corticosteroids or budesonide, immunomodulator (example: azathioprine [AZA], 6-mercaptopurine [6-MP], and methotrexate [MTX]), antimicrobial therapy specific for CD and diet, and anti-tumor necrosis factor (TNF) agents (infliximab, adalimumab, certolizumab pegol) for treatment of CD resistant to treatment with corticosteroids or refractory to MTX or thiopurine therapy. Agents targeting leukocyte trafficking such as vedolizumab (an anti-integrin) are currently used in patients who have failed other therapies. Ustekinumab, an IL-12/23 (anti-p40) antibody, is recommended in patients who

have failed prior treatments with corticosteroids, immunomodulators, or anti-TNF agents. Adalimumab and certolizumab pegol are recommended for treatment of perianal fistulas.

A sizable proportion of the population with moderately to severely active Crohn's disease is unresponsive to, fail to tolerate, or lose response to conventional therapies or approved biologic therapies. The estimated rates of clinical remission in patients failing conventional therapy range from approximately 20% to 50%, depending on the biologic therapy evaluated. The estimated rates of clinical remission in the biologic-failure population is around 20% in all treated patients at 12 months (Kamm et al. 2011). Thus, there remains considerable unmet medical need for new treatment options, especially therapies with novel mechanisms of action that have the potential to have improved efficacy and maximize the proportion of patients who achieve clinical remission while maintaining a reassuring safety profile.

2.2.3 Interleukin-23 as a Therapeutic Target in Crohn's Disease

The contribution of IL-12 and IL-23 in driving the pathophysiology of CD have been explored in genetic and animal model studies. These studies would suggest that IL-23 plays a predominant role in inflammatory bowel disease (IBD) and, indeed, blocking IL-23 alone may be a more effective strategy than blocking both IL-12 and IL-23.

A number of observations suggest that CD is mediated by IL-12 and/or IL-23, potentially through the Th1 and Th17 pathways they induce (Monteleone et al. 1997; Berrebi et al. 1998; Parrello et al. 2000). Moreover, the predominant role for IL-23 in CD has been suggested by genomics studies (Duerr et al. 2006; Barrett et al. 2008). The role of IL-23 in driving intestinal inflammation has been shown in several mouse models of IBD (Hue et al. 2006; Uhlig et al. 2006; Elson et al. 2007; Maxwell et al. 2015), and mice with a genetic deletion of the p19 subunit of IL-23 have been shown to be protected in several models of intestinal inflammation (Hue et al. 2006; Kullberg et al. 2006; Yen et al. 2006).

The relative contribution of IL-12 and IL-23 to disease pathology in IBD has been explored in several studies. The results of these studies would indicate that IL-23, but not IL-12, promotes intestinal inflammation (Hue et al. 2006; Kullberg et al. 2006; Uhlig et al. 2006; Yen et al. 2006). Data from murine models of psoriasis demonstrating a protective role in dermatologic inflammation (Kulig et al. 2016), as well as clinical trials (Blauvelt et al. 2017; Reich et al. 2017a), would imply that IL-12 blockade may actually be counterproductive to the control of intestinal inflammation. These data suggest that the efficacy obtained with IL-12/23p40 blockade may be through the inhibition of IL-23 and provide a strong rationale for inhibiting IL-23 in CD.

2.2.4 IL-23p19 Blockade in Crohn's Disease

The efficacy of IL-23p19 blockade in CD has been demonstrated in recent Phase 2 studies evaluating the short-term efficacy and safety of two different IL-23p19 mAbs, risankizumab and MEDI2070 (Feagan et al. 2017, 2018; Sands et al. 2017). These Phase 2 studies explored a range of doses from 200 mg to 700 mg IV given up to Q4W through up to Week 12 and provide information regarding the short-term dose-response profile of IL-23p19 blockade in patients with moderately to severely CD. The data from these studies showed evidence of improvements in clinical signs and symptoms, reduction in inflammatory disease burden as evaluated by biomarkers, and evidence of endoscopic healing after a typical short-term induction period. It

should be noted that although these studies were small, no safety signals were identified relative to placebo through 12 weeks of treatment, and no additional safety signals were seen in open-label extensions of up to 52 weeks of treatment.

2.2.5 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 SC injection of human IL-23. Mirikizumab does not prevent IL-12 signaling in vitro.

A number of clinical studies of mirikizumab have been completed or are currently ongoing in participants with psoriasis, ulcerative colitis (UC), and CD.

Clinical studies in ulcerative colitis

Study 16T MC AMAC (AMAC) was a Phase 2, placebo-controlled, double-blind clinical trial of mirikizumab in participants with moderate-to-severe UC, for which induction and maintenance results are available. In the 12-week induction period, mirikizumab demonstrated efficacy for both endoscopic as well as symptomatic indices as assessed by multiple measures (Sandborn et al. 2018). Overall adverse event (AE) frequencies were similar for mirikizumab-treated and placebo-treated participants (Sandborn et al. 2018). In the maintenance period through Week 52, mirikizumab demonstrated durable efficacy for both endoscopic as well as symptomatic indices: among participants in clinical remission at Week 12, 61.1% (Q4W) and 38.5% (every 12 weeks [Q12W]) remained in clinical remission at Week 52. There were few serious adverse events (SAEs) and few discontinuations due to AEs over 52 weeks (D'Haens et al. 2019).

The Phase 3 LUCENT program comprises Study 16T-MC-AMAN (AMAN), a 12-week double-blind, placebo-controlled, Phase 3 induction study of mirikizumab in participants with moderate to severe UC who had failed conventional and/or biologic treatments. Mirikizumab met the primary endpoint of clinical remission at Week 12 compared to placebo ($p<0.0001$). At Week 12, mirikizumab when compared to placebo also achieved highly statistically significant p-values, including reduced bowel urgency, clinical response, endoscopic remission, symptomatic remission and improvement in endoscopic histologic inflammation. Mirikizumab also reduced symptoms among participants who had previously not responded to or stopped responding to biologic and/or JAK inhibitor therapies. The incidence of treatment-emergent AEs and SAEs among participants treated with mirikizumab was consistent with that of the previous Phase 2 mirikizumab study in UC and studies with the anti-IL-23p19 antibody class. The most common AEs included nasopharyngitis, anemia and headache for both placebo and mirikizumab-treated participants (Lilly 2021).

The Phase 3 LUCENT program also comprises of 16T-MC-AMBG (mirikizumab/placebo maintenance) and 16T-MC-AMAP (mirikizumab open-label extension) in participants with moderately to severely active UC; these studies are ongoing at the time of this writing.

Clinical studies in Crohn's disease

Study 16T-MC-AMAG (AMAG) was a Phase 2, placebo-controlled, double-blind clinical trial of mirikizumab in participants with active CD. Unblinded results are available from the completed 12-week induction period. The primary efficacy objective is to test the hypothesis

that treatment with mirikizumab is superior to placebo in the proportion of participants with endoscopic response at Week 12, defined as a 50% reduction from baseline in Simple Endoscopic Score for Crohn's Disease (SES-CD) score.

At Week 12, endoscopic response was significantly higher by the predefined 2-sided significance level of 0.1 for all mirikizumab groups compared with placebo (200 mg: 25.8%, 8/31, 95% confidence interval [CI], 10.4–41.2, P = .079; 600 mg: 37.5%, 12/32, 95% CI, 20.7–54.3, P = .003; 1000 mg: 43.8%, 28/64, 95% CI, 31.6–55.9, P < .001; PBO: 10.9 %, 7/64, 95% CI, 3.3–18.6). Endoscopic response at Week 52 was 58.5% (24/41) and 58.7% (27/46) in the IV-C and SC groups, respectively. Thus, mirikizumab effectively induced endoscopic response after 12 weeks in participants with moderate-to-severe CD and demonstrated durable efficacy to Week 52. Frequencies of AE in the mirikizumab groups were similar to PBO. Treatment with mirikizumab has shown clinically relevant and consistent treatment effect in reducing or resolving endoscopic inflammation and patient-reported symptoms in participants with moderately to severely active CD. Through Week 52, frequencies of treatment-emergent AEs were similar across all groups. Frequencies of serious AE and discontinuations due to AE were higher in the nonrandomized maintenance cohort. There were no deaths in any study period, and no malignancies or instances of veno-occlusive disease (including pulmonary embolism) reported in the induction or maintenance period of the study (Sands et al. 2021).

Additional nonclinical and clinical trial data are summarized in the Investigator's Brochure (IB).

2.3 Benefit/Risk Assessment

At the time of this benefit/risk assessment, mirikizumab has demonstrated efficacy in blinded, placebo-controlled Phase 2 studies in psoriasis (Reich et al. 2017b), UC (Sandborn et al. 2018; D'Haens et al. 2019) and CD. In the Phase 2 CD study AMAG, treatment with mirikizumab has shown clinically relevant and consistent treatment effect in reducing or resolving endoscopic inflammation and patient-reported symptoms in participants with moderately to severely active CD. Evaluation of unblinded safety data in ongoing studies in psoriasis, UC and CD with dose regimens of up to 1000 mg IV Q4W for up to 52 weeks and up to 300 mg SC Q4W for up to 104 weeks have shown a safety profile generally consistent with the IL-23 antibody class. Across the ongoing Phase 2 mirikizumab studies, immediate hypersensitivity reactions, including 2 reports of immediate, infusion-related hypersensitivity events consistent with anaphylaxis, have been reported at the onset or during IV infusion of mirikizumab. Such reactions are considered by the sponsor to be related to mirikizumab and hence have been identified as adverse drug reactions (ADRs). The protocol includes specific measures for reducing the incidence and for management of such events including management of study drug infusion rate and observation during and after infusion. Consult the IB for information regarding ADRs and potential risks with mirikizumab.

Given the data from the Phase 2 study in CD and data from other clinical studies completed to date, potential benefits to participants who receive mirikizumab while participating in Study AMAM may be reasonably anticipated.

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 8.3.7 of this protocol. For all AESIs, including hypersensitivity events, the protocol and IB provide monitoring and 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 (Appendix 10.1.4). This independent assessment of clinical trial data will contribute to the overall ongoing evaluation and management of potential risks associated with mirikizumab administration.

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

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

3 Objectives and Endpoints

The study primary and secondary objectives will be assessed based on the Primary Analysis Set as defined in Section 9.3.

Objectives	Endpoints
Co-primary	
To evaluate the efficacy of mirikizumab is superior to placebo as assessed by • clinical response by PRO at Week 12 and endoscopic response at Week 52 • clinical response by PRO at Week 12 and clinical remission by CDAI at Week 52	• Proportion of participants achieving clinical response by PRO[c] at Week 12 and endoscopic response[d] at Week 52 • Proportion of participants achieving clinical response by PRO[c] at Week 12 and clinical remission by CDAI[e] at Week 52
Major Secondary [a,b]	
To evaluate the efficacy of mirikizumab is superior to placebo at Week 52 as assessed by • endoscopic response • clinical remission by CDAI	• Proportion of participants achieving endoscopic response[d] at Week 52 • Proportion of participants achieving clinical remission by CDAI[e] at Week 52
To evaluate the efficacy of mirikizumab is superior to placebo at Week 12 as assessed by • endoscopic response • endoscopic remission • clinical remission by CDAI • Urgency NRS	• Proportion of participants achieving endoscopic response[d] at Week 12 • Proportion of participants achieving endoscopic remission SES-CD≤4[j] at Week 12 • Proportion of participants achieving clinical remission by CDAI[e] at Week 12 • Change from baseline in Urgency NRS at Week 12

Objectives	Endpoints
To evaluate the efficacy of mirikizumab is superior to placebo as assessed by both clinical response by PRO at Week 12 and each below, individually: • clinical remission by PRO at Week 52 • endoscopic remission at Week 52 • corticosteroid-free and either clinical remission by CDAI or endoscopic remission at Week 52	Proportion of participants achieving clinical response by PRO[c] at Week 12 and each below, individually: • Clinical remission by PRO[f] at Week 52 • Endoscopic remission SES-CD≤4[j] at Week 52 • Corticosteroid-free from Week 40 to Week 52 and either clinical remission by CDAI[e] at Week 52 or endoscopic remission SES-CD≤4[j] at Week 52
To evaluate the efficacy of mirikizumab is superior to placebo at Week 52 as assessed by Urgency NRS	Change from baseline in Urgency NRS at Week 52
To evaluate the efficacy of mirikizumab in comparison to ustekinumab at Week 52 as assessed by • endoscopic response (superior) • endoscopic remission (superior) • clinical remission by CDAI (non-inferior)	Proportion of participants achieving • Endoscopic response[d] at Week 52 • Endoscopic remission SES-CD≤4[j] at Week 52 • Clinical remission by CDAI[e] at Week 52
Other Secondary	
To evaluate the efficacy of mirikizumab is superior to placebo at Week 12 as assessed by • Clinical remission by PRO • Clinical response by CDAI • Clinical response by PRO • Endoscopic remission SES-CD Total Score 0-2 • Endoscopic response and clinical response by CDAI • Endoscopic response and clinical remission by CDAI	Proportion of participants achieving • Clinical remission by PRO[f] at Week 12 • Clinical response by CDAI[g] at Week 12 • Clinical response by PRO[c] at Week 12 • Endoscopic remission[i] at Week 12 • Endoscopic response[d] and clinical response by CDAI[g] at Week 12 • Endoscopic response[d] and clinical remission by CDAI[e] at Week 12

Objectives	Endpoints
To evaluate the efficacy of mirikizumab is superior to placebo as assessed by both clinical response by PRO at Week 12 and each below, individually: • Urgency remission at Week 52 among participants with Urgency NRS ≥3 at baseline • Clinical response by CDAI at Week 52 • Clinical response by PRO at Week 52 • Endoscopic remission SES-CD Total Score 0-2 at Week 52 • Stability of clinical remission by CDAI from Week 12 to Week 52 • Durability of endoscopic response at Week 12 and Week 52 • Durability of endoscopic remission at Week 12 and Week 52 • Endoscopic response and clinical response by CDAI at Week 52 • Endoscopic remission and clinical remission by CDAI at Week 52 • Endoscopic response and clinical remission by CDAI at Week 52	Proportion of participants achieving clinical response by PRO[c] at Week 12 and each below, individually: • Urgency remission[h] at Week 52 in participants with Urgency NRS ≥3 at baseline • Clinical response by CDAI[g] at Week 52 • Clinical response by PRO[c] at Week 52 • Endoscopic remission[i] at Week 52 • Stability of Clinical remission by CDAI[e] from Week 12 to Week 52 • Durability of endoscopic response[d] at Week 12 and Week 52 • Durability of endoscopic remission[j] at Week 12 and Week 52 • Endoscopic response [d] and clinical response by CDAI [g] at Week 52 • Endoscopic remission[j] and clinical remission by CDAI[e] at Week 52 • Endoscopic response [d] and clinical remission by CDAI[e] at Week 52
To evaluate the efficacy of mirikizumab is superior to placebo in clinical response by CDAI at Week 4	Proportion of participants achieving Clinical response by CDAI[g] at Week 4
To evaluate the efficacy of mirikizumab is superior to placebo in Modified Intent-to-Treat population (mITT) as assessed by • clinical response by PRO at Week 12 and endoscopic response at Week 52 • clinical response by PRO at Week 12 and clinical remission by CDAI at Week 52	• Proportion of participants achieving clinical response by PRO[c] at Week 12 and endoscopic response[d] at Week 52 • Proportion of participants achieving clinical response by PRO[c] at Week 12 and clinical remission by CDAI[e] at Week 52

Objectives	Endpoints
To evaluate the efficacy of mirikizumab is superior to placebo in conventional-failed and biologic-failed subgroups	Proportion of participants achieving • Endoscopic response[d] at Week 12 • Clinical remission by CDAI[e] at Week 12 Proportion of participants achieving clinical response by PRO[c] at Week 12 and each below at Week 52, individually: • Endoscopic response[d] • Endoscopic remission SES-CD≤4[j] • Clinical remission by CDAI[e]
To evaluate the efficacy of mirikizumab in comparison to placebo in health outcomes and quality of life measures, symptomatic endpoints, inflammatory biomarkers	Proportion of participants achieving each below over time • Clinical remission by CDAI [e] • Clinical response by CDAI[g] • Clinical remission by PRO[f] • Clinical response by PRO[c] Change from baseline at Week 12 and Week 52 of each below: • C-reactive protein • Fecal calprotectin • FACIT-Fatigue scores • European Quality of Life 5-Dimensions 5 Level (EQ-5D-5L) index • Work Productivity and Activity Impairment Questionnaire Crohn's Disease (WPAI-CD) score • Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) Version 2 acute scores • Inflammatory Bowel Disease Questionnaire (IBDQ)

Objectives	Endpoints
To evaluate the efficacy of mirikizumab in comparison to placebo for other assessments	Proportion of participants • had EIMs among those who had EIMs at baseline • Crohn's related emergency room visits • Crohn's related hospitalization • Crohn's related surgeries Proportion of participants achieving clinical response by PRO[c] at Week 12 and each below evaluated at Week 24, and at Week 52, individually: • ≥50% reduction from baseline in the number of draining fistulae • draining fistulae at baseline with closure of draining fistulae
To evaluate the efficacy of mirikizumab in comparison to ustekinumab as assessed by • Endoscopic response at Week 12 (superior) • Clinical remission by CDAI at 12 (non-inferior) • Clinical response by CDAI at Week 12 (non-inferior) • Clinical response by CDAI at Week 52 (non-inferior) • Corticosteroid-free clinical remission by CDAI at Week 52 (non-inferior) • Clinical response by PRO at Week 12 • Clinical response by PRO at Week 52 • Clinical remission by PRO at Week 12 • Clinical remission by PRO at Week 52	Proportion of participants achieving • Endoscopic response[d] at Week 12 • Clinical remission by CDAI[e] at Week 12 • Clinical response by CDAI[g] at Week 12 • Clinical response by CDAI[g] at Week 52 • Corticosteroid-free clinical remission by CDAI[e] at Week 52 • Clinical response by PRO[c] at Week 12 • Clinical response by PRO[c] at Week 52 • Clinical remission by PRO[f] at Week 12 • Clinical remission by PRO[f] at Week 52

Objectives	Endpoints
To evaluate the efficacy of mirikizumab in comparison to ustekinumab in conventional-failed and biologic-failed subgroups	Proportion of participants achieving • Endoscopic response[d] at Week 52 • Endoscopic remission SES-CD ≤4[j] at Week 52 • Clinical remission by CDAI[e] at Week 52 • Endoscopic response[d] at Week 12 • Clinical remission by CDAI[e] at Week 12
To evaluate the pharmacokinetic and pharmacokinetic/pharmacodynamic relationships of mirikizumab	• Clearance and volume of distribution of mirikizumab • Relationship between mirikizumab exposure and efficacy
Tertiary/Exploratory	
CCI	

Abbreviations: AP = abdominal pain; CD = Crohn's disease; CDAI=Crohn's Disease Activity Index;EIM = extraintestinal manifestation; EQ-5D-5L= European Quality of Life 5–Dimension 5 Level; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; IBDQ = Inflammatory Bowel Disease Questionnaire; NRS = numeric rating scale; PRO = patient-reported outcome; SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency as per Bristol Stool Scale Category 6 or 7, SF-36v2 Acute = Medical Outcomes Study 36-Item Short Form Health Survey; WPAI-CD = Work Productivity and Activity Impairment Questionnaire Crohn's Disease.

Note: Modified Intent-to-Treat (mITT) Population is defined as all participants from ITT population who take at least one dose of study drug.

[a] All primary and major secondary endpoint analyses will utilize the multiplicity control approach based on 'graphical multiple testing procedure' to control the overall family-wise type I error rate at a 2-sided alpha level of 0.05. The graphical multiple testing procedure described in Bretz et al. (2009, 2011) will be used.

[b] The order of testing of the major secondary endpoints will be detailed in the statistical analysis plan (SAP). Therefore, the order of the secondary endpoints does not reflect the order of the statistical testing.

[c] Clinical response by PRO is defined as at least a 30% decrease in SF and/or AP with neither score worse than baseline.

[d] Endoscopic response is defined as ≥50% reduction from baseline in SES CD Total Score.

[e] Clinical remission by CDAI is defined as CDAI total score <150.

[f] Clinical remission by PRO is defined as SF≤3 and not worse than baseline (as per Bristol Stool Scale Category 6 or 7) and AP ≤1 and no worse than baseline at Week 52.

[g] Clinical response by CDAI is defined as a decrease from baseline ≥100 and/or CDAI <150

[h] Urgency remission is defined as Urgency NRS ≤1

[i] Endoscopic remission is defined as SES-CD Total Score ≤2

[j] Endoscopic remission SES-CD ≤4 is defined as SES-CD Total Score ≤4 and at least a 2-point reduction from baseline and no subscore >1

4 Study Design

4.1 Overall Design

Design Summary

Study AMAM is a Phase 3, multicenter, randomized, double-blind, double-dummy, parallel group, active- and placebo-controlled, treat-through design (see schema in Section 1.2). Three intervention groups in the first period and four intervention groups in the second period will be studied in participants with moderate-to-severe Crohn's disease:

- Mirikizumab 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W
- Ustekinumab ~6 mg/kg IV for one dose, then 90 mg SC every 8 weeks
- Placebo
    - When Period 1 concludes (Week 12), responders continue receiving placebo, and
    - NR at Week 12 will receive mirikizumab as described above.

The total duration of the combined treatment periods is up to 52 weeks.

The maximum total duration of study participation for each participant, including screening and the post-treatment follow-up period, is 73 weeks.

Participants in either active group will receive placebo to match the other active group using a double-dummy design. Participants in the placebo group will receive both IV and SC placebo administrations.

For further details see Section 6.1 (Study Intervention Administered).

Participant Visit Scheme

Study participants will undergo screening assessments; double-blind treatment with investigational product, active comparator product, or placebo; and two post-treatment follow-up visits.

Screening may be done on more than 1 day, as long as all activities are completed within ≤35 days from the baseline visit (Visit 2). It is recommended that at least 3 business days be allowed for receipt of laboratory test results before randomization and dosing at Visit 2. Randomization will be timed to begin no earlier than 14 days from the start of the screening procedures.

After screening and baseline visits, participants will receive their assigned therapy during the 52-week double-blind treatment period (Visits 2 to 17). Period 1 is from Weeks 0 to 12. Period 2 encompasses Weeks 12 to 52. Dosing visits are as specified in the SoA (Section 1.3).

Participants who complete Study AMAM through Visit 17 will be given the option to enroll in Study AMAX if they are eligible (Section 6.7.1). Participants who do not meet enrollment criteria for Study AMAX or who do not choose to participate in Study AMAX will return for 2 post-treatment follow-up visits in Study AMAM. The first such follow-up visit (Visit 801) will be 4 weeks after the last visit (LV) (LV/early termination visit [ETV] + 4 weeks). The second follow-up visit (Visit 802) will be from 12 to 16 weeks after the LV (LV/ETV + 12 to 16 weeks).

Participants who permanently discontinue study drug early will undergo early termination procedures, including an ETV and the post-treatment follow-up visits (Section 7).

Assessments and Procedures

Assessments and procedures to be conducted in each study period are described in the SoA (Section 1.3), and in "Study Assessments and Procedures" (Section 8).

Stratification

Participants who meet all criteria for enrollment will be randomized to double-blind treatment at Visit 2. To achieve between-group comparability, participants will be stratified to treatment groups based upon these factors: a) biologic-failed status (yes/no), b) baseline corticosteroid use (yes/no), c) baseline SES-CD total score (<12, ≥12), d) region (North America/Europe/Other) and e) either baseline SF ≥7 and/or baseline AP ≥2.5 (yes/no) (Section 9.4.1). This stratification will be controlled by an interactive web-response system (IWRS) (Section 6.3).

Placebo Nonresponders (NR)

Any participant in the placebo group who is considered a NR at Week 12 will be assigned blinded mirikizumab induction therapy followed by blinded mirikizumab maintenance therapy for the remainder of the study; doses and routes of administration will be the same as those described above for mirikizumab treatment groups. Nonresponse is defined as failing to achieve at least a 30% decrease in SF and/or AP and be no worse than baseline.

Placebo Responders

Participants in the placebo group who are in clinical response at Week 12 will continue to receive placebo for the remainder of the study. No rescue therapy will be provided after Week 12.

4.2 Scientific Rationale for Study Design

Study AMAM is designed to evaluate the safety and efficacy of mirikizumab in clinical remission and endoscopic response at Weeks 12 and 52 of treatment.

Endpoints

To evaluate the effect of mirikizumab on decreasing intestinal mucosa inflammation and symptoms of CD, the following endpoints will be used for the primary objective of Study AMAM: SES-CD, Crohn's Disease Activity Index (CDAI) and patient-reported symptoms of AP and SF.

The SES-CD will be determined at baseline, Week 12, and Week 52 (or end of study for participants with early discontinuation) with evaluation of endoscopic response (defined as ≥50% reduction from baseline in SES-CD total score) as a co-primary endpoint. At the GREAT 3 workshop, endoscopic response as a co-primary endpoint was considered clinically meaningful and relevant and would provide sufficient evidence of efficacy for CD trials at various time points. The 50% reduction from baseline in SES-CD as a definition of endoscopic response in CD was ranked first by 11 of 12 participants (Vuitton et al. 2016) in a modified Delphi process by members of the International Organization of Inflammatory Bowel Disease. Based on this consensus of gastroenterology experts, endoscopic response is considered a meaningful and

relevant endpoint for assessment of therapies in CD. Additionally, the 50% cutoff point was shown to correlate with steroid-free remission at a later time point based on a post hoc analysis of the SONIC trial (Ferrante et al. 2013). Thus, 50% improvement in the SES-CD correlates with long-term clinical improvement and provides a robust and meaningful assessment of endoscopic improvement.

To evaluate the effect of mirikizumab on decreasing symptoms of CD, AP and SF will be assessed. Qualitative patient research, clinical gastroenterological expert opinion, and a review of the peer-reviewed literature assert that AP and SF are the most important and clinically relevant symptoms associated with moderate-to-severe CD (Baumgart and Sandborn 2007; Khanna et al. 2015; Kim et al. 2015). Both AP and frequent bowel movements with the consistency of liquid or soft stools have a significant impact on the day-to-day function and life of a participant with moderate-to-severe CD.

To assess the effect of mirikizumab on SF and AP, clinical remission by PRO at Week 12 and Week 52 (or end-of-study for participants with early discontinuation) will be measured in Study AMAM. At baseline, participants will be required to have active CD as defined by the inclusion criteria (see Section 5.1). Clinical remission by PRO is as defined in Section 8.1. Participants will be provided with an electronic daily diary during the study to record their signs and symptoms on a daily basis.

To measure the number of liquid or very soft stools in the past 24 hours, participants will use the SF item of the CDAI (unweighted). To further define "liquid or very soft stools," participants will be referred to the Bristol Stool Scale Category 6 and/or 7, which provides a pictorial and verbal description of stool consistency and form, for example, liquid or watery stool. To measure the participant's AP, participants will be asked to record AP using the 4-point scale.

Use of placebo comparator

Placebo was selected as the primary comparator for Study AMAM. The use of a placebo comparator is reasonable in this study, as mirikizumab can be added to preexisting background therapy (FDA 2011). A week 12-timepoint was chosen for the assessment of induction efficacy to balance the timepoint at which substantial induction efficacy could be demonstrated against the longest time considered reasonable for participants to be maintained on placebo without receiving rescue treatment. This timepoint falls within the study duration (from 6 week to 12 weeks) recommended for demonstration of short-term efficacy. As the main noninferiority comparison of mirikizumab to ustekinumab will be conducted at Week 52, continuation of the placebo group to Week 52 is warranted to provide internal evidence of assay sensitivity (FDA 2011 [ICH E10]) and to document the efficacy of mirikizumab in long-term treatment. The protocol defines conditions under which the study participants may be switched to mirikizumab (placebo NR [Section 4.1]) or must be discontinued. Study participants and physicians may discontinue the study participation if they perceive no benefit. These conditions provide for a balance between a rigorous scientific evaluation of the efficacy of mirikizumab in comparison to placebo and in comparison to ustekinumab and provide for appropriate management of each individual's disease activity.

Ustekinumab as an active comparator

Ustekinumab is approved in several countries for the treatment of CD and is included in Study AMAM as an active comparator for comparisons with mirikizumab. The ustekinumab dosages selected for this study were found to be safe and effective in the pivotal Phase 3 studies of ustekinumab in participants with CD (Feagan et al. 2016; Stelara USPI) and are included in both the FDA and EMA labels (Stelara SmPC). In Study AMAM, participants enrolled in the ustekinumab group will receive a single IV induction dose of approximately 6 mg/kg (based on the weight tiers described in labeling), which is the approved induction dose for participants with CD. From Week 8, these participants will receive a maintenance dose regimen of 90 mg SC Q8W. Of note, the ustekinumab Q8W regimen was chosen for the maintenance dose regimen as opposed to the Q12W regimen as it more dependably demonstrated efficacy across a range of clinical endpoints, especially with more stringent measures of efficacy such as sustained remission and steroid free-remission, in the pivotal ustekinumab CD maintenance study (Feagan et al. 2016). Additionally, only the 90 mg Q8W dosing regimen demonstrated significant effects on endoscopic endpoints, with the 90 mg Q12W dose not appreciably differing from placebo. The 90 mg Q8W regimen would therefore provide the fairest comparison for testing the superiority of mirikizumab to ustekinumab, especially as regards the important outcomes of endoscopic response and remission.

4.3 Justification for Dose

The mirikizumab 900 mg IV Q4W induction and 300 mg SC Q4W maintenance dose regimens selected for this study were based primarily on analyses of interim pharmacokinetics (PK), safety, and efficacy data from the Phase 2 Study AMAG, safety data from other clinical studies evaluating mirikizumab, and nonclinical safety data.

Safety Considerations

The safety data collected for mirikizumab in completed and ongoing clinical studies and in nonclinical toxicology studies support the proposed dose regimen. As noted in Section 2.3, in the Phase 2 Study AMAG, the incidences of SAEs and TEAEs were similar between placebo and mirikizumab treatment groups, with no dose relationship noted in the first 12 weeks (Period 1). In Period 2 (Weeks 12 to 52), comparative data are limited. The incidence of overall TEAEs was similar across all mirikizumab dose groups and were generally mild to moderate in severity. Patients exposed to 1000 mg mirikizumab IV had a higher number of SAEs, including 2 reports of immediate, infusion-related hypersensitivity events consistent with anaphylaxis. For IV dose administration, mitigation measures that include slowing the infusion rate, and monitoring during and after drug infusion have been implemented. There were no deaths during Study AMAG. As noted in Section 2.3, for all AESIs, including hypersensitivity events, the protocol and IB provide monitoring and management guidance to the investigator.

Single IV doses of up to 600 mg were evaluated in Study AMAA (healthy participants and participants with psoriasis) and up to 2400 mg in Study I6T-JE-AMAD (AMAD) (healthy participants). No dose-related safety or tolerability issues were observed in either study. Evaluation of the unblinded safety data available to date in the ongoing Phase 2 study in participants with psoriasis (Study AMAF) and of the unblinded safety data available to date in

the ongoing Phase 2 study of mirikizumab in participants with UC (Study AMAC) has not revealed a safety concern that differs from the safety findings noted above for Study AMAG.

The nonclinical safety profile of mirikizumab supports the proposed dose regimens in this study on the basis of the no-observed-adverse-effect levels (NOAELs) established in studies in monkeys. CCI [redacted]

Considerations of Efficacy and Exposure–Response Relationships

Significant efficacy of mirikizumab relative to placebo was observed in the 600 mg and 1000 mg IV Q4W treatment groups in Study AMAG based on the Week 12 endoscopic response endpoint, with the highest rates observed in the 1000 mg treatment group. Significant efficacy relative to placebo was also observed at Week 12 for the PRO remission endpoints and indicated near-maximal efficacy between the 600 mg and 1000 mg doses.

A model-based analysis of the relationship between individual subject mirikizumab systemic exposures and Week 12 endoscopic response revealed a significant relationship, with higher mirikizumab exposures associated with higher rates of endoscopic response. The proposed 900 mg IV induction dose is expected to produce near-maximal effect based on this exposure-response analysis CCI [redacted]

In the Week 12 to Week 52 maintenance period of Study AMAG, the mirikizumab dose regimens that were evaluated ranged from 300 mg SC Q4W to 1000 mg IV Q4W. CCI [redacted] The Week 52 endoscopic response CCI [redacted] across the maintenance treatment groups were similar and did not appear to have any relationship to dose or mirikizumab exposure within any of the doses and range of exposures evaluated in Study AMAG. CCI [redacted]

CCI [redacted]

4.4 End of Study Definition

The end of the study is defined as the date of the LV or last scheduled procedure shown in the SoA (Section 1.3) for the last participant participating in this global study.

5 Study Population

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

The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

5.1 Inclusion Criteria

Participants with CD are eligible for enrollment only if they meet all of the following criteria during screening, unless otherwise specified below.

Informed Consent

[1] have given written informed consent approved by the Ethical Review Board (ERB) governing the site.

Participant Characteristics

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

[2a] male participants:

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

[2b] female participants:

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 participant 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 40 years of age with an intact uterus, not on hormone therapy, who has had either

- cessation of menses for at least 1 year without an alternative medical cause
- 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] have venous access sufficient to allow blood sampling and IV administration as per the protocol.

Disease-Specific Inclusion Criteria

[4] have had a diagnosis of CD or fistulizing CD established at least 3 months prior to enrollment confirmed by clinical, endoscopic, and histological criteria.
Note: A histopathology report supporting the diagnosis of CD must be available in the source documents prior to randomization, in order to satisfy this inclusion criterion. If a histopathology report supporting the diagnosis of CD is not available in the source documents prior to randomization, the investigator can obtain additional biopsies for this purpose at the screening endoscopy (sent to the local histopathology laboratory).

[5] have moderately to severely active CD as defined by unweighted daily average SF ≥4 (loose and watery stools defined as Bristol Stool Scale Category 6 or 7) AND/OR unweighted daily average AP ≥2 at baseline (Visit 2).

[6] have a centrally read SES-CD score ≥7 for participants with ileal-colonic or ≥4 for participants with isolated ileal disease within 21 days before randomization.

Note: Enrollment of participants meeting the below criterion will be limited to approximately 10% of total enrollment: Participants with a SES-CD score ≥3 and <7

(SES-CD <4 for participants with isolated ileal disease) and presence of at least one large ulcer (in the ileum, colon, or both) that results in a minimum score of 2 for the component of "size of ulcers" and a minimum score of 1 for the component of "ulcerated surface."

[7] Participants with a family history of colorectal cancer, personal history of increased colorectal cancer risk, age >50 years, or other known risk factor must be up-to date on colorectal cancer surveillance per local guidelines. If not, this documentation of negative colorectal cancer surveillance may be performed according to local guidelines during screening.

Prior Medication Failure Criteria

[8] Participants must have an inadequate response to, loss of response to, or intolerance to at least 1 of the medications described in Inclusion Criterion [8a] OR [8b]. For the relevant medication specified in these criteria, documentation of dose, frequency, route of administration, and duration of the qualifying failure is required.

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

- corticosteroids
  - corticosteroid-refractory disease, defined as signs and/or symptoms of active CD despite CCI :
    - oral prednisone (or equivalent) at doses of at least CCI , or
    - CCI
  - corticosteroid-dependent disease:
    a. defined as an inability to reduce corticosteroids below the equivalent of prednisone CCI
    b. CCI of completing a course of corticosteroids; or
  - history of intolerance of corticosteroids (which includes evidence of a side-effect sufficiently serious as to precluding continued treatment with 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 CCI
    - oral AZA CCI 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.

o history of intolerance to at least 1 immunomodulator (including but not limited to nausea/vomiting, AP, 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 approved for the treatment of CD.

Discontinuation despite clinical benefit does not qualify as having failed or being intolerant to CD conventional therapy.

[8b] **Biologic-failed participants:** Participants who have an inadequate response to, loss of response to, or are intolerant to an approved biologic therapy for CD (such as anti-TNF antibodies or anti-integrin antibodies). **Investigators must be able to document an adequate history of induction and/or maintenance dose use.** Participants 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

- Loss of response: Recurrence of signs and symptoms of active disease following prior clinical benefit during treatment with approved maintenance dosing,

  OR

- Intolerance: History of intolerance to infliximab, adalimumab, certolizumab pegol, vedolizumab, natalizumab, or other approved biologics (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).

Discontinuation despite clinical benefit does not qualify as having failed or being intolerant to CD biologic therapy.

Participants previously exposed to approved 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.

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

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

CD Medication Dose Stabilization Criteria

[9] are on stable doses of the following permitted drugs (see Appendix 10.7):

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

[9b] oral corticosteroid therapy (prednisone CCI or equivalent, or budesonide CCI : if the prescribed dose has been stable for at least 2 weeks before the screening endoscopy.

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

[9d] Antibiotics being used specifically for the treatment of CD: if the prescribed dose has been stable 4 weeks prior to baseline (Visit 2) or stopped treatment at least 3 weeks prior to screening endoscopy.

Study Procedure Inclusion Criteria

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

Note: In situations out of the control of the participant (example: Sudden death in family, sudden staff changes, or broken equipment), rescreening or assessing potential randomization (whichever applies) may be allowed ONLY if prior approval from the medical monitor is obtained.

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

[11a] Hematology:

- absolute neutrophil count $\geq 1.5 \times 10^9$/L ($\geq 1.5 \times 10^3$/μL or ≥1.5 GI/L)
- platelet count $\geq 100 \times 10^9$/L ($\geq 100 \times 10^3$/μL 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 ($\geq 0.50 \times 10^3$/μL or ≥0.50 GI/L), and
- total white blood cell count $\geq 3.0 \times 10^9$/L ($\geq 3.0 \times 10^3$/μL or ≥3.0 GI/L)

[11b] Chemistry:

- serum creatinine ≤2 × upper limit of normal (ULN)
- total bilirubin level (TBL) ≤1.5 × ULN
- alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2 × ULN, and
- alkaline phosphatase (ALP) ≤1.5 × ULN

Participants with diagnosis of Gilbert's syndrome (requires source documentation showing isolated unconjugated hyperbilirubinemia, with no evidence of hemolysis) can be included with bilirubin levels ≤3 × ULN.

Retesting within the screening period is allowed for hematology and chemistry; see Section 5.4.

5.2 Exclusion Criteria

Participants will be excluded from study enrollment if they meet any of the following criteria within the screening period, unless otherwise specified below.

For rescreening activities within the screening period, see Section 5.4.

Gastrointestinal Exclusion Criteria

[12] are participants who:

[12a] have a current diagnosis of UC or inflammatory bowel disease-unclassified (formerly known as indeterminate colitis).

[12b] currently have or are suspected to have an abscess. Recent cutaneous and perianal abscesses are not exclusionary if drained, adequately treated and resolved at least 3 weeks prior to baseline or 8 weeks prior to baseline for intra-abdominal abscesses, provided that there is no anticipated need for any further surgery.

[13] have a stoma, ileoanal pouch or ostomy.

[14] have had a bowel resection within 6 months, or any kind of intra-abdominal surgery within 3 months of baseline (Visit 2).

[15] have complications of CD such as symptomatic strictures or stenosis, short bowel syndrome, or any other manifestation that:

- might be anticipated to require surgery within 6 months after screening,
  OR
- could preclude the use of the SES-CD, CDAI, or PRO to assess response to therapy,
  OR
- would possibly confound the ability to assess the effect of treatment.

Adenoma, Dysplasia, and Gastrointestinal Cancer Exclusion Criteria

[16] have any history or current evidence of cancer of the gastrointestinal tract.

[17] have any current sporadic colonic adenomatous polyp[a] ≤10 mm that has not been removed. Once completely removed, the participant may be eligible for the study provided the local histology report confirms no or low-grade dysplasia and absence of malignancy.

[a] pedunculated or sessile polypoid, with a dome-shaped and symmetric contour, smooth surface, and well-delineated border occurred in the non-colitic area

[18] have any adenomatous polyp (including sporadic) >10 mm, any evidence of dysplasia (low-grade* or high grade) in GI tract, or presence of any serrated lesion (with or without dysplasia).

*Note: except for low grade sporadic colonic adenomatous polyp [a] ≤10 mm once completely removed (per [17] above)

[a] pedunculated or sessile polypoid, with a dome-shaped and symmetric contour, smooth surface, and well-delineated border which occurred in the non-colitic area

Criteria for Discontinuing Prohibited Medications

[19] have received any of the following for treatment of CD within the time frames specified below:

[19a] corticosteroid enemas, corticosteroid suppositories 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 within 4 weeks prior to the screening endoscopy.

- AZA, 6-MP, and MTX are allowed at stable doses (Appendix 10.7).
- Other immunomodulatory medications should be discussed with the sponsor prior to screening.

[19d] anti-TNF antibodies (for example, infliximab, adalimumab, or certolizumab pegol) within 4 weeks prior to screening endoscopy.

[19e] anti-integrin antibodies (for example, vedolizumab) within 4 weeks prior to screening endoscopy.

[19f] agents that deplete B or T cells (for example, rituximab, alemtuzumab, or visilizumab) within 12 months of baseline (Visit 2). Participants 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.

[19k] natalizumab within 12 months prior to screening endoscopy.

[20] have ever received 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] Subjects who discontinued an anti-IL 12/23p40 antibody (for example, ustekinumab) due to primary nonresponse or secondary loss of response or intolerance OR who received more than the IV induction dose and 1 SC dose are not eligible.

CCI [redacted]

[22] require systemic corticosteroids for non-CD conditions (except corticosteroids to treat adrenal insufficiency).

Infectious Disease Exclusion Criteria

[23] are participants who

[23a] have evidence of active tuberculosis (TB), or

[23b] have a past history of active TB, without documented appropriate treatment by the World Health Organization (WHO) and/or the Centers for Disease Control and Prevention (CDC), or

[23c] are diagnosed with latent tuberculosis infection (LTBI) at screening and/or have a past history of LTBI and have not started a course of an appropriate TB prophylaxis regimen (Section 8.2.6).

Participants diagnosed with LTBI at screening and/or history of LTBI without appropriate treatment (aligned with WHO/CDC guidance in place at the time of treatment) may be allowed to rescreen and may be eligible for the study, provided they fulfill all the criteria described in Section 8.2.6.

[24] have received a Bacillus Calmette-Guérin (BCG) vaccination within 12 months or received live attenuated vaccine(s) within 3 months of screening or intend to receive such during the study.

[25] have human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS).

[26] have acute or chronic hepatitis B infection; or test positive for hepatitis B virus (HBV) at screening, which is defined as:

- positive for hepatitis B surface antigen (HBsAg+)

  OR

- 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 8.2.8).

[27] 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 8.2.9).

Note: Participants with a previous HCV infection that has been successfully treated with anti-viral therapy are not excluded (see Section 8.2.9).

[28] have tested positive for *C. difficile* toxin or for other intestinal pathogens within 30 days of screening endoscopy or test positive at screening for *C. difficile* toxin or for other intestinal pathogens. Participants with a confirmed diagnosis of cytomegalovirus-associated colitis should have adequate treatment and resolution of symptoms at least 3 months prior to screening endoscopy (See Section 8.2.5).

[29] have serious, opportunistic, or chronic/recurring extraintestinal infections. Participants may be eligible for entry into the study if they have been adequately treated and off antibiotics for 30 days without recurrence of symptoms prior to screening. Such extraintestinal infections include but are not limited to the following:

[29a] infections requiring IV antibiotics.

[29b] infections requiring hospitalization.

[29c] infections that are considered "opportunistic" (see Appendix 10.5).

[29d] chronic, recurrent infections (for example, osteomyelitis, recurring cellulitis). Participants with only recurrent, mild, and uncomplicated orolabial and/or genital herpes may be discussed with the medical monitor to determine the relevance of this infection for entry into the study,

Participants with an opportunistic infection or chronic, recurrent infection (within the last 60 days prior to Visit 2) should be discussed on a case-by-case basis with the medical monitor.

[30] have a current or recent acute, active nonserious extraintestinal infection for which signs and/or symptoms are present or treatment, if indicated, is not yet complete 2 weeks prior to screening.

[31] have evidence of active/infectious herpes zoster infection ≤8 weeks prior to screening. Herpes zoster infections remain active until all vesicles are dry and crusted over.

General Exclusion Criteria

[32] 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,
b) cervical carcinoma in situ that has been adequately treated with no evidence of recurrence within the 3 years prior to baseline (Visit 2).

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

[34] are Lilly employees or employees of third-party organizations involved with the study.

[35] 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.

[36] have previously completed or discontinued from this study or any other study investigating mirikizumab. This criterion does not apply to participants undergoing rescreening procedures.

[37] have had extra-abdominal surgery and have not recovered fully following surgery, including complete wound healing, before screening.

[38] have 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 (Visit 1) prior to dosing at Visit 2;

OR

marked yes to suicide behaviors questions during the screening period (Visit 1) prior to dosing at Visit 2

AND

the ideation or behavior occurred within the past month.

[39] have an unstable or uncontrolled illness, including but not limited to cerebro-cardiovascular, respiratory, gastrointestinal (excluding CD), hepatic, renal, endocrine, hematologic, or neurological disorders that would potentially affect participant safety within the study or confound efficacy assessment.

[40] have a known hypersensitivity to any component of mirikizumab or ustekinumab

[41] have a solid organ transplant or hematopoietic stem cell transplantation.

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

Note: In situations out of the control of the participant (example: Sudden death in family, sudden staff changes, or broken equipment), rescreening or assessing potential randomization (whichever applies) may be allowed ONLY if prior approval from the medical monitor is obtained.

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

[44] are pregnant, breastfeeding, or women who are planning pregnancy while enrolled in the study, or within 20 weeks after receiving the last dose of study drug.

[45] have current or history of alcohol dependence and/or illicit drug abuse within the last year.

[46] have abnormal 12-lead electrocardiogram (ECG) that, in the opinion of the investigator or sponsor, increases the risks associated with participating in the study.

[47] requires parenteral nutrition delivered by central vein and/or central venous catheter for venous access or receives enteral feeding as the primary source of their diet with limited oral intake.

[48] participants who use marijuana (both recreational and medicinal uses [including cannabidiol oil]). Marijuana use must be stopped prior to screening and is prohibited for the duration of the study.

5.2.1 Rationale for Exclusion of Certain Study Candidates

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

Participants from ≥18 and ≤80 years of age at the time of screening will be eligible to be included in this study. Participants >80 years of age at screening will not be allowed in the study for the following reasons. The extent of CD is more limited in the elderly than in the adult population. Colonic involvement is more common than ileal involvement. Elderly CD participants have a longer postoperative stay and a higher in-hospital mortality rate (Sturm et al. 2017).

5.3 Lifestyle Considerations

Study participants should be instructed not to donate blood or blood products during the study and for 20 weeks following their last dose.

To participate in the study, participants must agree to the contraception, reproduction, and breastfeeding criteria detailed in study entry criteria (Section 5.1 and Section 5.2).

5.4 Screen Failures

Allowed rescreening of participants after initial screen failure

Participants who have failed screening because of the following entry criteria may be rescreened when the reason for screen failure has resolved:

- [4]
- [5]
- [6]
- [8]
- [9]
- [10] only in situations out of control of the participant and after medical review and approval
- [11]
- [12b] (once adequately treated)
- [14]
- [17] (once polyps are removed)
- [19a] to [19j]
- [22] Rescreening is only allowed if a participant is no longer receiving steroids and has met washout criteria.

- [24]
- [28] (See rescreening allowances below)
- [29] to [32]
- [37]
- [42] only in situations out of control of participant and after medical review and approval
- [43] situation related to participant's safety or data interpretation resolves
- [44], [47]
- [48] Participant must agree to stop marijuana use prior to screening and throughout participation in the study.

For the reasons above, participants may be rescreened up to 3 times (unless specified otherwise), for a maximum total of 3 rescreens; however, the maximum number of endoscopies should never exceed 3 (even if separated by more than 8 weeks) including the initial endoscopy and 2 rescreens

Participants who have failed screening because of Exclusion Criterion [23c] (if treated for LTBI for at least 4 weeks and compliant with LTBI therapy while on study) may be rescreened 1 time. See Section 8.2.6.

Participants who have failed screening because of Exclusion Criterion [28] may be rescreened 1 time for *C. difficile* stool toxin. Additionally, a participant may be rescreened 1 time for stool culture or ova parasite. In either situation, participant rescreening should only occur after the reason for screen failure has been resolved. It is recommended that the investigator confirms the participant has a negative *C. difficile* stool toxin/stool culture/stool ova parasite (as applicable) before performing additional rescreening investigations (see also Section 8.2.5 and Section 5.4.1).

The interval between rescreenings starts when the screen failure was first noted and 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 participant must sign a new informed consent form (ICF) and will be assigned a new identification number.

The interval between rescreening should be at least 8 weeks after time/date of screen failure for participants who screen failed because of Criterion [6].

Participants who screen fail because they are unable to complete their endoscopy prior to Visit 2 may undergo repeat rescreening sooner than 4 weeks between screen failure and rescreening. Participants rescreening sooner than 4 weeks for the inability to complete endoscopy, or who are allowed by the study's medical monitor to rescreen within less than 4 weeks, will not be required to undergo repeat TB testing; chest X-ray (CXR) or computed tomography (CT); HIV, HBV, and HCV testing; stool cultures; and *C. difficile* testing if these were normal or negative during screening. These tests should be repeated if, based on the principal investigator's judgment, the participant has risk factors and/or signs and symptoms of illness.

Disallowed rescreening of participants after initial screen failure

Participants who have failed screening because of the following criteria may not be rescreened:

- [10] with the exception noted above
- [12a]
- [13]
- [15]
- [16]
- [18]
- [20] and [21],
- [23a] and [23b] (if evidence of active TB or past history of active TB)
- [25] to [27]
- [33] to [36]
- [38] to [41]
- [42] with the exception noted above
- [45]
- [46]

5.4.1 Allowed Retesting of Screening Investigations

Retesting of screening investigations within a screening period (without a requirement for screen failure and rescreening) is allowed as described below. The following screening investigations may be retested 1 time 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, taking into account test-retest variability.
- Stool testing: if there is a technical difficulty in performing or reporting the *C. difficile* or stool culture assays (see Section 8.2.5).
- Retesting or confirmatory testing with an interferon-γ release assay (IGRA): for example, QuantiFERON®-TB Gold or T-SPOT® assay, in selected participants as part of screening for LTBI (see Section 8.2.6 for details).
- Endoscopy: where the endoscopist is unable to adequately visualize the mucosa (for example, due to poor bowel preparation, technical issues with equipment) or where the central readers are unable to determine the centrally read SES-CD score (for example, failure of the recording equipment).

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

6 Study Intervention

Study intervention is defined as any investigational intervention, marketed product, placebo, or medical device intended to be administered to a study participant according to the study protocol.

6.1 Study Intervention(s) Administered

The study interventions used in this study are

- Mirikizumab administered by IV infusion or SC injection
- Ustekinumab administered by IV infusion or SC injection
- Placebo administered by IV infusion or SC injection

The doses and routes of administration reflect the multi-part study design (Section 4.1).

A double-dummy design is used to preserve the study blinding.

Packaging and Labeling

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 intervention will be supplied as:

- Single-use solution vial containing mirikizumab, ustekinumab, or placebo with study-specific labels.
  - CCI
- Single-use solution prefilled syringe containing mirikizumab, ustekinumab, or placebo.
  - CCI

Vials and syringes will be supplied in cartons, with the appropriate quantity specific to the planned dispensing schedule. Investigational product will be provided with study-specific labels.

Preparation and Administration

The first dose of investigational product will be prepared at the site by unblinded pharmacists or other trained and qualified personnel as designated by the investigator. Subsequent doses of investigational product will not require an unblinded pharmacist.

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

Sites must have resuscitation equipment, emergency medications, and appropriately trained staff available during the infusion and monitoring period. All participants should be monitored for 1 hour or longer after IV dosing, according to investigator practice or local standard of care.

Intravenous infusions must be completed prior to administration of SC injections. Subcutaneous injections may be given during the IV observation period.

Detailed instructions for investigational product administration, including infusion rate and SC injections, will be provided separately by the sponsor.

Time of Doses

The actual time of all dose administrations will be recorded in the participant's electronic case report form (eCRF).

Investigator Responsibilities

The investigator or his or her designee is responsible for the following, in addition to the responsibilities listed in Section 6.2:

- explaining the correct use of the investigational interventions 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.

6.2 Preparation/Handling/Storage/Accountability

The investigator or his or 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 (interventions) will be supplied in accordance with current GMP and will be supplied with lot numbers, expiry dates, and certificates of analysis, as applicable.

6.3 Measures to Minimize Bias: Randomization and Blinding

Randomization

Assignment to treatment groups will be determined by a computer-generated random sequence using an IWRS.

The stratification for randomization, as described in Section 9.4.1 and Section 4.1, will be controlled by IWRS.

Blinding

This is a double-blind study. All treatments are blinded. To maintain the blind, placebo will be administered as appropriate, either by IV, SC, or both. All study assessments will be done by study personnel who are blinded to the participant's treatment assignment.

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 participant's well-being requires knowledge of the participant'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 participant's treatment assignment is warranted for medical management of the event. The participant safety must always be the first consideration in making such a determination. If a participant'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 participant is unblinded, the participant must be discontinued from the study drug and must complete the ETV and post-treatment follow-up visits (Section 7.1). In cases where there are ethical reasons to have the participant continue on the study drug, the investigator must obtain specific approval from the sponsor or designee for the participant continue.

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.

A limited number of preidentified individuals may gain access to unblinded data, as specified in the unblinding plan, prior to the database lock, in order to initiate the final population PK/pharmacodynamic (PD) model development processes for analyses. Information which 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 statistical analysis plan (SAP) or a separate unblinding plan document.

See also provisions for ongoing safety monitoring as described in Section 8.2.

6.4 Study Intervention 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 participants 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 participant before randomization.

In particular, the investigator is responsible for ensuring that study participants receive adequate training on and appropriate understanding of

- the importance of complete bowel prep prior to colonoscopies
- how to evaluate their CD symptoms and to record them on the eDiary, and
- the importance of being compliant with the daily eDiary recording.

If a participant is noncompliant with study procedures and/or investigational product administration, the investigator should assess the participant to determine the reason for noncompliance and educate and/or manage the participant as appropriate to improve compliance.

If, in consultation with Lilly or its designee, the noncompliance is deemed to be significant or if further noncompliance occurs, the participant may be discontinued. See Section 7.1.1 for treatment noncompliance leading to permanent discontinuation from study drug.

6.5 Concomitant Therapy

Recording of information about concomitant medications

All concomitant medications, including endoscopy preparation medications taken during the study, must be recorded on the Concomitant Medication eCRF. This includes concomitant medications for CD as well as underlying conditions or diseases, and for AEs.

Use of concomitant medications during the study

All participants are encouraged to maintain their usual medication regimens for concomitant conditions or diseases throughout the study unless those medications are specifically prohibited (Appendix 10.6).

6.5.1 Permitted Therapy

Participants taking permitted CD concomitant medications are to keep doses stable unless modifications are needed due to AEs or for appropriate medical management. CCI [redacted] Instructions regarding guidance for use are detailed in Appendix 10.7.

6.5.2 Prohibited Therapy

Use of such medications should not be withheld if, in the opinion of the investigator, failure to prescribe them would compromise participant safety. Participants who require a prohibited medication should be discontinued from study drug as described in Section 7.1.1 and should complete an ETV and post-treatment follow-up visits as described in the SoA (Section 1.3). Some exceptions, IV corticosteroid, systemic corticosteroids for non-CD indications, and marijuana, may result in discontinuation; consult your medical monitor prior to discontinuing the participant (see Appendix 10.6).

If a concomitant medication is needed to treat an AE or for appropriate medical management, the investigator should base decisions on the participant and clinical factors, considering the list of prohibited medication.

Vaccinations

Use of BCG vaccination is prohibited throughout the duration of the study and for 12 months after discontinuation of study drug.

Use of live, attenuated vaccines are prohibited during the study and for 3 months after discontinuation of study drug.

Use of nonlive (killed, inactivated, subunit, and RNA-based) vaccinations are allowed; however, their efficacy with concomitant mirikizumab is unknown.

For more information

The list of prohibited medications is provided in Appendix 10.6.

The list of permitted medications with dose stabilization guidance is provided in Appendix 10.7.

6.5.3 Corticosteroid Taper

Participants who achieve clinical response (clinical response by PRO [Section 8.1]) CCI

[redacted]

For participants who cannot tolerate the corticosteroid taper without recurrence of clinical symptoms, CCI

[redacted]

6.5.4 Rescue Medicine

As noted in Section 6.5, participants who require a prohibited medication as described above to treat their CD should be discontinued from study drug as described in Section 7.1.1 and should complete an ETV and post-treatment follow-up visits as described in the SoA (Section 1.3).

Participants assigned to active study drug

This study does not include rescue therapy for participants who are assigned to active study drug.

Participants assigned to placebo

Participants in the placebo group who are NR at Week 12 will be treated as described in the Overall Design (Section 4.1).

6.6 Dose Modification

Dose modification of study drug is not permitted in this study.

6.7 Intervention after the End of the Study

6.7.1 Study Extension

Participants who complete Study AMAM through Visit 17 will be assessed for eligibility to enter Study AMAX. If a participant does not meet enrollment criteria for Study AMAX or does not opt to continue into Study AMAX, he or she will be asked to complete the post-treatment follow-up period, as described in the SoA (Section 1.3), which will complete his or her study participation.

6.7.2 Treatment after Study Completion

Mirikizumab and ustekinumab will not be made available to study participants after conclusion of the study; however, participants who are eligible may choose to participate in Study AMAX (Section 6.7.1).

6.7.3 Special Treatment Considerations

6.7.3.1 Premedication for Infusions

Premedication for the study drug infusions or injections is not planned. Any premedication for infusions or injections should be discussed with the medical monitor. Any premedication given will be documented as a concomitant therapy (Section 6.5).

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

During and after study drug administration, participants should be closely monitored for signs or symptoms of AEs, including hypersensitivity events, other infusion-related events, and infusion or injection site reactions. See Section 8.3.7.2 for more information about blood sampling and data collection.

Hypersensitivity events

If a participant experiences a systemic hypersensitivity reaction involving two or more organ systems (that is, mucocutaneous, respiratory, cardiovascular, or gastrointestinal systems), during or up to 6 hours after an infusion of study drug, the following guidance should be followed:

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

- After the participant's stabilization, blood samples should be obtained as described in the SoA (Section 1.3).
- The participant should be monitored until resolution or stabilization of the symptoms, as clinically appropriate.
- Study drug should be discontinued (Section 7.1.1). The participant should undergo an ETV and post-treatment follow-up procedures after study drug discontinuation.

For nonsystemic hypersensitivity reactions involving a single organ system, all of the above should be followed, except the participant may be allowed to continue in the study. Continuation of a participant in the clinical study based on the investigator's assessment of the event must be discussed and agreed upon with the medical monitor. If it is agreed the participant can continue, premedication prior to subsequent study drug administration may be considered, if judged by the investigator to be appropriate for the individual participant.

Other infusion-related events

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

- The study drug infusion should be interrupted and appropriate medical care should be administered (for example, non-steroidal anti-inflammatory drugs, antipyretics, or antihistamines).
- Blood samples for anti-drug antibodies (ADA) and PK analysis should be obtained as described in the SoA (Section 1.3).
- Resumption of study drug infusion after interruption, possibly at a slower rate of administration, can be considered if symptoms resolve and it is deemed to be medically appropriate based on the investigator's discretion, and considering the risk/benefit of readministration.
- Premedication prior to subsequent study drug administration may be considered, if judged by the investigator to be appropriate for the individual participant.
- If the participant develops systemic hypersensitivity symptoms or signs, he or she should be managed as described above for a systemic hypersensitivity reaction. The participant should remain in observation, as is clinically appropriate for the participant's symptoms.

Injection site reactions or infusion site reactions

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

- The participant should be instructed to contact the study site to report any symptoms experienced following a SC injection or an infusion site reaction.
- If the participant develops systemic hypersensitivity symptoms, he or she should be managed as described above for a systemic hypersensitivity reaction.

- Premedication prior to subsequent study drug administration may be considered as appropriate for the individual participant.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

These sections describe reasons for

- permanent or temporary discontinuation of study drug, or
- participant's discontinuation (withdrawal) from the study.

Discontinuation of the study as a whole or of particular study sites is described in Appendix 10.1.8.

7.1 Discontinuation of Study Intervention

Study drug may be permanently discontinued or temporarily withheld during the study.

Participants who permanently discontinue study drug early will undergo early termination procedures, which include

- an ETV and,
- post-treatment follow-up visits (Visit 801 and Visit 802).

The investigator will complete any AE reporting and necessary follow-up (Section 8.3).

7.1.1 Criteria for Permanent Discontinuation of Study Drug

Possible reasons leading to permanent discontinuation of study drug include, but are not limited to:

Subject Decision

- The participant requests to discontinue the study drug.

Disease Worsening

- The participant requires treatment with a specified prohibited CD medication (Appendix 10.6).
- The participant undergoes surgery for CD (with the exception of drainage of a perianal or other cutaneous abscess or seton placement).

Safety Considerations

- The participant has a diagnosis of any of the following during the study:
  - cancer other than squamous cell or basal cell carcinoma of the skin
  - any colonic adenomatous polyp (including sporadic) >10 mm, any evidence of dysplasia (low-grade* or high grade) in GI tract, or presence of any serrated lesion (with or without dysplasia).
    *Note: except for low grade sporadic colonic adenomatous polyp [a] ≤10 mm once completely removed.
    [a] pedunculated or sessile polypoid, with a dome-shaped and symmetric contour, smooth surface, and well-delineated border which occurred in the non-colitic area

  - active TB (Section 8.2.6)
  - HIV/AIDS
  - hepatitis B or development of detectable HBV DNA (Section 8.2.8).
  - hepatitis C or development of detectable HCV RNA (Section 8.2.9).
- The participant has a systemic hypersensitivity event or anaphylaxis to mirikizumab (Section 6.7.3.2). Study drug should be discontinued after a systemic hypersensitivity event or anaphylaxis.
- The participant has absolute lymphocyte count <0.5 x 10^3/μL after retesting (see Section 7.1.2).
- The participant becomes pregnant. Pregnant participants will not undergo an endoscopy at the ETV (Section 8.1.1.3).
- Noncompliance with LTBI treatment (see Section 8.2.6).
- The participant has an AE or SAE which, in the opinion of the investigator or sponsor, would preclude the participant from continuing to receive study drug.
- It is recommended that the participant be assessed by an appropriately trained professional to assist in deciding whether the participant is to be discontinued if:
  - The participant 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 participant reports suicidal ideation or suicidal behaviors during the study.

Hepatic Event or Liver Test Abnormality

- Participants who are discontinued from study drug because of a hepatic event or liver test abnormality should have additional hepatic safety data collected via the hepatic eCRF packet.

  Discontinuation of study drug because of abnormal liver tests should be considered by the investigator when a participant meets one of the following conditions after consultation with the medical monitor (see Section 8.2.10):

  - ALT or AST >8 × ULN
  - ALT or AST >5 × ULN for more than 2 weeks
  - ALT or AST >3 × ULN and TBL >2 × ULN or international normalized ratio (INR) >1.5
  - ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
  - alkaline phosphatase (ALP) >3 × ULN
  - ALP >2.5 × ULN and TBL >2 × ULN
  - ALP >2.5 × ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

Other Reasons

- Unblinding: If an investigator, site personnel performing assessments, or participant is unblinded, the participant must be discontinued from the study drug and continue to post-treatment follow-up. In cases where there are ethical reasons to have the participant continue on study drug, the investigator must obtain specific approval from the sponsor or designee for the participant to continue.
- Treatment noncompliance: participant missed CCI of study drug (Section 6.4).

Participants discontinuing from the study drug prematurely for any reason will complete AE and other follow-up procedures as specified in Section 1.3 (Schedule of Activities), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events and Serious Adverse Events), including ETV and post-treatment follow-up visits (Visit 801 and Visit 802).

7.1.2 Criteria for Temporary Interruption (Withholding) of Study Drug

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

Some possible reasons for temporarily withholding study drug include, but are not limited to:

- The participant develops a clinically important intestinal or extraintestinal infection (including LTBI) during the study (see Section 5.2).
- The participant requires major surgery. Administration of study drug may be restarted only after adequate wound healing.
- The participant develops a confirmed absolute neutrophil count <1 x 10^9/L (<1 x 10^3/µL or <1 GI/L (2 consecutive assessments below this threshold).
- Participants who develop an absolute lymphocyte count <500 cells/µL (<0.5 × 10^3/µL or <0.50 GI/L) will be retested approximately every 2 weeks for up to 8 weeks unless the lymphocyte count becomes ≥0.5 × 10^3/µL or ≥0.50 GI/L.
    - Azathioprine, methotrexate, or 6-mercaptopurine must be discontinued, if applicable, after the first retest confirming absolute lymphocyte count <0.5 × 10^3/µL (2^{nd} assessment below threshold), and the next dose of study drug held. The participant must be retested in approximately 2 weeks.
    - The third retest (4^{th} assessment below threshold) should occur prior to the next monthly dosing and if still below <0.5 × 10^3/µL, the next dose of study drug should also be held. The participant must be retested in approximately 2 weeks.
    - After the fourth retest (fifth assessment below threshold), the participant may be permanently discontinued. Consult your medical monitor. White blood cell and lymphocyte counts will be followed for these participants until they return to an acceptable level.
- The participant has laboratory abnormalities that may lead investigator to hold the study drug until resolution of the abnormalities.

7.1.3 Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, the participant should be discontinued from study drug unless there are extenuating circumstances that make it medically necessary for the participant to continue on study drug. If the investigator and the sponsor agree that it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor to allow the inadvertently enrolled participant to continue in the study. Participants who are discontinued from study drug will complete AE and other follow-up as specified in Section 1.3 (Schedule of Activities), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events and Serious Adverse Events), including ETV and post-treatment follow-up visits (Visit 801 and Visit 802).

7.2 Participant Discontinuation/Withdrawal from the Study

Participants will be discontinued (withdrawn) from the study in the following circumstances:

- enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- investigator decision
  - the investigator decides that the participant should be discontinued from the study
- subject decision
  - the participant requests to be withdrawn from the study.

Participants discontinuing from the study prematurely for any reason should have AE and other safety follow-up specified for the ETV. See Section 1.3 (Schedule of Activities), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events and Serious Adverse Events).

7.3 Lost to Follow up

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

8 Study Assessments and Procedures

Study procedures and their timing, including tolerance limits for timing, are listed in the SoA (Section 1.3). Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

The disease activity measurements are used in clinical practice and CD clinical trials.

The safety parameters in this study are routine elements of clinical health assessment and Phase 3 drug development.

Safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study drug.

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.

8.1 Efficacy Assessments

The following table defines efficacy endpoints used in this study.

Endpoint	Definition
Endoscopic response	≥50% reduction from baseline in SES-CD total score
Endoscopic remission SES-CD ≤4	SES-CD Total Score ≤4 and at least a 2-point reduction versus baseline and no subscore >1
Endoscopic remission SES-CD 0-2	SES-CD Total Score ≤2
Clinical remission by PRO	unweighted daily average SF ≤3 (number of liquid or very soft stools [as taken from the Crohn's Disease Activity Index, CDAI], defined using the Bristol Stool Scale Category 6 or 7 [Lewis and Heaton 1997], that is, liquid or watery stools) and the unweighted daily average AP ≤1 (AP [4-point scale: 0=none, 1=mild, 2=moderate, 3=severe]) and both SF and AP no worse than baseline
Clinical response by PRO	as at least a 30% decrease in SF and/or AP and neither score worse than baseline
Clinical remission by CDAI	CDAI score <150
Clinical response by CDAI	A reduction in CDAI score by ≥100 points compared to baseline and/or being in clinical remission by CDAI

Abbreviations: AP = abdominal pain; CDAI = Crohn's Disease Activity Index; PRO = patient-reported outcome; SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency.

8.1.1 Primary Efficacy Assessment

The co-primary endpoints (mirikizumab versus placebo) are:

- Proportion of participants achieving clinical response by PRO at Week 12 and endoscopic response at Week 52; and
- Proportion of participants achieving clinical response by PRO at Week 12 and clinical remission by CDAI at Week 52.

Clinical Response by PRO

Clinical Response by PRO is defined in the table in Section 8.1.

The PROs used for the co-primary endpoint are: SF per Bristol Stool Scale Category 6 or 7, and AP based on the 0-3 scale of CDAI (Section 4.2). Refer to Appendix 10.8 for more information on PROs.

Endoscopic Response

Endoscopic response is based on the SES-CD score (Vuitton et al. 2016) and is defined in the table in Section 8.1.

The SES-CD tool will be utilized by central readers to evaluate the endoscopy video that is collected during the participant endoscopic examination. The SES-CD is discussed further in Section 8.1.1.1.

Refer to Sections 8.1.1.3 and 8.1.1.4 for more information on Endoscopy and Endoscopic Biopsies.

Clinical Remission by CDAI

Clinical remission by CDAI is defined in the table in Section 8.1.

The CDAI is discussed further in Section 8.1.1.1.

8.1.1.1 Crohn's Disease Activity Index (CDAI)

The CDAI is an 8-item disease activity measure comprised of a composite of 3 patient-reported and 5 physician-reported/laboratory items (physical signs and a laboratory parameter [hematocrit]). Participant responses are summed over a 7-day period and all items are subsequently weighted, yielding a total score range of 0 to 600 points. See Appendix 10.8 for additional descriptions of PROs (CDAI-Stool Frequency [CDAI-SF], CDAI-Abdominal Pain [CDAI-AP], and CDAI-Well-Being).

8.1.1.2 Simple Endoscopic Score for Crohn's Disease (SES-CD)

The SES-CD (Daperno et al. 2004) is an endoscopic scoring system for CD based on 4 endoscopic variables (presence and size of ulcers, proportion of surface covered by ulcers, proportion of surface affected by disease, and presence and severity of stenosis), which are assessed in 5 ileocolonic bowel segments (ileum; right, transverse, and left colon; and rectum). Each of the 4 endoscopic variables is scored from 0 to 3: presence and size of ulcers (none = score 0; diameter 0.1 cm to 0.5 cm = score 1; 0.5 cm to 2 cm = score 2; >2 cm = score 3); extent of ulcerated surface (none = 0; <10% = 1; 10% to 30% = 2; >30% = 3); extent of affected surface (none = 0; <50% = 1; 50% to 75% = 2; >75% = 3); and presence and type of narrowing (none = 0; single, can be passed = 1; multiple, can be passed = 2; cannot be passed = 3). The grand total is obtained as the sum of all endoscopic scores across all bowel segments. Scores range from 0 to 56, with higher scores indicating more severe disease.

8.1.1.3 Endoscopy

An endoscopy will be performed on all participants during screening, 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 participants have clinically acceptable central laboratory test results. Stool culture and *C. difficile* must be negative at screening prior to randomization.

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

During the study, the SES-CD will be determined by central readers blinded to study treatment, to determine study eligibility and endoscopic efficacy evaluation. A detailed imaging review charter from the central reading laboratory will outline the endoscopic procedures, video recordings, and equipment to be used for video capture and transmission of endoscopic recordings. For each participant, video recording of the entire endoscopic procedure will be performed using a storage medium provided by the sponsor or designee. The endoscopic recordings will be read centrally in a blinded manner by qualified gastroenterologists according to the image review charter.

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

8.1.1.4 Endoscopic Biopsies

Biopsies will be collected during the endoscopy procedure. Biopsies will be used for the assessment of exploratory biomarkers where permitted (Section 8.8) and to support assessment of the histopathology endpoints (Section 8.1.3.2). The biopsy samples will be sent to the central study laboratory for processing. To ensure quality data and standardization, bowel tissue histopathologic scoring will be performed by blinded central readers. The details of biopsy sample collection will be provided in both the imaging manual and laboratory manual. A detailed endoscopy and 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 during the study.

At the scheduled endoscopies, additional biopsies may be taken as clinically indicated for participant management. These specimens will be sent to a local laboratory. Any clinically significant findings must be recorded as an AE on the eCRF.

8.1.2 Secondary Efficacy Assessments

8.1.2.1 Patient Reported Outcomes (PROs)

The following PROs will be collected:

- Via patient eDiary
  - bowel movement count (BMC)
  - CDAI-SF
    - Note: Bristol Stool Scale is used as a reference to complete CDAI-SF.
  - CDAI-AP

  - CDAI-Well-Being
  - Abdominal Pain numeric rating scale (NRS)
  - Urgency NRS
  - Patient Global Rating of Severity (PGRS)
- Via tablet device
  - Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)
  - 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, Acute
  - Work Productivity and Activity Impairment Questionnaire – Crohn's Disease (WPAI-CD)
  - Inflammatory Bowel Disease – Disability Index (IBD-DI)
  - Patient Global Impression of Change (PGIC)

As noted in Section 6.4, the investigator is responsible for ensuring that study participants receive adequate training on, and have appropriate understanding of, how to evaluate their CD symptoms and to record them on the eDiary.

See Appendix 10.8 for details on the above PROs.

8.1.2.2 Inflammatory Biomarkers

High-sensitivity C-Reactive Protein (hsCRP)

High-sensitivity C-reactive protein is an acute phase protein expressed by hepatocytes in response to inflammatory cytokines, particularly IL-6, TNF, and IL-1β (Sands 2015). High-sensitivity C-reactive protein will be obtained at time points described in the SoA (Section 1.3). Investigators will be blinded to hsCRP 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 calprotectin 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 SoA (Section 1.3). Investigators will be blinded to fecal calprotectin results.

8.1.2.3 Extraintestinal Manifestations (EIMs)

Review of EIMs will be performed at the time points described in the SoA (Section 1.3). Extraintestinal manifestations include ankylosing spondylitis, anal fissure, fistula or abscess, other fistulae, arthritis/arthralgia, cholelithiasis, erythema nodosum, nephrolithiasis, aphthous stomatitis, primary sclerosing cholangitis, pyoderma gangrenosum, sacroiliitis, iritis/uveitis, and thrombosis (deep vein/portal vein).

8.1.2.4 Fistulas

Additional data on bowel fistulas will be collected on an eCRF at the time points described in the SoA (Section 1.3).

8.1.3 Exploratory Assessments

Other exploratory endpoints will be defined in the SAP.

8.1.3.1 Disease Severity Index-Crohn's Disease (DSI-CD)

The DSI-CD is a clinician's reported 16-item measurement scored by reviewing participant symptoms, physical assessment, labs, medications, physical activity, and pain. Scores range from 0 to 100, with a higher score indicating worse disease severity.

This assessment will only be performed at screening.

CCI [redacted]

[redacted]

8.2 Safety Assessments

Visits and order of safety assessments

Safety assessments occur at visits specified in the SoA (Section 1.3). When multiple assessments are scheduled for the same visit, the preferred order of completion is:

- vital signs first,
- ECG (if applicable), and then
- blood sampling last.

Adverse event collection should occur before the collection of the C-SSRS or QIDS-SR16 (Section 8.2.11 and Section 8.3.2.1).

Data collection and reporting

The AE data collection and reporting requirements are described in Section 8.3. The additional requirements for collection of data regarding AESIs are noted in Section 8.3.7.

Safety monitoring

The sponsor 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 DMC (Appendix 10.1.4) or by the sponsor, through its Internal Review Committee (IRC) process.

8.2.1 Vital Signs

Measurements of vital signs (body temperature, blood pressure, and pulse rate) will be conducted at the study visits specified in the SoA (Section 1.3).

Sitting blood pressure and pulse rate should be measured after the participant 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 participant receives the first dose of study drug should be reported to Lilly or its designee as an AE via eCRF.

8.2.2 Physical Examinations

Physical examinations are mandated and will be performed as specified in the SoA (Section 1.3). Physical examinations 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.

At screening, one complete physical examination (excluding pelvic, rectal, and breast examinations) will be performed and will include an assessment of peripheral lymph nodes.

After screening, physical examinations should include a symptom-directed evaluation as well as examination of eyes, heart, lungs, abdomen, and visual examination of the skin. For participants with a risk factor, a thorough exam to evaluate for TB will be performed (Section 8.2.6).

Any clinically significant findings from physical examination that result in a diagnosis and that occur after the participant receives the first dose of study drug should be reported to Lilly or its designee as an AE via eCRF.

8.2.3 Electrocardiograms

Electrocardiograms (12-lead) will be conducted at the study visits specified in the SoA (Section 1.3).

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

Electrocardiograms will be read locally.

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

8.2.4 Chest Radiography

A posterior-anterior CXR, interpreted and reported by a radiologist or pulmonologist, will be obtained at screening, as specified in the SoA (Section 1.3). A lateral CXR can also be obtained if, in the opinion of the investigator, a lateral view is indicated.

Participants need not have a CXR at screening if, based on the judgement of the investigator, all the following conditions are met:

- the CXR was performed within 3 months before initial screening, and
- documentation of the CXR, read by a qualified radiologist or pulmonologist, is sufficient for TB evaluation according to local standard of care.

A CT scan can be performed as an alternative to the CXR based on regional standard of practice.

For all participants, CXR films or images or a radiology report must be available to the investigator for review.

Certain findings from CXR may be consistent with a condition that excludes a participant from the study; see Section 5.2.

8.2.5 Stool Testing

Stool Culture

A stool sample for culture will be obtained at screening. In order to be randomized, participants must have a negative stool culture from which no enteric pathogens are isolated.

Retesting is allowed within the screening period if there is a technical difficulty in performing or reporting the stool culture assay, as stated in Section 5.4.1.

Participants who have a "positive" stool culture result can be rescreened once, as stated in Section 5.4, provided that the following conditions have been met:

- the participant has been adequately treated, and
  - if antibiotics were prescribed, participant has been off antibiotics for 30 days, or
  - if antibiotics were not prescribed, 30 days or more has elapsed since resolution of acute symptoms and signs associated with the underlying intestinal infection.

Additional local stool culture/testing is allowed at the investigator's discretion.

Participants with a positive stool culture result are excluded from the study (see Section 5.2).

C. difficile Toxin

A stool sample for *C. difficile* testing (including *C. difficile* toxin A and B, GDH with reflex to PCR testing as needed) will be obtained at screening.

Participants with a positive test for *C. difficile* are excluded from the study (Section 5.2).

Retesting is allowed within the screening period if there is a technical difficulty in performing or reporting the *C. difficile* result, as stated in Section 5.4.1.

Participants who test positive at screening for *C. difficile* can be rescreened once, as stated in Section 5.4, provided that the following conditions have been met:

- the participant has been adequately treated, and
- the participant has been off antibiotics for 30 days.

Participants who have been adequately treated for *C. difficile* with fecal microbial transplantation or IV immunoglobulin therapy can be rescreened once for the study, 30 days after completing their therapy.

8.2.6 Tuberculosis Testing

Initial screening

All participants will be screened for active TB and LTBI.

Screening for LTBI will include the following:

- Thorough medical and social history to determine risk factors for TB infection over lifetime, symptoms or signs of active TB, and physical examination, including body temperature measurement and assessment of peripheral lymph nodes, as described in Section 8.2.1 and Section 8.2.2.
- CXR or CT, as described in Section 8.2.4, and
- A test to assess immune response to mycobacterial antigens (unless participant has a history of a positive IGRA):
    - Interferon-γ release assay (IGRA; for example, 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. Interferon-γ release assay is also the preferred screening test for LTBI in participants 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 participants.

Participants 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.

Participants 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 CXR or CT, may be rescreened once, as indicated in Section 5.4.

Participants may be enrolled in the study if they are treated for LTBI and meet the following requirements:

- no history of risk of re-exposure since their treatments were completed,
- have received at least 4 weeks of appropriate ongoing prophylactic therapy for LTBI, based on national or international guidelines, for example, the CDC (CDC 2016) or the WHO (WHO 2018), with documentation of having completed the appropriate TB prophylaxis regimen,
- no evidence of reactivation of LTBI, and

- have no evidence of hepatotoxicity (ALT and AST levels must remain ≤2 × ULN) upon retesting of serum ALT and AST levels before randomization).

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

Retesting and confirmatory testing

One retest is allowed for participants with an "indeterminate" QuantiFERON-TB Gold assay or "borderline" T-SPOT assay, as stated in Section 5.4.1. Participants 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 participants 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, as detailed in Appendix 10.4.

Participants who have been assessed by the PI to have a false positive TB test and meet the criteria to allow a retest must have confirmatory testing performed by an IGRA (QTF or T-SPOT). The TST should **not** be used for confirmatory testing.

If the confirmatory test is positive, the participants will be excluded from the study unless he or she completes at least 4 weeks of appropriate therapy for LTBI, based on national or international guidelines (as defined above) and has no evidence of hepatotoxicity (ALT and AST levels must remain ≤2 × ULN) upon retesting of serum ALT and AST levels after at least 4 weeks of LTBI treatment. Such participants 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.

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

Monitoring for TB during the study

For all participants, monitoring for TB is to be continuous throughout the study. Every 3 months, the participants will be assessed for risk factors for TB (Appendix 10.4). If the participant has a risk factor, the investigator should conduct a thorough exam to evaluate for TB, including examination of peripheral lymph nodes and documentation of body temperature. If the participant has a risk factor(s), the investigator should conduct a thorough exam to evaluate for TB, including examination of peripheral lymph nodes and documentation of body temperature. If there are relevant physical findings, an IGRA and CXR or CT should be performed.

Diagnosis of LTBI during the study

Participants diagnosed with LTBI during the study must be temporarily discontinued from study drug (Section 7.1.2). If treatment for LTBI is considered to be appropriate, the participant 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 ≤2 × ULN) upon retesting of serum ALT and AST levels after at least 4 weeks of LTBI treatment. Such participants may then resume study drug and must continue with and complete a full course of treatment for LTBI in order to continue on the study drug. Noncompliance with LTBI treatment during the study is a reason for permanent discontinuation from study drug (Section 7.1.1).

Household contact

Throughout the study, participants who have had household contact with a person with active TB must be evaluated for TB infection.

Prior treatment for LTBI

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

Active TB

Participants with a past history of active TB, without documented treatment by WHO and/or CDC criteria are excluded from the study (Section 5.2).

Participants diagnosed with active TB at screening will be excluded (Section 5.2) and should be referred by the investigator for appropriate TB treatment and follow-up.

If a participant is diagnosed with active TB during the study, the study drug will be permanently discontinued (Section 7.1.1), and the participant will undergo an ETV and then enter the post-treatment follow-up period. The participant should also be referred by the investigator for appropriate TB treatment and follow-up.

8.2.7 Clinical Laboratory Tests

Visits and times

The clinical laboratory tests listed in Appendix 10.2 will be conducted at the study visits specified in the SoA (Section 1.3).

Retesting is allowed during the screening period (see Section 5.4.1).

Additional clinical laboratory tests, including local tests, may be performed at any time during the study as determined necessary by the investigator for immediate participant management or safety or as required by local regulations.

Except where otherwise stated (for example, for postdosing PK sample), samples for laboratory tests should be collected prior to dosing.

Central and local Testing

Unless noted as locally performed (for example, urine pregnancy tests), clinical laboratory tests will be sent to a central laboratory for testing.

Provision of laboratory test results

With the exception of laboratory test results that may unblind the study (Section 8.1.2.2), Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor.

Investigator responsibilities

Investigators or their designees are expected to review laboratory reports in a timely manner throughout the study.

Investigators must document their review of each laboratory safety report.

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

8.2.7.1 Pregnancy Testing

Pregnancy testing is to be performed on all women unless they meet the criteria describing women not of childbearing potential, as outlined Section 5.1. Participants who are pregnant will be discontinued from the study (Section 7.1.1).

Visits and times

Serum pregnancy test will be done at screening only, and results will be confirmed by the central laboratory.

Urine pregnancy testing will be performed locally during designated scheduled visits through Week 52. The urine pregnancy test must be "negative" within 24 hours prior to each administration of study drug at every study visit.

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 Section 5.1. Follicle-stimulating hormone can be optionally obtained during screening, at the discretion of the investigator. Follicle-stimulating hormone can also be optionally obtained during the study to determine postmenopausal status (see Section 1.3).

8.2.7.2 Immunogenicity Assessment

Visits and times

At the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected to determine antibody production against mirikizumab.

- Predose samples will be obtained per the SoA.
- The actual date and time (24-hour clock time) of each sample collection will be recorded.

To aid interpretation of these results, a predose blood sample for PK analysis will be collected at the same time points.

In the event of a systemic allergic/hypersensitivity reaction (Section 8.3.7.2), additional blood samples will be obtained as specified in the SoA (Section 1.3).

Sample collection, handling, and use

Instructions for the collection and handling of blood samples will be provided by the sponsor.

Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of mirikizumab at a laboratory approved by the sponsor. Samples may be further evaluated for antibodies that neutralize the activity of mirikizumab.

Sample retention

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

8.2.8 Hepatitis B Testing

HBV screening and interpretation

Participants with acute or chronic hepatitis B infection are excluded from the study (see Section 5.2).

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 participants who are HBsAg-, anti-HBc+.

Exclusion based on HBV serology and HBV DNA testing

Participants with the following screening test results will be excluded from the study (Section 5.2).

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

Participants potentially allowed into the study, based on HBV serology and HBV DNA testing

Participants with the following screening test results may be eligible for inclusion, provided they meet the other study entry criteria:

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

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

Randomized participants with the following serological pattern at screening will undergo HBV DNA monitoring as described in the SoA (Section 1.3):

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

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

Management of participants with detectable HBV DNA during the study

If HBV DNA is detected during the study, the study drug will be discontinued, and the participant will have an ETV; the participant will then enter the post-treatment follow-up period (Section 7.1). Prior to discontinuing investigational product, the sponsor recommends that a hepatologist (or a physician with expertise in viral hepatitis) is consulted and that it is determined whether it is appropriate to start antiviral therapy prior to discontinuation of IP or any immunosuppressant or immunomodulatory therapy. However, study drug should not be administered until this consultation has been completed and after discussion with the Medical Monitor. Such participants should also receive appropriate follow-up medical care.

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

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

8.2.9 Hepatitis C Testing

Participants with current hepatitis C infection are excluded from the study (see Section 5.2).

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. Participants with a positive HCV antibody test and detectable HCV RNA will be excluded from the study (Section 5.2).

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

Participants who have spontaneously cleared hepatitis C infection, defined as

- a positive HCV antibody test and
- 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 participant with a history of hepatitis C infection who develops elevated ALT >3 × ULN within the study will be tested for HCV RNA.

Participants 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 24 weeks after completion of a full, documented course of an approved, potentially curative antiviral therapy for HCV.

If a participant is diagnosed with hepatitis C during the study (detectable HCV RNA), the study drug will be discontinued, and the participant will have an ETV; the participant will then enter the post-treatment follow-up period (Section 7.1). Such participants should also receive appropriate follow-up medical care.

8.2.10 Hepatic Safety Monitoring

If a study participant experiences elevated ALT ≥3 × ULN, ALP ≥2 × ULN, or elevated TBL ≥2 × ULN, liver testing (described in Appendix 10.3) 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 participant experiences an ALT or AST >3 × ULN and TBL >2 × ULN or INR >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 ≥5 × ULN on 2 or more consecutive blood tests
- elevated serum TBL to ≥2 × ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2 × ULN on 2 or more consecutive blood tests
- participant discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be a SAE
- participant with a history of HCV infection develops elevated ALT >3 × ULN. Participant will be tested for HCV RNA.
- participant experiences an ALT or AST >3 × ULN and TBL >2 × ULN or INR >1.5. The study medical monitor should be consulted as soon as possible for further guidance.

8.2.11 Depression, and Suicidal Ideation and Behavior

Suicide-related events (behavior and/or ideations) will be assessed at screening with the administration of the C-SSRS.

Depressive symptomology will be assessed with the QIDS-SR16 at the visits specified in the SoA (Section 1.3).

These assessments are described below, and further information is provided in Appendix 10.9.

Columbia Suicide Severity Rating Scale: The C-SSRS (CUIMC 2016) is a scale that captures the occurrence, severity, and frequency of suicidal ideation and/or behavior 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 healthcare professional. Participant data for the C-SSRS will be recorded 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 (APA 2013). Participants will record their responses to the QIDS-SR16 electronically as source data in the tablet device.

See Section 8.3.2.1 for information about AE collection relative to collection of the C-SSRS or QIDS-SR16.

See Section 7.1.1 for information regarding discontinuation of study drug for participants who have suicidal ideation or suicidal behaviors.

8.3 Adverse Events and Serious Adverse Events

Investigators are responsible for monitoring the safety of participants 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 participant.

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

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 participant to discontinue the investigational product before completing the study. The participant should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is otherwise 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 participant'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 CD, 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 participant'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.

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences (see Section 8.3.2.1).

8.3.1 Serious Adverse Events

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

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

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the participant 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 8.3.2) 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. Participants with a serious hepatic AE should have additional data collected using the hepatic eCRF packet (see Section 8.2.10).

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.

8.3.1.1 Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 Code of Federal Regulations (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.

8.3.2 Time Period and Frequency for Collecting AE and SAE Information

AEs that begin before the first dose of study drug but after signing of the ICF will be recorded on the Adverse Event eCRF.

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

8.3.2.1 Adverse Event Monitoring with a Systematic Questionnaire

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. However, if an event is serious or leads to discontinuation, the event should be included on the AE form, and the process for reporting SAEs, if applicable, should be followed.

8.3.3 Follow-up of AEs and SAEs

The investigator responsibility for follow-up of AEs sand SAEs is described in Section 8.3.

8.3.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE as stated in Section 8.3 and Section 8.3.2 is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to

the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy Reporting

For all pregnancies in female participants and female partners of male participants, details will be collected (via the procedures outlined in Section 8.3) for pregnancies that begin at any point after the start of study drug and until at least 20 weeks after the participant's last dose of study drug.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 8.3.

CCI

Sites should collect additional details and data regarding AESIs, as instructed on the applicable eCRFs.

8.3.7.1 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). See Appendix 10.5 for more information.

8.3.7.2 Systemic Allergic Reactions and Hypersensitivity Events

All biologic agents carry the risk of systemic allergic/hypersensitivity reactions. Clinical manifestations of these reactions may include but are not limited to:

- Skin rash
- Pruritus (itching)
- Dyspnea
- Urticarial (hives)
- Angioedema (for example, swelling of the lips and/or tongue)
- Hypotension
- Anaphylactic reaction

Participants with clinical manifestations of systemic allergic/hypersensitivity reactions should be treated per local standard of care. Additional data describing each symptom should be provided to the sponsor in the eCRF.

In case of a systemic hypersensitivity reaction involving two or more organ systems (that is, mucocutaneous, respiratory, cardiovascular, or gastrointestinal systems), additional blood samples for laboratory testing should be collected at the times specified in the SOA (Section 1.3). The lab results are provided to the sponsor via the central laboratory.

Site personnel should educate participants 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 6.7.3.2.

8.3.7.3 Injection/Infusion Site Reactions

Symptoms of a local injection/infusion site reaction may include erythema, induration, pain, pruritus, and edema at the site of the injection/infusion. If an injection/infusion site event is reported, the AE will be recorded, and additional data will be provided to the sponsor in the eCRF.

For recommendations on the management and follow-up of injection site or infusion site events, see Section 6.7.3.2.

8.3.7.4 Cerebro-cardiovascular Events Adjudication

Potential cerebro-cardiovascular events will be identified by the investigative site or by a medical review conducted by the sponsor or designee. Additional data about each identified potential event should be provided to the sponsor via specific event adjudication forms. A blinded external Clinical Event Committee will adjudicate the events in a consistent and unbiased manner.

8.3.8 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.

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

8.4 Treatment of Overdose

In case of suspected overdose, participants should be monitored for any signs or symptoms of adverse reactions or effects, and hematology, chemistry, vital signs, and oxygen saturation should be monitored; supportive care should be provided as necessary. The medical monitor and sponsor must be informed as soon as possible when an overdose has been identified, and all AEs associated with the overdose will be recorded in the eCRF. There is no known antidote for mirikizumab or ustekinumab.

8.5 Pharmacokinetics

Visits and times

At the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected to determine the serum concentrations of mirikizumab.

Collection, handling, and storage of samples

Instructions for the collection and handling of blood samples will be provided by the sponsor. 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 participants will be analyzed.

Additional samples

A maximum of 3 additional samples for exploratory analyses such as bioanalytical method development or validation exercises may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. In the case of systemic allergic/hypersensitivity reactions (Section 8.3.7.2), additional blood samples will be obtained, as described in the SoA. The results will not be provided to the investigator.

Blinding

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

Sample retention

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

8.6 Pharmacodynamics

See Section 8.8 for biomarkers.

8.7 Pharmacogenomics

8.7.1 Whole Blood Sample for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in the SoA (Section 1.3) where local regulations allow.

Sample use

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to mirikizumab and to investigate genetic variants thought to play a role in CD, the biology of IL-23, immune responses, and responses to cytokines. Assessment of variable response may include evaluation of AEs or differences in efficacy.

The genetic markers on the immunochip (Illumina Infinium® ImmunoArray-24 v2.0BeadChip [WWW]) may be tested. These are genetic markers that are related to the biology of inflammatory and autoimmune disease.

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the investigator site personnel.

Sample retention

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last participant visit for the study, or for a shorter period if local regulations and/or ERBs/investigational review boards impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of mirikizumab or after mirikizumab becomes commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome wide association studies, and candidate gene studies. Regardless of technology utilized genotyping data generated will be used only for the specific research scope described in this section.

8.8 Exploratory Biomarkers

Serum, plasma, whole blood RNA, whole blood for epigenetics, fecal matter, and gastrointestinal tissue samples for biomarker research will be collected at the visits and times specified in the SoA (Section 1.3) where local regulations allow.

Sample use

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of participant response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including DNA, RNA, proteins, lipids, and other cellular elements.

Samples will be used for research on the drug target, CD disease process, variable response to mirikizumab, pathways associated with CD, mechanism of action of mirikizumab, and/or research method or in validating diagnostic tools or assays related to CD or the study drug.

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the investigator site personnel.

Sample retention

Samples will be retained at a facility selected by Lilly or its designee for a maximum 15 years after the last participant visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of mirikizumab or after mirikizumab becomes commercially available.

8.9 Medical Resource Utilization and Health Economics

Sites should provide information regarding healthcare visits, including hospitalizations and surgeries for CD, as instructed on the eCRF.

9 Statistical Considerations

9.1 Statistical Hypotheses

The primary hypothesis that will be tested in this study is that mirikizumab is superior to placebo in the Primary Analysis Set on below co-primary endpoint.

- Clinical response by PRO at Week 12 and endoscopic response at Week 52
- Clinical response by PRO at Week 12 and clinical remission by CDAI at Week 52

Major secondary hypotheses are that mirikizumab is superior to placebo with regards to

- Endoscopic response at Week 52
- Clinical remission by CDAI at Week 52
- Clinical response by PRO at Week 12 and clinical remission by PRO at Week 52
- Endoscopic response at Week 12
- Clinical remission by CDAI at Week 12
- Clinical response by PRO at Week 12 and endoscopic remission SES-CD ≤4 at Week 52
- Clinical response by PRO at Week 12 and either clinical remission by CDAI at Week 52 or endoscopic remission SES-CD ≤4 at Week 52 who were also corticosteroid-free from Week 40 to Week 52
- Endoscopic remission SES-CD ≤4 at Week 12
- Change from baseline in Urgency NRS at Week 12 and Week 52

Additional major secondary hypotheses are that mirikizumab is superior to ustekinumab with regards to:

- endoscopic response at Week 52
- endoscopic remission SES-CD ≤4 at Week 52.

Another major secondary hypothesis is that mirikizumab is noninferior to ustekinumab at Week 52 with regards to clinical remission by CDAI.

9.2 Sample Size Determination

Approximately 3000 participants may be screened to achieve a total of approximately 1100 participants randomly assigned to study intervention. Based on a 6:3:2 randomization ratio, approximately 600 participants will be randomized to mirikizumab, 300 participants to ustekinumab, and 200 participants to placebo.

Approximately 90% of randomized participants are expected to meet the Primary Analysis Set definition as described in Section 9.3. A sample size of 990 participants (540 participants in mirikizumab and 180 participants in placebo) provides >90% power to demonstrate that mirikizumab is superior to placebo for the co-primary endpoint of (1) clinical response by PRO at Week 12 and clinical remission by CDAI at Week 52 and (2) clinical response by PRO at Week 12 and endoscopic response at Week 52. This estimated power is based on a 2-sided chi-square test with alpha = 0.005 and the assumed treatment response rates of the co-primary endpoint are 33% for mirikizumab and 10% for placebo.

The sample size based on the Primary Analysis Set also provides >90% power to demonstrate that mirikizumab is superior to ustekinumab for endoscopic response at Week 52. This calculation is based on a 2-sided chi-square test with alpha = 0.045 and assuming a difference of at least 16% between mirikizumab and ustekinumab in endoscopic response at Week 52.

Blinded sample-size re-estimation may be performed before the last participant has been enrolled in the study. For this re-estimation, response rates using blinded data will be evaluated and compared with the assumed response rates.. The sample size from the study is estimated to be between a minimum sample size, 1100 participants, and a predefined, maximum sample size upto 1210 participants. If the re-estimated sample size is smaller than the planned minimum sample size, the study may enroll to the recalculated sample size. If the re-estimated sample size is larger than the planned minimum sample size, the team will decide whether to increase the sample size, up to a predefined maximum, or to accept the re-assessed reduced power reduction in power.

9.3 Populations for Analyses

For purposes of analysis, the following populations are defined.

Intent-to-Treat (ITT) Population

The ITT Population is defined as all randomized participants, even if the participant does not receive the correct treatment, or otherwise does not follow the protocol. Participants will be analyzed according to the treatment to which they were randomized.

Modified Intent-to-Treat (mITT) Population

All participants from ITT population who take at least one dose of study drug.

Primary Analysis Set

All participants from mITT population who have baseline SES-CD ≥7 (or ≥4 for isolated ileal disease).

Safety Population

Same as mITT.

9.4 Statistical Analyses

9.4.1 General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. A detailed SAP describing the statistical methodologies will be developed by the sponsor or its designee.

Unless otherwise specified, efficacy analyses will be conducted on the Primary Analysis Set. Selected efficacy analysis may also be conducted on the mITT population. Safety analyses will be conducted on the safety population. Definitions are described in Section 9.3.

When reported, descriptive statistics will include the number of participants; mean, standard deviation, median, minimum, and maximum for continuous measures; and frequency counts and percentages for categorical measures.

Treatment comparisons of categorical efficacy measures between mirikizumab versus placebo, and mirikizumab versus ustekinumab will be made using the Cochran-Mantel-Haenszel (CMH) chi-square test with the following covariates: biologic-failed status (yes/no), baseline SES-CD total score (<12, ≥12), and either baseline SF ≥7 and/or baseline AP ≥2.5 (yes/no). The CMH chi-square p-value will be provided. The percentages, difference in percentages, and CI of the difference in percentages will be reported.

When evaluating continuous measures over time, a restricted maximum-likelihood-based mixed effects model of repeated measures (MMRM) will be used. The model will include treatment, biologic-failed status (yes/no), baseline SES-CD total score (<12, ≥12), and either baseline SF ≥7 and/or baseline AP ≥2.5 (yes/no), visit, and treatment by visit interaction as fixed categorical effects and, if a baseline score for the measure is available, baseline score and baseline score by visit interaction as fixed continuous effects. An unstructured covariance structure will be used to model the between- and within-subject errors. If this analysis fails to converge, 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 degrees of freedom. Type III sums of squares for the least squares means will be used for the statistical comparison; CI will also be reported. Contrasts will be set up within the model to test treatment groups at specific time points of interest.

Fisher's exact test will be used for categorical safety data (example, AEs) for between treatment group comparisons. Continuous safety variables (example, laboratory variables) will be analyzed by an analysis of covariance with treatment and baseline value in the model.

All tests for the co-primary and major secondary endpoints will be conducted under the multiplicity-controlled framework described in Section 9.4.1.4. For other secondary endpoints, superiority comparisons will be tested at a 2-sided alpha level of 0.05 and noninferiority comparisons will be tested at a 1-sided alpha level of 0.025. Full details of all apriori specified analyses and finalized graphical testing scheme will be provided in the SAP. Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

9.4.1.1 Definition of Baseline

Visit 2 (Week 0) is the baseline randomization visit. The centrally read baseline SES-CD score from the screening endoscopy is considered the baseline for endoscopic response and endoscopic remission. Daily diary entries obtained prior to Visit 2 are also considered baseline for clinical remission by PRO, clinical response by PRO, CDAI clinical remission, and CDAI clinical response. For other efficacy, and health outcome assessments, baseline is defined as the last nonmissing assessment recorded on or prior to the date of Visit 2 (Week 0), unless otherwise specified. For safety assessments, the baseline period is defined as the start of screening and ends at the first dose of study treatment at Visit 2, unless otherwise specified. Based on the type of safety analysis, the baseline period or the last nonmissing assessment during the baseline period will be used for baseline. Baseline definitions for safety assessments will be described in the SAP by analysis type.

9.4.1.2 Estimand

The estimand (ICH 2017) associated with each endpoint/analysis is documented in the following places:

- The population of interest is described in the inclusion/exclusion criteria (Section 5.1 and Section 5.2) and in "Populations for Analyses" (Section 9.3)
- The endpoints and variables are listed in Objectives and Endpoints (Section 3)
- The handling of intercurrent events is summarized in "Missing Data Imputation" (Section 9.4.1.3)
- Population summary measures are described in "General Statistical Considerations" (Section 9.4.1)

Additional details will be provided in the SAP.

9.4.1.3 Missing Data Imputation

Analysis of categorical efficacy and health outcomes variables will use a nonresponder imputation (NRI) method for missing data. A participant will be considered NR for the NRI-based analysis if he or she:

- does not achieve the endpoint(s) being analyzed,
- has missing data at time point of interest that results in non-assessment of an endpoint(s) at the time point of interest,
- discontinues treatment prior to time point of interest,
- specified changes in concomitant CD medications (to be detailed in the SAP).

In selected analyses, participants in the placebo group who begin treatment with mirikizumab at Week 12, due to not achieving clinical response by PRO, will be considered NR for all visits subsequent to Week 12 for NRI-based analyses on categorical endpoints at Week 52. Details will be provided in the SAP.

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.

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

9.4.1.4 Multiple Comparisons/Multiplicity

For testing the primary and major secondary hypotheses, a prespecified graphical scheme (Bretz et al. 2009, 2011) will be implemented to control the overall Type I error rate (FWER) at a 2-sided alpha level of 0.05 as described below:

Two groups including co-primary and major secondary hypotheses will be used. Group 1 will include the co-primary endpoint and all major secondary endpoints that involve comparisons of mirikizumab versus placebo, and Group 2 will include all major secondary endpoints that involve comparisons of mirikizumab versus ustekinumab. Within each group, the graphical scheme will control the FWER at a prespecified level. For Group 1, a FWER at 0.005 will be

used. If all comparisons in Group 1 are achieved, following the pre-specified graphical scheme, testing will proceed to Group 2 with a FWER at 0.05. If one or more hypotheses in Group 1 are failed to be rejected, following the pre-specified graphical scheme, testing will proceed to Group 2 with a FWER at 0.045. The graphical approach is a closed testing procedure; hence, it strongly controls the FWER across all endpoints (Alosh et al. 2014).

9.4.2 Treatment Group Comparability

9.4.2.1 Participant Disposition

The number of randomized participants (that is, participants in ITT) will be summarized by treatment group. Frequency counts and percentages of all participants who are randomized and complete the study or who discontinue the study or treatment intervention early will be presented. Reasons for early discontinuation of the study drug or of the study will be summarized.

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

9.4.2.2 Participant Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group; no testing will be performed for baseline characteristics. For continuous measures, summary statistics will include sample size, mean, standard deviation, median, minimum, and maximum. For categorical measures, summary statistics will include sample size, frequency, and percentages.

9.4.2.3 Concomitant Therapy

Concomitant therapy will be collected at each visit, and the reported term will be classified by the WHO drug dictionary. A summary of preferred names of concomitant medication by treatment group will be generated for the mITT population.

9.4.2.4 Treatment Compliance

Deviations from the prescribed dosage regimen (as described in Section 6.4) will be described in a patient listing. Additional details will be described in the SAP.

9.4.3 Efficacy Analyses

Primary and secondary analyses will be based on the Primary Analysis Set (defined in Section 9.3).

9.4.3.1 Primary Analyses

The co-primary endpoint is comprised of two separate endpoints:

- the proportion of participants achieving clinical response by PRO at Week 12 and endoscopic response at Week 52, and
- the proportion of participants achieving clinical response by PRO at Week 12 and clinical remission by CDAI at Week 52.

Endoscopic response is defined as ≥50% improvement from baseline in SES-CD total score where the SES-CD total score will be calculated as the sum of its 5 subscores: ileum; right

colon, transverse colon, left colon; and rectum. If at least one subscore is non-missing, missing subscores will be imputed with a zero value when deriving the SES-CD total score. Endoscopies performed for Week 52 that occur up to a maximum of 14 days after the Week 52 visit date but before any additional dosing will be used for the analysis of Week 52.

Clinical response by PRO is defined as ≥ 30% decrease in SF and/or AP and neither score worse than baseline. AP average and SF average will be calculated from daily electronic diary data by averaging the most recent 7 days (possibly nonconsecutive) in the 12 days prior to the day of the visit, after removing the day(s) of the endoscopy prep, the day of endoscopy procedure, and the 2 days following the endoscopy procedure. If less than 4 days of data are available, the value for AP average or SF average will be set to missing.

Clinical remission by CDAI is defined as the total CDAI score <150. CDAI total score will be calculated as the sum of 3 participants reported and 5 physician reported/laboratory items. Participant responses are collected from daily electronic diary data and calculated as described for Clinical response by PRO per visit.

Primary analyses will use the CMH chi-square test to compare mirikizumab to placebo as described in Section 9.4.1. The co-primary endpoint will also be conducted for mITT population as a secondary analysis.

9.4.3.2 Secondary Analyses

The CMH test, as described for primary analyses, will be used to analyze categorical secondary endpoints. The previously described MMRM model will be used to analyze continuous secondary endpoints.

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

Noninferiority Analysis

To assess noninferiority of mirikizumab to ustekinumab, the lower bound of the 2-sided 95% CI of the difference in proportions between mirikizumab and ustekinumab response will be compared to the noninferiority margin. The CMH test, as described for primary analyses, will be used to estimate the CI for difference between ustekinumab and mirikizumab proportions. To establish that mirikizumab is noninferior to ustekinumab, the upper bound for the ustekinumab minus mirikizumab proportions must be less than the prespecified noninferiority margin.

Justification of Noninferiority Margin

There is no universally accepted value for what is considered to be a clinically unimportant difference between 2 treatments based on CDAI remission. Global regulatory guidance (EMA 2005 and FDA 2016 guidelines) indicate that selection of the noninferiority margin is based upon a combination of statistical and clinical grounds.

The data from two induction studies (UNITI-1 and UNITI-2) followed by a single maintenance study (IM-UNITI) were used to demonstrate the efficacy of ustekinumab versus placebo in CDAI remission. Participants who were randomized to ustekinumab in UNITI-1 or UNITI-2 and who achieved CDAI response at Week 8 were eligible to enroll in the randomized placebo-withdrawal portion of IM-UNITI as the primary population. All placebo participants and participants who did not achieve clinical response at Week 8 after being dosed with ustekinumab

were eligible to enroll in the nonrandomized portion of IM-UNITI. These participants received ustekinumab at Week 8 and were assessed for CDAI response at Week 16. Those who achieved CDAI response at Week 16 were eligible to continue dosing with ustekinumab while the participants who did not achieve clinical response were discontinued (Feagan et al. 2016).

For Study AMAM, the CDAI remission rate for ustekinumab 90 mg Q8W at Week 52 will be estimated as below:

> Prob (CDAI Remission at Week 52) = Prob (Week 52 CDAI Remission |Week 8 CDAI Response) * Prob (Week 8 CDAI Response) + Prob (Week 52 CDAI Remission |^CDAI Response at Week 8) * Prob (^Week 8 CDAI Response).

The following table shows the CDAI response rates at Week 8 for the 6 mg/kg ustekinumab group:

Induction Study	CDAI Response at Week 8	CDAI Nonresponse at Week 8
UNITI 1	94/249 (37.8%)	155/249 (62.2%)
UNITI 2	121/209 (57.9%)	88/209 (42.1%)
Overall	215/458 (46.9%)	243/458 (53.1%)

Note: Values in the table are n/N (%) where: n = number of participants achieving a response; N = total number of patients in category. Data based on nonresponder imputation.

Source: Feagan et al. 2016.

CDAI Remission rates for Week 52 are estimated as follows:

1. Probability of CDAI Remission at Week 52 for the 90 mg q8w treatment group for participants achieving CDAI Response at Week 8 was 68/128 (53.1%).
2. Probability of CDAI Remission at Week 52 for the 90 mg Q8W treatment group for participants not achieving CDAI Response at Week 8 is estimated as 126/467 (27.0%). This probability assumes that participants who received ustekinumab at both weeks 0 and 8 and did not achieve CDAI response at Week 8 and at Week 16 did not achieve CDAI remission at Week 52

Based on the above, the expected CDAI Remission rate at Week 52 for the 90 mg Q8W treatment group is 39.2% with 95% CI (34.6, 43.9).

CDAI remission rates for participants who were randomized to placebo and continued in placebo during maintenance are not available at Week 52 in IM-UNITI. However, CDAI response and CDAI remission rates from Week 2 through Week 26 were shown to be stable with a slow decrease (approximately 5%) from Week 8 to Week 26 in PRECISE 1 (Sandborn et al. 2007). Assuming that CDAI remission rates in placebo participants have a similar decrease of approximately 5% between Week 8 and Week 52, CDAI remission at Week 52 for the placebo group will be 12.3% (6.8%, 17.9%) based on the summary below.

The following table shows the CDAI remission rates for the placebo group at Week 8:

Induction Study	CDAI Remission at Week 8
UNITI-1	18/247 (7.3%)
UNITI-2	41/209 (19.6%)
Overall	59/456 (12.9%)

Values in the table are n/N (%) where: n = number of participants achieving a response; N = total number of participants in category. Data based on nonresponder imputation.

Source: Feagan et al. 2016.

Based on these rates, the expected treatment effect for ustekinumab 6 mg/kg followed by 90 mg Q8W versus placebo at Week 52 in a treat-through study is 26.9% with 95% CI (19.5, 34.6). CIs were estimated based on bootstrap re-sampling.

Using the fixed 95%/95% margin method, a 10% NI margin represents clinical judgement about the amount of the active control effect that must be retained. Assuming that Study AMAM will have similar proportions of biologic-failed and conventional-failed participants as those observed in the UNITI program and that the constancy assumption holds, the proposed NI margin is expected to preserve 50% of the expected ustekinumab effect in CDAI remission at Week 52 in a treat-through study. If the lower 97.5% lower bound of the CI for the difference between mirikizumab and ustekinumab is greater than -10%, it would rule out a loss of more than half of the benefit expected for ustekinumab for CDAI remission at Week 52.

Since a placebo group will be included in study AMAM, assay sensitivity as well as the constancy assumption will be checked by comparing ustekinumab to placebo for CDAI remission at Week 52. Study AMAM is adequately powered (>90%) to detect a difference between ustekinumab and placebo in CDAI remission at Week 52 (with treatment rates of 12% for placebo and 29% for ustekinumab) based on a chi-square test using 2-sided alpha of 0.05.

9.4.3.3 Tertiary/Exploratory Analyses

The proportion of participants in response to histologic endpoints at Week 12 and Week 52 will be compared across treatment groups. Analysis details are specified in the SAP. Additional analyses of exploratory health outcome endpoints may be considered and will be fully detailed in the SAP.

9.4.4 Safety Analyses

Safety will be assessed by evaluating exposure, AEs, laboratory analytes, vital signs, and AESIs (Section 8.3.7).

Duration of exposure to therapy during the treatment periods will be calculated for each participant and summarized by treatment group.

The AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). A TEAE is defined as an event that first occurred or worsened in severity after baseline. The MedDRA Lowest Level Term will be used in the treatment-emergent computation. If a participant reports the occurrence of a particular event more than once, the most severe of those events will be included in the summary tables of TEAEs.

In an overview table, the number and percentage of participants with at least 1 TEAE, SAE, fatal SAE, or discontinuation from study treatment due to an AE will be summarized by treatment. TEAEs (all and by maximum severity), SAEs including deaths, AEs that lead to treatment discontinuation will be summarized and analyzed by MedDRA System Organ Class and Preferred Term (PT) or by PT alone.

Laboratory and vital signs measurements will be summarized using boxplot displays and treatment emergent shifts to low/high tables.

Potential AESIs will be identified by one or more standardized MedDRA queries by a Lilly-defined MedDRA PT listing based upon the review of the most current MedDRA version, or by treatment-emergent relevant laboratory changes. Definitions of the AESIs and associated analyses will be described in the SAP.

Categorical and continuous safety parameters will be analyzed as described in Section 9.4.1. All safety analyses will be fully detailed in the SAP.

9.4.5 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 co-medications) will be investigated to assess their influence on model parameters. Model evaluation will include a visual predictive check. Estimates of PK model parameters and covariate effects and 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 change in SES-CD score, PRO2 score, and CDAI score versus exposure of mirikizumab at Weeks 12 and 52. For this purpose, PRO2 score is defined as a 2-item index comprised of the SF and AP items from the CDAI; the total PRO2 comprises the average daily scores over 7 days and is weighted using the CDAI multiplication factors for SF and AP items. Measures of exposure may include population PK estimated average concentrations (C_{avg}), or estimated or observed trough concentrations. 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 the efficacy endpoints. These models may be used to evaluate participant factors that may impact the relationship between exposure and the probability of achieving the endpoint. Longitudinal exposure-response models for SF and AP 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.

9.4.6 Evaluation of Immunogenicity

Frequencies and percentages will be tabulated for the following:

- participants with preexisting ADA, and
- participants who are treatment-emergent ADA positive (TE-ADA+) to mirikizumab.

Treatment-emergent ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA). The frequency of neutralizing antibodies may also be tabulated in TE-ADA+ participants.

The relationship between the presence of antibodies and their relationship to PK parameters, safety, and efficacy, may be assessed. Additional details will be provided in the SAP.

9.4.7 Other Analyses

9.4.7.1 Health Economics

The health outcome and quality of life measures including Urgency NRS, FACIT-Fatigue, EQ-5D-5L, WPAI-CD, SF-36, and IBDQ will be analyzed using methods described for continuous data as described for efficacy measures in Section 9.4.1.

9.4.7.2 Subgroup Analyses

Subgroup analyses for selected endpoints specified in Section 3 will be conducted. Additional subgroup analyses will be conducted for the co-primary and selected secondary endpoints. Subgroups to be evaluated may include gender, age, body weight, race, ethnicity, geographic region, baseline SES-CD category, baseline AP/SF category, corticosteroid use at baseline, duration of disease, and disease location. A detailed description of the subgroup variables and analyses will be provided in the SAP.

This study is not powered for subgroup analyses; therefore, all subgroup analyses will be treated as exploratory.

9.5 Interim Analyses

A primary database lock is planned after all participants complete the Week 52 visit or the ETV. The analysis based on data from the primary database lock will be conducted by the sponsor or a designee and no multiplicity adjustment will be implemented. The final database lock will occur after all participants complete the study, including safety follow-up.

A DMC consisting of members external to Lilly will be established for interim safety monitoring across all the sponsor's Phase 3 studies in participants with CD. See Appendix 10.1.4 for more information.

A limited number of preidentified Lilly employees or their designees who are not in direct contact with clinical sites may gain access to unblinded data, as specified in the unblinding plan prior to the Week 52 database lock in order to initiate the PK/PD model development process for the final analysis. Information that may unblind the study during the analyses will not be shared with study sites or the blinded study team until the primary database lock has occurred.

Unblinding details can found in the unblinding plan. PK/PD analysis details can be found in the Population PK/PD Analysis Plan.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) GCP Guidelines
- Applicable laws and regulations

The protocol, protocol amendments and addenda, ICF(s), IB, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

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

10.1.2 Informed Consent Process

The investigator or his or her representative will explain the nature of the study to the participant or his or her legally authorized representative, explain the risks and benefits of participating in the study, and answer all questions regarding the study.

Participants must be informed that their participation is voluntary.

Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; local regulations; ICH guidelines; Health Insurance Portability and Accountability Act requirements, where applicable; and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant participated in any study procedure or received the investigational intervention. The statement must include the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF(s).

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative. A copy of the ICF(s) is kept on file.

Participants who are rescreened are required to sign a new ICF.

10.1.3 Data Protection

Participants will be assigned a unique identifier by the investigator. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his or her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.4 Committees Structure

Cerebro-Cardiovascular Adjudication Committee

The role of the committee is described in Section 8.3.7.4.

Data Monitoring Committee

A DMC consisting of members external to Lilly will be established. The purpose of the DMC is to conduct periodic monitoring of clinical trial data for the Phase 3 CD program. The DMC will consist of a minimum of 3 members, including physicians with expertise in adult gastroenterology, pediatric gastroenterology and a statistician.

No member of the DMC will 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. The SAC members 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 a DMC charter.

The DMC is authorized to evaluate unblinded interim efficacy and safety analyses. In addition, the DMC may request key efficacy data to put safety observations into context and to assess a reasonable benefit/risk profile for ongoing participants in the study. 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 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 participants.

10.1.5 Dissemination of Clinical Study Data

Report Preparation

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

Public Access to Reports and Data

Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

Data

The sponsor provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once they are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, SAP, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment for up to 2 years per proposal. For details on submitting a request, see the instructions provided at www.clinicalstudydatarequest.com.

Publications

For policies on publications, see Section 10.1.9.

10.1.6 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
- provide 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 verify data reported to detect potential errors

In addition, Lilly or its representatives will periodically check a sample of the participant 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.

Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture system (EDC) will be used in this study for the collection of eCRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the eCRF.

Additionally, clinical outcome assessment (COA) data (questionnaires) will be collected by the investigator site personnel, via a paper source document and will be transcribed by the investigator site personnel into the EDC system.

Additionally, electronic clinical outcome assessment (eCOA) data (questionnaires, self-reported diary data, etc.) will be directly recorded by the participant and investigator site personnel, into an instrument (for example, hand-held smart phone or tablet). The eCOA data will serve as the source documentation and the investigator does not maintain a separate, written or electronic record of these data.

Data collected via the sponsor-provided data capture systems will be stored at third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture systems. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

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

10.1.7 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

What constitutes source data is described in Section 10.1.6.

10.1.8 Study and Site Closure

10.1.8.1 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.

10.1.8.2 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.

10.1.9 Publication Policy

The publication policy is described in the letters of agreement between the sponsor and the investigators and institutions.

10.2 Appendix 2: Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology [a,b]	**Clinical Chemistry** [a,b]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBCs)	Chloride
Mean cell volume	Bicarbonate
Mean cell hemoglobin	Potassium
Mean cell hemoglobin concentration	Total bilirubin
Leukocytes (WBCs)	Total protein
Cell morphology	Direct bilirubin
Neutrophils, segmented	Alkaline phosphatase (ALP)
Lymphocytes	Alanine aminotransferase (ALT)
Monocytes	Aspartate aminotransferase (AST)
Eosinophils	Gamma-glutamyl transferase (GGT)
Basophils	Blood urea nitrogen (BUN)
Platelets	Creatinine
	Uric acid
Urinalysis [a,b]	Calcium
Specific gravity	Glucose
pH	Albumin
Protein	Cholesterol (total)
Glucose	Triglycerides
Ketones	Lipid Panel (fasting)[c]
Bilirubin	High-density lipoprotein
Urobilinogen	Low-density lipoprotein
Blood	Creatine kinase (CK)
Nitrite	
Urine leukocyte esterase	**Other Tests** [a]
Microscopic examination of sediment	Hepatitis B core antibody [b,d]
	Hepatitis B surface antigen [b,d]
Other Tests (Local)	HBV DNA [b,e]
Pregnancy test (urine [g])	Hepatitis C antibody [b,d,f]
T-SPOT [d] or TST [d]	HCV RNA [b,d,f]
	HIV [b,d]
	Pregnancy test (serum [b,d])
	FSH[b]
Exploratory Biomarker Samples [a]	QuantiFERON-TB Gold test [d]
	Pharmacogenomic sample
Exploratory samples (serum, plasma, whole blood, RNA, tissue RNA, and fecal sample)	Immunogenicity testing (ADA)
	Serum mirikizumab concentration (PK)
	C-reactive protein, high-sensitivity (hsCRP)
	Clostridium difficile [b,h] (Toxin A and B, GDH, with reflex Toxin PCR)
	Stool Culture [b,h]
	Fecal calprotectin
	Tryptase [i]
	Complements (C3, C4) [i]
	Cytokine panel [i]

Abbreviations: ADA = Anti-drug antibodies (immunogenicity testing); FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HIV = human immunodeficiency virus; TST = tuberculin skin test.

[a] Assayed by Lilly-designated laboratory.

[b] Results will be confirmed by the central laboratory at the time of initial testing.

[c] For the fasting lipid profile, participants should not eat or drink anything except water for 12 hours prior to test.

[d] At screening and as described in the SoA (Section 1.3). QuantiFERON-TB Gold test can be assayed locally or by Lilly-designated laboratory. TST and T-Spot are performed locally.

[e] Hepatitis B DNA testing will be performed in participants 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] Test required only at screening to determine the participant's eligibility for the study but may be performed at investigator discretion throughout the study. Stool sample will be used for *Clostridium difficile* and stool culture.

[i] In the event of systemic allergic/hypersensitivity events, along with ADA and PK.

10.3 Appendix 3: 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 participants in consultation with the medical monitor of Lilly or its designee.

These tests will be performed at a Lilly-designated laboratory.

Hepatic Monitoring Tests

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

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

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

10.4 Appendix 4: Risk Factors for Latent Tuberculosis Infection

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

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

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

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

Source: adapted from Horsburgh and Rubin 2011.

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 2015

10.5 Appendix 5: Examples of Infections that May Be Considered Opportunistic in the Setting of Biologic Therapy

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 criteria. 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 criteria. Winthrop et al. (2015) consider TB and non-TB mycobacterial disease to be opportunistic infections in the context of biologic therapy.

Bacterial
Bartonellosis (disseminated disease only)
Campylobacteriosis (invasive disease only)
Legionellosis
Listeriosis (invasive disease only)
Nocardiosis
Tuberculosis
Non-tuberculous mycobacterial disease
Salmonellosis (invasive disease only)
Shigellosis (invasive disease only)
Vibriosis (invasive disease due to *Vibrio vulnificus*)
Viral
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
Fungal
Aspergillosis (invasive disease only)
Blastomycosis
Candidiasis (invasive disease or oropharyngeal, esophageal. Not isolated lingual)
Coccidioidomycosis
Cryptococcosis
Histoplasmosis
Paracoccidioides infections
Penicilliosis
Pneumocystosis
Sporotrichosis
Other invasive molds: Mucormycosis (zygomycosis) (*Rhizopus*, *Mucor,* and *Lichtheimia*), *Scedosporium*/*Pseudallescheria boydii*, *Fusarium*
Parasites
Leishmaniasis (visceral only)
Strongyloidosis (hyperinfection syndrome or disseminated disease)
Microsporidiosis
Toxoplasmosis
Trypanosoma cruzi infection (Chagas' disease progression) (disseminated disease only)
Cryptosporidiosis (chronic disease only)

Source: Adapted from Winthrop et al. 2015.

10.6 Appendix 6: Prohibited Medications

This section outlines medications that are prohibited during the treatment phase of the study and during 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 participant discontinues study drug and completes the ETV.

Drug Class	Guidance for Use
Anti-TNF antibodies (for example, infliximab, adalimumab, or certolizumab pegol)	Discontinue at least 4 weeks prior to screening endoscopy and prohibited throughout duration of study.
Anti-integrin antibodies:	
Natalizumab	Discontinue at least 12 months prior to screening endoscopy and prohibited throughout duration of study.
Other anti-integrin antibodies (for example, vedolizumab)	Discontinue at least 4 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. Participants remain excluded if there is 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	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 corticosteroids (enemas or suppositories)	Discontinue at least 2 weeks prior to screening endoscopy and prohibited throughout duration of study.
IV corticosteroids	Discontinue at least 2 weeks prior to screening endoscopy. A course of IV corticosteroids is prohibited throughout duration of study, except for use as premedication for infusion or for short-term treatment of acute non-CD events (for example, allergic reactions). Intravenous corticosteroids used for CD may result in discontinuation; therefore, consult your medical monitor.

Drug Class	Guidance for Use
Systemic corticosteroids for non-CD indications (oral or parenteral)	From Week 0 to Week 12, initiation or adjustment of systemic corticosteroids is prohibited. From Week 12 through Week 52, participants may transiently initiate or increase doses (that is, for <4 weeks) of corticosteroids for reasons other than loss of response to treatment for Crohn's disease (for example, stress doses of corticosteroids for surgery, asthma, and allergic reaction). Locally administered corticosteroids (for example, inhaled, intranasal, intra-articular, or topical) are allowed. Systemic corticosteroid use is allowed for adrenocortical insufficiency.
Any biologic investigational therapy	Discontinue at least 8 weeks, or 5 half-lives whichever is longer, prior to screening endoscopy and prohibited throughout duration of study.
Any nonbiologic investigational therapy	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.
Anti-IL-23p19 antibodies (for example, risankizumab [BI-655066], brazikumab [MEDI-2070], guselkumab [CNTO1959], tildrakizumab [MK-3222]) for any indication, including investigational use	Participants with any previous exposure are excluded from the study.
Anti-IL 12/23p40 antibodies (for example, ustekinumab)	Participants meeting protocol criteria (See Exclusion Criteria [21]) must have discontinued Anti-IL 12/23p40 antibodies at least 16 weeks prior to screening endoscopy.
Bacillus Calmette-Guérin (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.
Medicinal and recreational marijuana (includes CBD Oil)	Must be stopped prior to screening. Marijuana use is prohibited for the duration of the study. If use is identified during the trial, it may result in discontinuation; consult your medical monitor.

Abbreviations: 5-ASA = 5-aminosalicyclic acid; CBD = cannabidiol; CD = Crohn's disease; IV = intravenous; JAK = Janus kinase; TNF= tumor necrosis factor.

10.7 Appendix 7: Permitted Medications

Drug Class	Guidance for Use
Oral 5-ASAs (for example, mesalamine, balsalazide, olsalazine)	Prescribed dose must have been stable for at least 2 weeks before screening endoscopy; doses should remain stable throughout the study unless medication is discontinued due to a toxicity related to the medication.
Oral corticosteroids (prednisone CCI or equivalent, or budesonide CCI)	Prescribed dose must have been stable for at least 2 weeks before screening endoscopy and should remain stable until Week 12. After Week 12, see Section 6.5.3.
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.
Antibiotics being used specifically for the treatment of Crohn's disease (for example: rifaximin, Cipro)	May continue if the prescribed dose has been stable 4 weeks prior to baseline
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.
Nonlive (killed, inactivated, subunit, and RNA-based) vaccines	Allowed during the study. The efficacy of nonlive vaccinations with concomitant mirikizumab treatment is unknown.

Abbreviations: 5-ASA = 5-aminosalicyclic acid; 6-MP = 6-mercaptopurine; AZA = azathioprine.

10.8 Appendix 8: Patient-Reported Outcome Instruments

This appendix describes PRO instruments used in this study. For the physician items of the CDAI and other clinician efficacy assessments, see Section 8.1.

Daily Diary (eDiary)	Tablet Device
BMC	QIDS-SR16 [a]
CDAI-SF/Bristol Stool Scale (Reference to Types 6 & 7)	FACIT-Fatigue
CDAI-AP	IBDQ
CDAI well-being	EQ-5D-5L
Abdominal Pain NRS	SF-36 v2 Acute
Urgency NRS	WPAI-CD
PGRS	IBD-DI
	PGIC

Abbreviations: AP = abdominal pain; BMC = bowel movement count; CDAI = Crohn's Disease Activity Index; EQ-5D-5L = European Quality of Life 5-Dimension 5 Level; FACIT = Functional Assessment of Chronic Illness Therapy-Fatigue; IBD-DI = Inflammatory Bowel Disease-Disability Index; IBDQ = Inflammatory Bowel Disease Questionnaire; NRS = numeric rating scale; PGRS = Patient Global Rating of Severity; PGIC = Patient Global Impression of Change; QIDS-SR16 = Quick Inventory of Depressive Symptomatology—Self-Report (16 Items); SF = stool frequency; SF-36 v2 = Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) Version 2; WPAI-CD = Work Productivity and Activity Impairment Questionnaire — Crohn's Disease.

[a] QIDS-SR16 is described in Section 8.2.11 and Appendix 10.9.

The following are descriptions of additional PRO instruments for this study, using Patient eDiary (listed in order of administration).

Bowel Movement Count (BMC): A single item that measures "stool frequency in the past 24 hours." Participants are asked to count each toilet visit during which any amount of stool was passed. A separate bowel movement is counted if little time has passed since leaving the toilet and the participant returned and passed stool again. If stool was passed before making it to the toilet (an accident) that is also counted as a bowel movement. Participants will be provided with an electronic diary tool during screening to record information daily pertaining to their SF.

Crohn's Disease Activity Index (CDAI)-(SF: stool frequency, AP: abdominal pain and general well-being): CDAI is an 8-item disease activity measure that includes three patient reported items: AP (4-point scale: 0=none, 1=mild, 2=moderate, 3=severe); SF (number of liquid or very soft stools); and general well-being (0=generally well, 1=slightly under par, 2=poor, 3=very poor, 4=terrible). Participants will be provided with an electronic diary tool during screening to record information daily pertaining to their AP, frequency of liquid or very soft stools, and well-being.

Bristol Stool Scale (used as a reference for CDAI-SF): The Bristol Stool Scale provides a pictorial and verbal description of stool consistency and form ranging from Type 1 (Hard Lumps) to Type 7 (Watery/liquid). To further define "liquid or very soft stools," when responding to the CDAI SF item, participants will be referred to the Bristol Stool Scale Category 6 and/or 7, that is liquid or watery stool. Participants will be provided with an electronic diary tool during screening to record information daily pertaining to their frequency/count of liquid or very soft stools.

Abdominal Pain Numeric Rating Scale (NRS): A single item that measures the "worst level of abdominal pain in the past 24 hours" using an 11-point NRS ranging from 0 (no pain) to 10 (pain as bad as you can imagine). Participants will be provided with an electronic diary tool during screening to record information daily pertaining to their worst AP experience.

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). Participants will be provided with an electronic diary tool during screening to record information daily pertaining to their severity of urgency.

Patient Global Rating of Severity (PGRS): The PGRS is a 1-item patient-rated questionnaire designed to assess the participants' 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 participant has no symptoms (that is, "none") and a score of 6 indicates that the participant's symptom(s) are "very severe." Participants will be provided with an electronic diary tool during screening to record information daily pertaining to their disease experience.

The following are descriptions of additional PRO instruments for this study, using the Tablet Device at visits.

Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) (version 4): FACIT-Fatigue is a 13-item instrument developed to measure fatigue in chronic illness participants. Total score ranges from zero to 52 based on a rating of 5-point Likert scale. Participants will record their responses to the FACIT-Fatigue 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 participants' 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. Participants 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-5L 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 participant rates their perceived health state from 0 (the worst health you can imagine) to 100 (the best health you can imagine). Participants 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, Acute: 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 participant'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 (acute version) will be used, which utilizes the recall period of "the past week" (Ware and Sherbourne 1992; Ware 2000; Maruish 2011). Participants 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: Crohn's Disease (WPAI-CD): A patient-reported instrument developed to measure the impact on work productivity and regular activities attributable to a specific health problem (WPAI-CD). 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]); that is, worse outcomes. Participants will record their responses to the WPAI-CD electronically as source data in the tablet device at appropriate visits.

Inflammatory Bowel Disease-Disability Index (IBD-DI): A 15-item patient reported questionnaire developed to measure IBD-related disability by reviewing the participant's symptoms, mood and overall well-being over the past 7 days. Total scores range from 0 to 100, with higher scores representing greater levels of IBD-related disability. Participants will record their responses to the IBD-DI electronically as source data in the tablet device at the appropriate visit.

Patient Global Impression of Change (PGIC): The PGIC scale is a patient-rated instrument designed to assess the participants' rating of symptom severity. Responses are graded on a 7-point Likert scale in which a score of 1 indicates that the participant's symptom(s) is "very much better," a score of 4 indicates that the participant's symptom has experienced "no change," and a score of 7 indicates that the participant's symptom(s) is "very much worse." Participants will

record their response to the PGIC electronically as source data in the tablet device at appropriate visit.

10.9 Appendix 9: 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 participant is asked to consider each statement as it relates to the way he or she has 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.

10.10 Appendix 10: Definitions and Selected Abbreviations

Term	Definition
ADA	anti-drug antibody
ADR	Adverse drug reaction
AE	adverse event: Any untoward medical occurrence in a participant 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 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 the 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 population.
ALT	alanine aminotransferase
Anti-HBc	anti-hepatitis B core antibody
Anti-HBc+	positive for anti-hepatitis B core antibody
AP	abdominal pain
AST	aspartate aminotransferase
AZA	azathioprine
BCG	Bacillus Calmette-Guérin
blinding	A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the participants are aware of the treatment received.
BMC	bowel movement count
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CDAI-AP	CDAI-Abdominal Pain
CDAI-SF	CDAI-Stool Frequency
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval

Term	Definition
CIOMS	Council for International Organizations of Medical Sciences
CMH	Cochran-Mantel-Haenszel
COA/eCOA	clinical outcome assessment/electronic clinical outcome assessment
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 (GCP), and applicable regulatory requirements
CT	computed tomography
CXR	chest x-ray
C-SSRS	Columbia Suicide Severity Rating Scale
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DSI-CD	Disease Severity Index-Crohn's Disease
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EIM	extraintestinal manifestation
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been randomized and assigned to a treatment.
Enter	Participants 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-Dimensions 5 Level
ERB	Ethical Review Board
ETV	early termination visit
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FSH	follicle-stimulating hormone
FWER	overall Type I error rate
GCP	good clinical practice

Term	Definition
GMP	good manufacturing practices
HBsAG	hepatitis B surface antigen
HBsAG+/-	positive/negative for hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV/AIDS	human immunodeficiency virus/acquired immune deficiency syndrome
hsCRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IBD-DI	Inflammatory Bowel Disease-Disability Index
ICF	informed consent form
ICH	International Conference for Harmonisation
IEC	Independent Ethics Committee
IgG4	immunoglobulin G4
IGRA	interferon-γ release assay
IL	interleukin
INR	international normalized ratio
informed consent	A process by which a participant 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 participant'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.
Intervention	See "study intervention."
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. See "study intervention."

Term	Definition
IRB	Institutional Review Board
IRC	Internal Review Committee
ITT/mITT	intent-to-treat/modified intent-to-treat
IV	intravenous(ly)
IWRS	interactive web-response system
LTBI	latent tuberculosis infection
LV	last visit
MedDRA	Medical Dictionary for Regulatory Activities
medical monitor	The sponsor's designated medical monitor for the study
MMRM	mixed effects model of repeated measures
MTX	methotrexate
NOAEL	no-observed-adverse-effect level
NR	nonresponder, or nonresponse
NRI	nonresponder imputation
NRS	numeric rating scale
patient	See "participant" when used in the context of clinical studies.
Participant	Equivalent to "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PD	pharmacodynamics
PGIC	Patient Global Impression of Change
PGRS	Patient Global Rating of Severity
PK	pharmacokinetics
PPD	purified protein derivative
PRO	patient-reported outcome
PT	Preferred Term
QIDS-SR16	Quick Inventory of Depressive Symptomatology – Self Report (16 items)
Q12W	every 12 weeks

Term	Definition
Q4W	every 4 weeks
RNA	ribonucleic acid
SAC	Statistical Analysis Center
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF	stool frequency
SF-36	Medical Outcomes Study 36-Item Short Form Health Survey
SoA	Schedule of Activities
study drug	See "study intervention"
study intervention	Any investigational intervention, marketed product, placebo, or medical device intended to be administered to a study participant according to the study protocol
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TBL	total bilirubin level
TE-ADA+	treatment-emergent ADA positive
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TNF	tumor necrosis factor
TST	tuberculin skin test
UC	ulcerative colitis
ULN	upper limit of normal
WHO	World Health Organization
WPAI-CD	Work Productivity and Activity Impairment Questionnaire Crohn's Disease

Term	Definition
5-ASA	aminosalicylic acid
6-MP	6-mercaptopurine

10.11 Appendix 11: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment [a]

This amendment is considered to be **Overall Rationale for the Amendment:**

The overall changes and rationale for the changes made to this protocol were to provide more clarity to specific sections or items, to better fit the protocol to the clinical reality and to correct errors.

The plan for a blinded sample size re-estimation before the last participant has been enrolled in the study has been added to compare the blinded response rates with the assumed response rates and allow for a potential sample size adjustment.

The following global changes in terminology or corrected errors were made throughout the protocol for clarification and consistency:

- Corrected ">50% reduction" to "≥50% reduction" for the Endoscopic Response definition throughout document to correct a preexisting error.
- Terminology of "deep response" was deleted as this is not a standardized definition and was replaced by the factual description "endoscopic response and clinical response by PRO."
- Terminology of "deep remission" was deleted as this is not a standardized definition and was replaced by the factual description "endoscopic remission and clinical remission by PRO."
- Terminology of "SES-CD response" or "SES-CD remission" was replaced by "endoscopic response" and "endoscopic remission."

Other minor typographical corrections and clarifications or semantic changes not affecting content have also been made in the document.

Changes specific to certain protocol sections and a brief rationale are provided in the below table.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	• Screening Period was prolonged by 1 week (from 4 to 5 weeks), resulting in a maximum total study duration of 73 weeks (previously 72 weeks)	Improve feasibility to complete all assessments within a clinically acceptable interval
Section 1.2 Schema	• Schema adjusted to reflect the prolonged screening period from 4 to 5 weeks	Consistency
Section 1.3 Schedule of Activities	• Changes reflecting the extended Screening Period • Added more details to footnotes t (stool collection) and v (endoscopy) • Added footnote to existing TB Monitoring during the study • Added optional unscheduled visit for QIDS-SR16 collection and reflected in footnote	Clarifications for accuracy Fit to clinical reality
Section 3 Objectives and Endpoints	• Added Other Secondary for efficacy of mirikizumab compared to placebo in clinical response by CDAI • Added Other Secondary for efficacy of mirikizumab compared to placebo in both endoscopic response and clinical remission by PRO • Added FACIT-Fatigue score to the list of health outcomes/quality of life endpoints	Update for consistency with approved SAP
Section 4.1 Overall Design	• Timing of follow-up visits Visit 801 & Visit 802 are defined relative to "last visit," not "last dose"	Clarify original content
Section 5.1 Inclusion Criteria & 5.2 Exclusion Criteria	• Criteria 2b: women not of childbearing potential. Minimal required age relative to definition B, of postmenopausal women was adjusted from 50 to 40 years • Criteria 6: broadened window between endoscopy result and randomization from 14 days to 21 days • Criteria 9b: Allowed stable corticosteroid dose at entry changed from ≤20mg/day to ≤30mg/day	Reflect most recent internal safety guidance Accommodate clinical reality and/or clarify original content

Section # and Name	Description of Change	Brief Rationale
	• Criteria 10: note added to specify that if, out of control of the participant, certain assessments could not be completed in the specified timelines, Medical to assess potential randomization or rescreening (whichever applies) • Criteria 12: divided into chronic conditions vs an infection that allows for treatment and rescreening • Criteria 14: removed extra abdominal surgery • Criteria 21: noted that short-term prior exposure to ustekinumab is permitted if specific conditions are met • Criteria 42: noted that exclusion does not apply in situations out of control of the participant • Criteria 47: newly added criteria relative to total parenteral nutrition delivery	Correction of error Accommodate clinical reality and/or clarify original content
Section 5.4 Screen Failures	• Clarified rescreening criteria for Inclusion Criteria 4, 5, 6, 10, and 42 • Clarified that participants who screen fail because of inability to complete their endoscopy in time may not need to repeat certain specific assessments when rescreening	Clarify original content
Section 6.5 Concomitant therapy	• Additional clarifications have been added relative to permitted vs prohibited therapy	Clarify original content
Section 8.2.8 Hepatitis B Testing	• Clarified IP discontinuation criteria relative to HBV DNA	Reflect clinical practice
Section 8.2.11, Depression, and Suicidal Ideation and Behavior	• Relative to the HCP assessing the CCI removal of requirement of 1 year of patient care/clinical experience	Clarify original content
Section 9.2, Sample Size Determination	• Added additional considerations relative to sample size	Clarify original content
Section 9.4.1 General Statistical Considerations	• Removed the treatment comparisons of ustekinumab vs placebo	Clarify original content

Section # and Name	Description of Change	Brief Rationale
Section 9.4.3.1 Primary Analysis	• Clarified the analysis window for the endoscopic measure at Week 52	Clarify original content
Section 9.4.3.3 Tertiary/Exploratory Analyses	• Clarified histologic endpoints at Week 12 and Week 52	Clarify original content
Section 9.5 Interim Analyses	• Language for the planned PK interim analysis already included in Section 6.3 has been added to Section 9.5	Clarify original content

Amendment [b]

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The primary rationale for this amendment is the addition of Appendix 12: Provisions for Changes in Study Conduct During Exceptional Circumstances. The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator. Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Other minor typographical corrections and clarifications or semantic changes not affecting content have also been made in the document.

Changes specific to certain protocol sections and a brief rationale are provided in the below table.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	• Added timepoints for various evaluation criteria to allow for additional optional data collection at Visit 997 or for unscheduled assessments during a scheduled visit (UA/SV). • Changed Visit 5 to a phone visit; removed requirements for vital signs, physical exam, extraintestinal manifestation (EIMs), fistula evaluation, Crohn's Disease Activity Index (CDAI), and serum chemistry and hematology.	• Updated to reflect all assessments that may be collected at the discretion of the investigator at scheduled or unscheduled visits. • Aim to avoid risk of an unnecessary visit to the site during the COVID-19 pandemic, and as participants do not receive study drug at Visit 5, on-site assessments are not required.
	• Updated list of abbreviations. • Footnote g: Modified text.	• To reflect changes to table • Computed tomography (CT) scan can be performed as an alternative to the chest

Section # and Name	Description of Change	Brief Rationale
		x-ray (CXR).
	• Footnote q: Modified text.	• Clarified collection of stool sample prior to endoscopy, and visits where endoscopy is not scheduled to be performed.
	• Footnote x: Modified text.	• Optional testing may be performed during unscheduled visits at the discretion of the investigator.
	• Footnote aa: Modified text.	• Clarification
	• Footnote ab: Modified text.	• Clarification that CT scan can be performed as an alternative to the CXR based on regional standard of practice.
	• Footnote ac: Added.	• UA/SVs may be performed at the discretion of the investigator.
2.2.2 Currently Available Treatments and Unmet Need	• Reworded the information on clinical remission.	• Reordered text to improve clarity and readability.
4.3 Justification for Dose	• Change to NOAEL number to align with adolescent addendum.	• Correction of error
5.1 Inclusion Criteria	• Criterion [8]: Updated text relative to conventional-failure and prior budesonide use.	• Improved clarity relative to prior budesonide use.
	• Criterion [10]: Revised note to account for when participants are not able to complete study assessments due to situations beyond their control.	• Consistency with other criteria.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	• Criterion [12]: Removed short bowel syndrome from criterion. • Criterion [15]: Replaced short gut syndrome with short bowel syndrome.	• Avoid redundancy and improve clarity of Criteria [12] and [15] relative to management of patients with short bowel syndrome.
	• Criterion [21]: Lengthened required timeframe between last dose of anti-interleukin (IL) 12/23p40 antibodies and screening endoscopy from at least 8 weeks to at least 16 weeks, and updated Appendix 6 (Prohibited Medications) accordingly.	• Timeframe extended to 16 weeks to rule out participants not responding to ustekinumab.
	• Criterion [42]: Revised note to account for when participants are not able to complete study assessments due to situations beyond their control.	• Consistency with other criteria.
	• Criterion [47]: Updated text regarding delivery of parenteral nutrition.	• Parenteral and enteral nutrition as primary source of diet is excluded due to potential to confound efficacy assessments.
	• Criterion [48]: Added new criterion on prohibited marijuana use and updated Appendix 6 (Prohibited Medications) accordingly.	• Avoid potential impact on protocol assessments as cannabinoids have shown a potential role in inflammation and mucosal permeability of the gastrointestinal tract.

Section # and Name	Description of Change	Brief Rationale
5.4 Screen Failures	• Removed restriction of only 1 rescreening permitted for entry Criteria [4], [5], and [6].	• Criteria [4], [5], and [6]: Crohn's disease (CD) activity can change over time; thus, participants may qualify upon rescreening.
	• Criterion [22]: Specified that rescreening is allowed if a participant is no longer receiving steroids and has met washout criteria.	• Criterion [22]: Improve clarity.
	• Added Criterion [28] to list of entry criteria with allowance for rescreening and updated text to include that rescreening may be permitted once for *C. difficile* and once for stool culture or ova parasite.	• Criterion [28]: Correct prior inadvertent omission and improve clarity.
	• Moved Criteron (43) from Screening not allowed.	• Criterion [43] revised to allowed rescreen if patient situation changes over time.
	• Added Criterion [48] to list of entry criteria with allowance for rescreening provided participant is no longer using marijuana at the time of rescreening.	• Criterion [48]: Added due to addition of exclusion criteria for marijuana (see above).
	• Updated text to specify assessments will not repeated at rescreening for patients who screen fail due to inability to complete endoscopy prior to Visit 2.	• Participants may avoid CT, human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) retest within a 4-week timeframe provided there are no risk factors or signs/symptoms
	• Modified text disallowing rescreening: Now allow rescreening for Criterion [22].	• Non-CD treatment can change.

Section # and Name	Description of Change	Brief Rationale
	• Added that a total maximum of 3 rescreens are permissible. • Only 3 total endoscopies are permissible.	• Correction of error. • Provide additional information relative to rescreen.
6.1 Study Intervention(s) Administered	• Modified text stating that intravenous (IV) infusions must be completed prior to administration of subcutaneous (SC) injections.	• Provide clearer distinction between hypersensitivity, infusion-related events, and events related to SC dosing.
6.5 Concomitant Therapy	• Renumbered from 6.5.1 to 6.5.	• Correction/Clarification.
6.5.1 Permitted Therapy	• Added as third level heading; modified text to permit dose adjustments to concomitant CD medications for appropriate medical management, and added in-text reference for information on corticosteroid tapering.	• Correction/Clarification.
6.5.2 Prohibited Therapy	• Added exceptions to prohibited CD medications, IV corticosteroid and marijuana use, that may result in discontinuation. Clarified that RNA-based vaccines are permitted.	• Allow medical discretion to prevent unnecessary discontinuation.
6.5.3 Corticosteroid Taper	• Removed text prohibiting initiation of corticosteroid unless there is a medical necessity.	• Clarification.
7.1.1 Criteria for Permanent Discontinuation of Study Drug	• Revised Disease Worsening, bullet 1 to require treatment with a specified prohibited CD medication • Revised Disease Worsening, bullet 2 to include exception of drainage of a perianal or other cutaneous abscess or seton placement.	• Clarification. • Clarification.
7.1.2 Criteria for Temporary Interruption	• Revised text for patients who develop decreased absolute	• Improve clarity and

Section # and Name	Description of Change	Brief Rationale
(Withholding) of Study Drug	lymphocyte count.	readability.
7.2 Participant Discontinuation/ Withdrawal from the Study	• Removed text related to participant requiring prohibited medications.	• Redundant.
8.1.1.3 Endoscopic Biopsies	• Revised text referencing source of details of biopsy sample collection.	• Correction/Clarification.
8.2.4 Chest Radiography	• Clarified that a CT scan can be performed as an alternative to the CXR based on regional standard of practice.	• Clarification.
8.2.6 Tuberculosis Testing	• Clarified that CT scan can be performed as an alternative to the CXR.	• Clarification and consistency with Section 8.2.4.
8.5 Pharmacokinetics	• Deleted "Other PK samples on or after CCI [redacted]	• Corrected to align with intended collection and SoA
8.2.7.2 Immunogenicity Assessment	• Revised wording regarding the frequency of the tabulation of neutralizing antibodies.	• Align with analysis approach.
8.8 Exploratory Biomarkers	• Modified the section title.	• Improve accuracy.
9.2 Sample Size Determination	• Updated wording.	• Improve clarity.
9.4.1.3 Missing Data Imputation	• Deleted bullets regarding status of mandatory stable medication use and taking of prohibited medications in defining a participant as a nonresponder.	• Revision to plan for missing data imputation.

Section # and Name	Description of Change	Brief Rationale
	• Added text relative to handling of concomitant medications and noted specifics will be provided in the statistical analysis plan (SAP).	• As noted.
9.4.6 Evaluation of Immunogenicity	• Revised wording regarding the frequency of the tabulation of neutralizing antibodies.	• Clarification of sentence to align with analysis approach.
Section 10.2 Appendix 2: Clinical Laboratory Tests	• Updated information on exploratory biomarker storage samples.	• Separate exploratory biomarkers from non-exploratory biomarkers.
Section 10.6 Appendix 6: Prohibited Medications	• Revised column heading to table for Column 2. • Added text to include information on IV corticosteroid used for CD that may result in discontinuation.	• Clarification. • Allow medical discretion to prevent unnecessary discontinuation. Aligned with Exclusion Criteria [19g] and [19h].
	• Changed requirement for discontinuing of anti-IL 12/23p40 antibodies (ustekinumab) prior to screening endoscopy from 8 weeks to 16 weeks. • Revised text to clarify that systemic corticosteroid use is allowed for adrenal insufficiency. • Changed requirement for discontinuing of biologic investigational therapy prior to screening endoscopy from 4 weeks to 8 weeks. • Added information about any	• Corrected discrepancy related to biologic and nonbiologic washout periods. • Timeframe extended to 16 weeks to rule out participants not responding to ustekinumab. • Clarification. • Aligned with Exclusion Criteria [19g] and [19h]. • Corrected discrepancy

Section # and Name	Description of Change	Brief Rationale
	nonbiologic investigational therapy. • Added text to include information on prohibited marijuana use.	related to biologic and nonbiologic washout periods. • Avoid potential impact on protocol assessments as cannabinoids have shown a potential role in inflammation and mucosal permeability of the gastrointestinal tract.
Section 10.7 Appendix 7: Permitted Medications	• Renamed section and revised table column header. • Revised guidance for use for oral corticosteroid stabilization and updated type of permitted vaccines.	• To align with development program. • Clarification.
Section 10.10 Appendix 10: Definitions and Selected Abbreviations	• Updated the list.	• To include new additions.
Section 10.11 Appendix 11: Protocol Amendment History	• Updated with information from prior protocol amendment (a).	• To provide continuity of recorded updates.
Section 10.12 Appendix 12: Provisions for Changes in Study Conduct During Exceptional Circumstances	• Added appendix.	• Provides for temporary changes to procedures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.
Throughout	• Minor editorial changes.	• Corrections

Amendment [c]

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Published literature suggests that appropriate endoscopic disease measuring cutoffs in clinical trials are those that account for the presence of a minimal degree of ulceration reflecting moderate to severely active disease, rather than a higher degree of overall inflammation (Vuitton et al. 2016). Completed and ongoing clinical trials evaluating biologic treatment effect (adalimumab, ustekinumab, risankizumab, and guselkumab) in participants with moderately to severely active Crohn's Disease (CD) have enrolled all or up to 10% of the total population with a Simple Endoscopic Score for Crohn's Disease (SES-CD) of ≥3. Therefore, inclusion criterion 6 has been updated to allow up to 10% of the participant population with SES-CD score of ≥3 with the provision that ulceration be present as a component of this total score (presence of at least one large ulcer [in the ileum, colon, or both] that results in a minimum score of 2 for the component of "size of ulcers" and a minimum score of 1 for the component of "ulcerated surface"). The purpose of inclusion of this subset is to increase understanding of these patients and their response to treatment. The analysis population in which the primary and key secondary endpoints will be evaluated does not change; this patient population remains defined by SES CD of ≥7, as per the original protocol.

The below table summarizes overall protocol changes, specific to certain protocol sections, together with a brief rationale.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Added above table "The study primary and secondary objectives will be assessed based on the Primary Analysis Set as defined in Section 9.3."	Alignment with Section 3.
1.3 Schedule of Activities	Removed Self-Harm Supplement Form and Self-Harm Follow-Up Form. Removed "with the exception of screening" from Footnote q.	Information currently collected via safety reporting provides sufficient information on self-harm cases. Correction.
3 Objectives and Endpoints	Added above table "The study primary and secondary objectives will be assessed based on the Primary Analysis Set as defined in Section 9.3." Added an Other Secondary objective and Endpoint to evaluate endoscopic response and clinical remission.	Clarification.

Section # and Name	Description of Change	Brief Rationale
4.2 Scientific Rationale for Study Design	Removed definition for active CD; specified that definition is provided in the inclusion criteria.	Adapted to more concise language.
5.1 Inclusion Criteria	Updated Criterion 6 to allow for enrollment of a subset of participants with a SES-CD score ≥3 and <7 (for patients with isolated ileal disease SES-CD ≥3 and <4) and presence of at least one large ulcer (in the ileum, colon, or both) that results in a minimum score of 2 for the component of "size of ulcers" and a minimum score of 1 for the component of "ulcerated surface".	Rationale provided in the text preceding this table.
	Modified Criterion 40 to specify ustekinumab instead of "monoclonal antibodies".	Clarification.
5.4 Screen Failures	Removed interval requirement for rescreening for Criterion 5. Modified text "Participants who screen fail because they are unable to complete their endoscopy prior to Visit 2 may undergo repeat rescreening sooner than 4 weeks between screen failure and rescreening. Participants rescreening sooner than 4 weeks for the inability to complete endoscopy, or who are allowed by the study's medical monitor to rescreen within less than 4 weeks, will not be required to undergo repeat…".	Variability of PRO measures. Added flexibility to avoid unnecessary repetition of certain tests within short timeframe.
6.5.3 Corticosteroid Taper	Added "Investigators must contact the Study Medical Monitor to discuss any participant who does not initiate CS tapering upon achieving clinical response."	Tapering is mandatory unless medically unfeasible, in which case discussion with the medical monitor is required.

Section # and Name	Description of Change	Brief Rationale
6.7.3.2 Management of Hypersensitivity, Infusion-Related Events, Infusion Site Reactions, and Injection Site Reactions	Modified instructions for nonsystemic hypersensitivity reactions.	Clarification.
7.1.2 Criteria for Temporary Interruption (Withholding) of Study Drug	Added text back (erroneously removed in Amendment b) for participants who develop decreased absolute neutrophil count, and corrected unit for lymphocyte count.	Correction of errors.
8.2.11 Depression, and Suicidal Ideation and Behavior	Removed text related to the Self-Harm Supplement Form and Self-Harm "Follow-Up" Form.	Alignment with the Schedule of Activities.
9.1 Statistical Hypotheses	Added population description to the primary statistical hypothesis.	Clarification: added detail.
9.2 Sample Size Determination	Added the analysis population to sample size determination.	Clarification.
9.3 Populations for Analyses	Added definition for the Primary Analysis Set.	Clarification.
9.4.1 General Statistical Considerations	Removed text specifying the SAS version to be used for statistical analysis. Defined population to be used in analyses.	Correction: analysis is not limited to using SAS only. Clarification: added detail.
9.4.1.3 Missing Data Imputation	Modified text "…For placebo participants who begin treatment with mirikizumab at Week 12, participants who discontinue study treatment early, and participants who change specified concomitant CD medications ~~increase mandatory stable medications or take prohibited medications,~~ the data collected after any of these events occur will be censored in the primary analysis…"	Correction: alignment with modifications made in Amendment b.

Section # and Name	Description of Change	Brief Rationale
9.4.3 Efficacy Analyses	Moved first sentence (regarding both primary and secondary analyses populations) of following subsection (9.4.3.1) to parent subsection (9.4.3).	Organization.
9.4.3.1 Primary Analyses	Added statement that the co-primary endpoint will be evaluated in the mITT population as a secondary analysis.	Alignment with Section 3.
9.4.7.1 Health Economics	Added “FACIT-Fatigue.”	Correction.
9.4.7.2 Subgroup Analyses	Removed statement that analyses requested by regulatory agencies will be labeled as appropriate.	Correction.
Throughout	Minor editorial changes.	Corrections.

Amendment [d]

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The main purpose of this protocol amendment is to revise the co-primary and secondary objectives and endpoints in response to Food and Drug Administration (FDA) feedback.

Changes specific to certain protocol sections and a brief rationale are provided in the below table. Other minor typographical corrections not affecting content have also been made in the document.

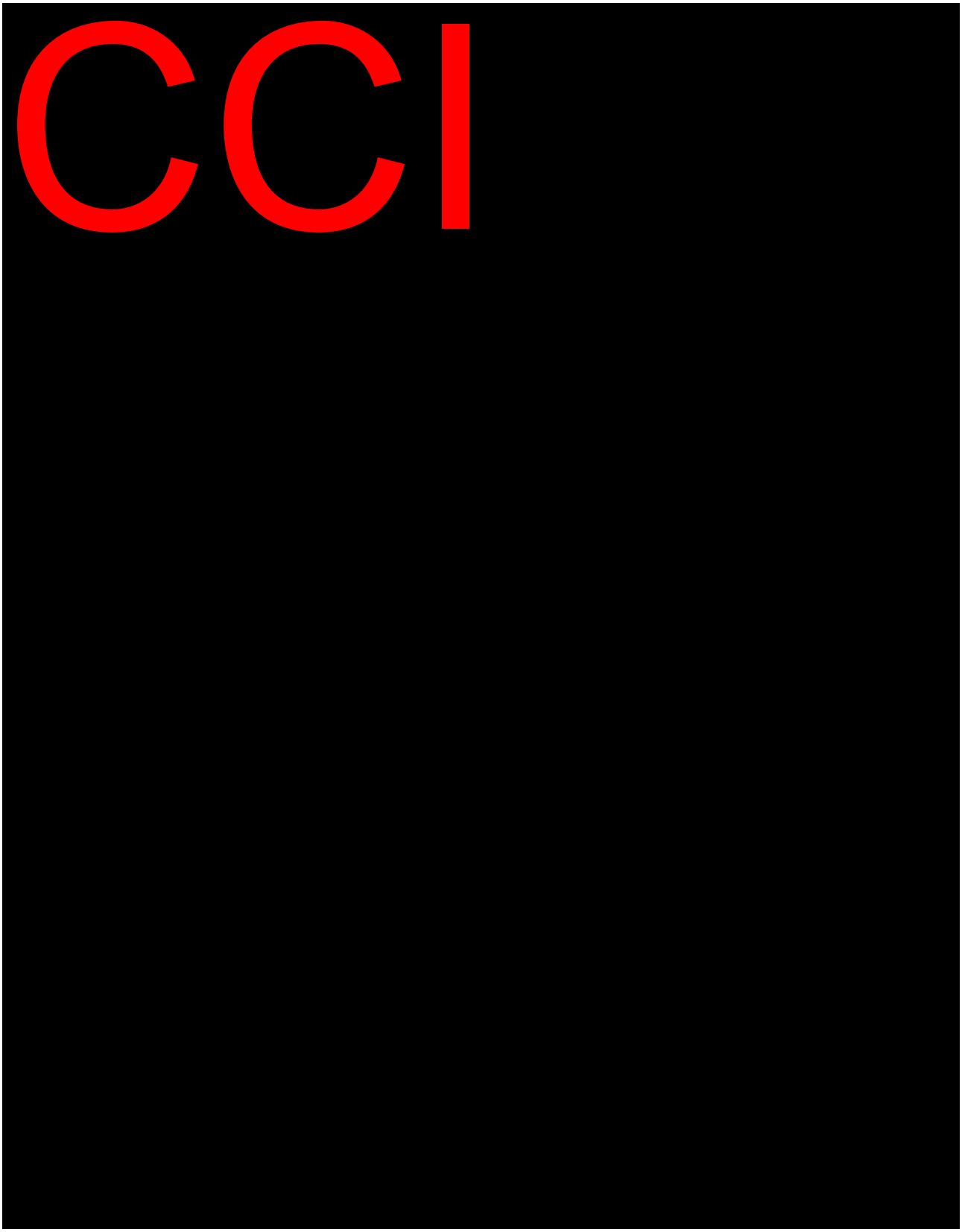
Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Updated objectives and endpoints	Address FDA feedback and editorial consistency
1.3. Schedule of Activities	Revised footnote ‘o’ to indicate that results from the PK, immunogenicity (ADA) and exploratory hypersensitivity analyses in the event of a systemic allergic/hypersensitivity event will not be provided to the investigator	Clarification
1.3. Schedule of Activities	Revised footnote ‘u’ for diary compliance check to specify compliance percentage threshold	Clarification
1.3. Schedule of Activities	Added a footnote to allow Visit 2 assessments and dosing to be performed over 2 days after consultation with the medical monitor	Clarification
2.2.1. Disease State and Treatment Goals	Replaced assessment by PRO to CDAI	Address FDA feedback
2.2.5. Preclinical and Clinical Studies of Mirikizumab	Updated the results of Studies 16T-MC-AMAN and 16T-MC-AMAG	Reflect most recent data
3. Objectives and Endpoints	Updated co-primary endpoints to include clinical response by PRO at Week 12, endoscopic response and clinical remission by CDAI at Week 52	Address FDA feedback

Section # and Name	Description of Change	Brief Rationale
3. Objectives and Endpoints	Updated the following efficacy assessments in major and other secondary objectives and endpoints, • clinical remission by CDAI at Week 12 and 52, • clinical response by PRO at Week 12, • clinical remission by PRO at Week 52 • corticosteroid-free and either clinical remission by CDAI (removed by PRO) at Week 52 • stability of clinical remission by CDAI (removed by PRO)	Alignment to FDA feedback
3. Objectives and Endpoints	Added the following efficacy assessments in secondary objectives and endpoints • Urgency NRS at Week 12 and Week 52 • urgency remission at Week 52 • clinical response by CDAI (removed by PRO) at Week 4	Alignment to FDA feedback
3. Objectives and Endpoints	Added footnotes defining the mITT population and the efficacy endpoints (Clinical response by PRO, Endoscopic response, Clinical remission by CDAI, Clinical remission by PRO, Clinical response by CDAI, Urgency remission, Endoscopic remission, Endoscopic remission SES-CD ≤4)	Editorial consistency
3. Objectives and Endpoints	Revised the section to remove duplicate objectives and endpoints	Editorial consistency
4.2. Scientific Rationale for Study Design	Added CDAI as an endpoint used for the primary objective	Alignment to FDA feedback
5.1. Inclusion Criteria Inclusion criterion 9d	Revised language for Crohn's disease treatment	Clarification

Section # and Name	Description of Change	Brief Rationale
5.1. Inclusion Criteria Inclusion criterion 11b	Removed 'an established' from diagnosis of Gilbert's syndrome	Clarification
5.2. Exclusion Criteria Inclusion criterion 17	Removed adenoma without dysplasia and added colonic adenomatous polyp	Reflect most recent data
5.2. Exclusion Criteria Inclusion criterion 18	Removed colonic dysplasia and added dysplasia in GI tract or presence of any serrated lesion	Reflect most recent data
6.5.3. Corticosteroid Taper	Added oral corticosteroid dose initiation for participants not on corticosteroids at randomization	Clarification
6.5.4. Rescue Medicine	Removed "other than oral 5 ASA compounds or immunomodulators"	Correction
7.1.1. Criteria for Permanent Discontinuation of Study Drug	Removed intestinal dysplasia and added dysplasia in GI tract or presence of any serrated lesion in safety considerations	Reflect most recent data
8.1.1. Primary Efficacy Assessments	Updated co-primary endpoints with the changes made in Section 3 (Objectives and Endpoints)	Alignment to FDA feedback
8.1.1. Primary Efficacy Assessments	Crohn's Disease Activity Index (CDAI) description added as part of Primary Efficacy Assessments Removed CDAI description	Alignment to co-primary objectives
8.2.5 Stool Testing	Updated *C. difficile* toxin testing	Clarified intended collection and testing
8.2.6. Tuberculosis Testing	Updated retesting and confirmatory testing for participants who have been assessed by the PI to have a false positive TB test	Clarified intended collection and testing
8.5. Pharmacokinetics	Revised the additional samples to indicate that results from these samples in the event of a systemic allergic/hypersensitivity event will not be provided to the investigator	Clarification

Section # and Name	Description of Change	Brief Rationale
9.1. Statistical Hypotheses	Revised primary hypothesis and major secondary hypotheses with the changes made in Section 3 (Objectives and Endpoints)	Address FDA feedback
9.2. Sample Size Determination	Revised estimated power for the co-primary endpoint	Address FDA feedback and editorial consistency
9.4.1. General Statistical Considerations	Replaced stratification factors with covariates and removed region and 95% confidence interval in Cochran-Mantel-Haenszel chi-square test Removed baseline corticosteroid use and region from restricted maximum-likelihood-based mixed effects model of repeated measures Added finalized graphical testing scheme to be provided in the SAP	Clarification and editorial consistency
9.4.1.3. Missing Data Imputation	Revised selected analysis for participants in placebo group	Clarification
9.4.1.4. Multiple Comparisons/Multiplicity	Added 'mirikizumab' to compare with placebo for Group 1 and to compare with ustekinumab for Group 2 Added pre-specified graphical scheme for comparisons in Group 1	Clarification and editorial consistency
9.4.3.1. Primary Analyses	Updated primary analyses with the changes made in Section 3 (Objectives and Endpoints) and added definitions for clinical response by PRO and clinical remission by CDAI	Address FDA feedback
10.2. Appendix 2: Clinical Laboratory Tests	Updated *C. difficile* toxin testing	Clarified intended collection and testing
10.7. Appendix 7: Permitted Medications	Revised language for Crohn's disease treatment	Clarification
10.12. Appendix 12: Provisions for Changes in Study Conduct During Exceptional Circumstances	Revised changes in study conduct during exceptional circumstances	Clarification for flexibility outlined for study conduct during exceptional circumstances

Section # and Name	Description of Change	Brief Rationale
10.12. Appendix 12: Provisions for Changes in Study Conduct During Exceptional Circumstances	Added the following to 'Local laboratory testing option', "Local collection of screening laboratories for eligibility may be collected after approval by the sponsor and may not be allowed in all circumstances."	Clarification for local labs during exceptional circumstances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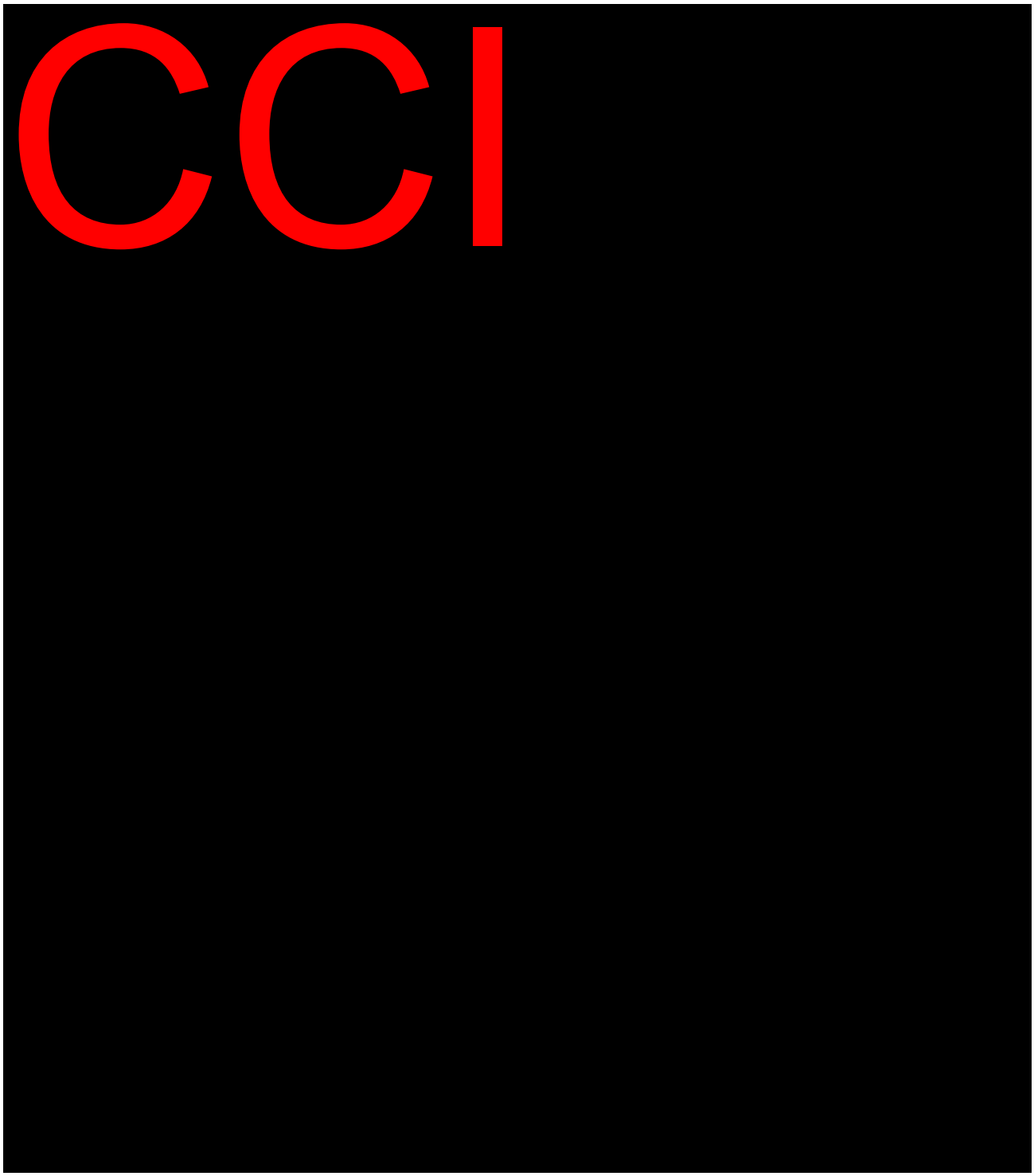
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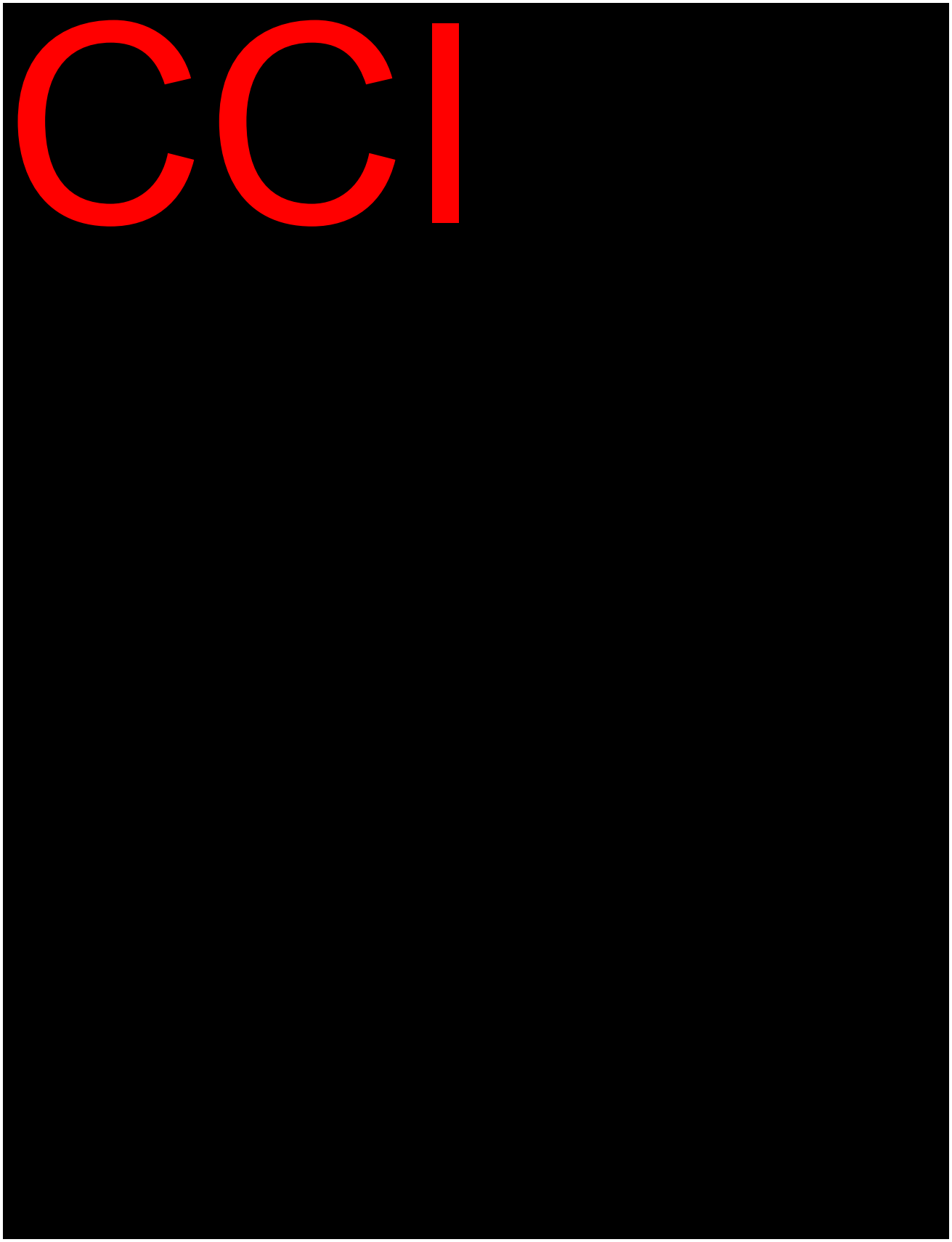
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11 References

Alosh M, Bretz F, Huque M. Advanced multiplicity adjustment methods in clinical trials. *Stat Med*. 2014;33(4):693-713

[APA] American Psychiatric Association. Diagnostic and statistical manual of mental disorders, fifth edition (DSM-V). Arlington, VA: American Psychiatric Publishing. 2013.

Barrett JC, Hansoul S, Nicolae DL, Cho JH, Duerr RH, Rioux JD, Brant, SR, et al. Genome-wide association defines more than thirty distinct susceptibility loci for Crohn's disease. *Nat Genet*. 2008;40(8):955-962.

Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet*. 2007 ;369 :1641-57.

Berrebi D, Besnard M, Fromont-Hankard G, Paris R, Mougenot JF, De Lagausie P, Emilie D, et al. Interleukin-12 expression is focally enhanced in the gastric mucosa of pediatric patients with Crohn's disease. *Am J Pathol*. 1998;152:667-672.

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

Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. *Stat Med.* 2009;28(4):586-604.

Bretz F, Posch M, Glimm E, Kinglmueller F, Maurer W, Rohmeyer K. Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. *Biom J.* 2011;53(6):894-913.

[CDC] Centers for Disease Control and Prevention. Treatment regiments for latent TB infection (LTBI). April 2016. CDC webpage. Available at: https://www.cdc.gov/tb/topic/treatment/ltbi.htm. Accessed 9 March 2019.

[CUIMC] Columbia University Irving Medical Center. Columbia-Suicide Severity Rating Scale (C-SSRS). The Columbia Lighthouse Project web site. Available at: www.cssrs.columbia.edu. Accessed 9 March 2019.

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

D'Haens G, Sandborn WJ, Ferrante M, Bhandari BR, Berliba E, Hibi T, Tuttle J, et al. OP38 maintenance treatment with mirikizumab, a p19-directed IL-23 antibody: 52-week results in patients with moderately-to-severely active ulcerative colitis. *J Crohns Colitis*. 2019;13:S026-S027.

Duerr RH, Taylor KD, Brant SR, Rioux JD, Silverberg MS, Daly MJ, Steinhart AH, et al. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. *Science*. 2006;314(5804):1461-1463.

Elson CO, Cong Y, Weaver CT, Schoeb TR, McClanahan TK, Fick RB, Kastelein RA. Monoclonal anti-interleukin 23 reverses active colitis in a T cell-mediated model in mice. *Gastroenterology*. 2007;132:2359-2370.

[EMA] European Medicines Agency. Guideline on the choice of non-inferiority margin. Jul 2005. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003636.pdf. Accessed 8 March 2019.

[EuroQol Group] EuroQol Group. EQ-5D-5L user guide. Version 5.1. 2015. Available at: http://www.euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf. Accessed 6 March 2018.

[FDA] Food and Drug Administration: Guidance for industry: Non-inferiority clinical trials to establish effectiveness. Nov 2016. FDA website. Available at: https://www.fda.gov/downloads/Drugs/.../Guidances/UCM202140.pdf. Accessed 8 March 2019.

[FDA] Food and Drug Administration: Guidance for industry: E10 choice of control group and related issues in clinical trials. May 2011. FDA web site. Available at: http://www.fda.gov/downloads/Drugs/Guidances/UCM073139.pdf. Accessed 20 Aug 2017.

Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, Blank MA, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2016;375:1946-60.

Feagan BG, Sandborn WJ, D'Haens G, Panes J, Kaser A, Ferrante M, Louis E, et al. Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomized, double-blind, placebo-controlled phase 2 study. *Lancet*. 2017;389:1966-709.

Feagan BG, Panes J, Ferrante M, Kaser A, D'Haens GR, Sandborn WJ, Louis E, et al. Risankizumab in patients with moderate to severe Crohn's disease: an open-label extension study. *Lancet Gastroenterol Hepatol*. 2018;3:671-80.

Ferrante M, Colombel J, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, et al. Validation of endoscopic activity scores in patients with Crohn's disease based on a post hoc analysis of data from SONIC. *Gastroenterology*. 2013;145:978-86.

Guyatt G, Mitchell A, Irvine EJ, Singer J, Williams N, Goodacre R, Tompkins C. A new measure of health status for clinical trials in inflammatory bowel disease. *Gastroenterology.* 1989;96(30):804-810.

Herdman M, Gudex C, Lloyd A, Janssen MF, Kind P, Parkin D, Bonsel G, Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res.* 2011;20:1727-1736.

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

Hue S, Ahern P, Buonocore S, Kullberg MC, Cua DJ, McKenzie BS, Powrie F, Maloy KJ. Interleukin-23 drives innate and T cell-mediated intestinal inflammation. *JEM*. 2006;203(11):2473-83.

[ICH] International Council for Harmonisation. Estimands and sensitivity analysis in clinical trials E9(R1). June 2017. Available at: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/E9-R1EWG_Step2_Guideline_2017_0616.pdf. Accessed 8 March 2019.

Illumina. Infinium® ImmunoArray-24 v2.0 BeadChip product information sheet. 2015. Webpage. Available at: https://www.illumina.com/content/dam/157uropa157m-marketing/documents/products/product_information_sheets/157uropa157m-human-immunoarray-24-product-info-sheet-370-2015-002.pdf. Accessed 5 March 2019.

Irvine EJ, Feagan B, Rochon J, Archambault A, Fedorak RN, Groll A, Kinnear D, et al. Quality of Life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. *Gastroenterol*. 1994;106(2):287-296.

Irvine EJ, Zhou Q, Thomson AK. The short inflammatory bowel disease questionnaire: a quality of life instrument for community physicians managing inflammatory bowel disease. *Am J Gastroenterol.* 1996;91(8)1571-1578.

Gordon JP, McEwan PC, Maguire A, Sugrue DM, a and Jorge Puelles J. Characterizing unmet medical need and the potential role of new biologic treatment options in patients with ulcerative colitis and Crohn's disease: a systematic review and clinician surveys. Eur J Gastroenterol Hepatol. 2015;27(7):804-12.

Kamm MA, Ng SC, De Cruz P, Allen P, Hanauer SB. Practical application of anti-TNF therapy for luminal Crohn's disease. *Inflamm Bowel Dis*. 2011;17:2366-2391.

Khanna R, Zou G, D'Haens G, Feagan BG, Sandborn WJ, Vandervoort MK, Rolleri RL, et al. A retrospective analysis: the development of patient reported outcome measures for the assessment of Crohn's disease activity. *Aliment Pharmacol Ther*. 2015;41:77-86.

Kim DH, Carucci LR, Baker ME, Cash BD, Dillman JR, Feig BW, Fowler KJ, et al. ACR appropriateness criteria Crohn disease. *JACR.* 2015;12(10):1048-1057.e4.

Kulig P, Musiol S, Freiberger SN, Schreiner B, Gyulveszi G, Russo G, Pantelyushin S, et al. IL-12 protects from psoriasiform skin inflammation. *Nature Comm*. 2016;7(13466):1-14.

Kullberg MC, Jankovic D, Feng CG, Hue S, Gorelick PL, McKenzie BS, Cua DJ, et al. IL-23 plays a key role in Heliobacter hepaticus-induced T cell-dependent colitis. *JEM*. 2006;203(11):2485-2494.

[Lilly]. Lilly's Mirikizumab Helps Patients Achieve Clinical Remission and Improves Symptoms in Adults with Ulcerative Colitis in 12-Week Phase 3 Induction Study. News Release. Published March 16, 2021. URL: https://investor.lilly.com/news-releases/news-release-details/lillys-mirikizumab-helps-patients-achieve-clinical-remission-and.

Lewinsohn DM, Leonard MK, LoBue PA, Cohn DL, Daley CL, Desmond E, Keane J, et al. Official American Thoracic Society / Infectious Diseases Society of America / Centers for Disease Control and Prevention Clinical Practice Guidelines: diagnosis of tuberculosis in adults and children. *Clin Infect Dis.* 2017;64(2):111-115.

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

Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: management of Crohn's disease in adults. *Am J Gastroenterol*. 2018;113:481-517.

Maruish ME, ed. User's manual for the SF-36v2 health survey. 3rd ed. Lincoln, RI: QualityMetric Incorporated; 2011.

Maxwell JR, Zhang Y, Brown WA, Budelsky AL, Symons A, Towne JE, et al. Differential roles for interleukin-23 and interleukin-17 in intestinal immunoregulation. *Immunity*. 2015;43:739-750.

Monteleone G, Biancone L, Marasco R, Morrone G, Marasco O, Luzza F, Pallone F. Interleukin 12 is expressed and actively released by Crohn's disease intestinal lamina propria mononuclear cells. *Gastroenterology*. 1997;112:1169-1178.

Parrello T, Monteleone G, Cucchiara S, Monteleone I, Sebkova L, Doldo P, Luzza F, Pallo F. Up-regulation of the IL-12 receptor B2 chain in Crohn's disease. *J Imunol*. 2000;165:7234-7239.

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

Reich K, Bissonnette R, Menter A, et al. Efficacy and safety of mirikizumab (LY3074828) in the treatment of moderate-to-severe plaque psoriasis: results from a phase 2 study. Poster presented at: 8th International Psoriasis from Gene to Clinic Congress; November 30 to December 2, 2017b; London, UK.

[Reilly Associates] Reilly Associates WPAI Scoring. Available at: http://www.reillyassociates.net/WPAI_Scoring.html. Accessed 12 March 2018.

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics.* 1993;4(5):353-365.

Sandborn WJ, Feagan BG, Stoinov S, Honiball PJ, Rutgeerts P, Mason D, Bloomfield R, et al. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med*. 2007;357:228-38.

Sandborn WJ, Ferrante M, Bhandari BR, D'Haens GR, Berliba E, Feagan BG, Laskowski J, et al. Efficacy and safety of anti-interleukin-23 therapy with mirikizumab (LY3074828) in patients with moderate-to-severe ulcerative colitis in a phase 2 study. *Gastroenterology.* 2018;154(6):S1360-S1361.

Sands BE. Biomarkers of inflammation in inflammatory bowel disease. *Gastroenterology*. 2015;149(5):1275-1285.

Sands BE, Chen J, Feagan BG, Penney M, Rees WA, Danese S, Higgins PDR, et al. Efficacy and safety of MEDI2070, an antibody against interleukin 23, in patients with moderate to severe Crohn's disease: a phase 2a study. *Gastroenterology*. 2017;153:77-86.

Sands BE, Peyrin-Biroulet L, Kierkus J et al. Efficacy and Safety of Mirikizumab in a Randomized Phase 2 Study of Patients With Crohn's Disease. *Gastroenterology*. 2021; 162(2):495-508.

Stelara [Summary of Product Characteristics]. Beerse, Belgium: Janssen-Cilag International NV; 2013. Available at: https://www.ema.europa.eu/en/documents/product-information/stelara-epar-product-information_en.pdf. Accessed 6 March 2019.

Stelara® (ustekinumab) [prescribing information]. Horsham, PA: Janssen Biotech, Inc.; 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761044lbl.pdf. Accessed 7 March 2019.

Sturm, A, Maaser C, Mendall M, Karagiannis D, Karatzas P, Ipenburg N, Sebastian S, et al. European Crohn's and Colitis Organisation topical review on IBD in the elderly. *J Crohns Colitis*. 2017;11(3):263-273.

Uhlig HH, McKenzie BS, Hue S, Thompson C, Joyce-Shaikh B, Stepankova R, Robinson N, et al. Differential activity of IL-12 and IL-23 in mucosal and systemic innate immune pathology. *Immunity*. 2006;25:309-318.

Vuitton L, Marteau P, Sandborn WJ, Levesque BG, Feagan B, Vermeire S, Danese S, et al. IOIBD technical review on endoscopic indices for Crohn's disease clinical trials. *Gut*. 2016;65:1447-1455.

Ware JE Jr, Sherboune CD. The MOS 36-item short-form health survey (SF-16). I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473-483.

Ware JE Jr. SF-36 health survey update. *Spine*. 2000;25(24):3130-9.

[WHO] World Health Organization. Use of high burden country lists for TB by WHO in the post-2015 era. Available at: http://www.who.int/tb/publications/global_report/high_tb_burdencountrylists2016-2020.pdf. Accessed 21 November 2017.

[WHO] World Health Organization. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. 2018. WHO webpage. Available at: https://apps.who.int/iris/bitstream/handle/10665/260233/9789241550239-eng.pdf;jsessionid=E70CB8EF5698843C11B55E8D24622809?sequence=1. Accessed 9 March 2019.

Winthrop KL, Novosad SA, Baddley JW, Calabrese L, Chiller T, Polgreen P, Bartalesi F, et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. *Ann Rheum Dis.* 2015;74(12):2107-2116.

Yen D, Cheung J, Scheerens H, Poulet F, McClanahan T, Mckenzie B, Kleinschek MA, et al. IL-23 is essential for T cell-mediated colitis and promotes inflammation via IL-17 and IL-6. *J Clin Invest*. 2006;116:1310-1316.

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