Protocol: I6T-MC-AMBZ

A Multicenter, Phase 3b, Open-Label, Single-Arm Study to Investigate Bowel Urgency and its Relationship with Other Outcome Measures in Adults with Moderately to Severely Active Ulcerative Colitis Treated with Mirikizumab

NCT05767021

Approval Date: 30-Nov-2023

Title Page

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A Multicenter, Phase 3b, Open-Label, Single-Arm Study to Investigate Bowel Urgency and its Relationship with Other Outcome Measures in Adults with Moderately to Severely Active Ulcerative Colitis Treated with Mirikizumab

Protocol Number: I6T-MC-AMBZ

Amendment Number: b

Compound: Mirikizumab (LY3074828)

Brief Title: A Study to Investigate Bowel Urgency in Adults with Moderately to Severely Active Ulcerative Colitis Treated with Mirikizumab

Study Phase: 3b

Acronym: LUCENT-URGE

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Numbers:
IND: 125444
EU trial number: 2022-502393-16-00

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

Document ID: CCI [redacted]

Medical monitor name and contact information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment a	16 Feb 2023
Original Protocol	04 Nov 2022

Amendment [b]

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The purpose of this amendment is to achieve the following:

Correct and further clarify the Stool collection guidelines for stool culture/*C difficile* and fecal calprotectin testing at applicable visits
Clarify and emphasize the daily diary compliance requirements for calculating UNRS, SF, RB, and MMS scores at applicable visits
Clarify and emphasize the role of site personnel in ensuring participant understanding of Normal Number of Stools Questionnaire
Correct and clarify the recommendations and requirements for stool cultures/*C difficile* testing in participants undergoing rescreening, after resolution of prior screen failure due to positive stool culture/*C difficile* test results
Provide examples of mirikizumab access under related discontinuation criterion in the Continued Access Period (Appendix 12)

Minor editorial changes are not included in this table.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA)	Diary compliance check, retraining as needed added. Another check at V1 added. Comments: added requirement of D)×µ)G) days prior to bowel preparation at V1, V6, and V10. Text regarding monitoring compliance and retraining removed.	To further clarify and reinforce diary completion requirements at critical timepoints.
	Normal Number of Stools Comments: Modified wording to further address required role of site personnel.	To further clarify and emphasize the role of site personnel in ensuring participant understanding
	Dispense Stool Collection Kit Comments: corrected instructions for V1 and added detail for V1, V5, and V9	To correct V1 instructions and clarify the number and type of stool collection kits to dispense at all relevant visits.
	Stool culture/*C difficile* Comments: added wording to describe timing of collection and results at V1.	To clarify timing of sample collection and receipt of results at V1.

Section # and Name	Description of Change	Brief Rationale
	Fecal calprotectin Comments: added wording to describe timing of collection for V2, V6, and V10.	To clarify timing of sample collection for V2, V6, and V10.
	Endoscopy with Biopsies Comments: Note added for diary completion.	To further clarify and emphasize requirements for daily diary completion.
5.1. Inclusion Criteria	Criterion 4: Added reference to Section 9.3.2.	To connect and further clarify the diary completion requirements for calculating the screening UNRS score.
5.4.1. Allowed Rescreening of Participants after Initial Screen Failure	Correction of inadvertent wording errors: (inclusive) was removed from a sentence describing a time period within the screening period. ○Δ×Δ)≠×)m–β+)B)↓ xβ)x≤<≥)≠×)≠–≥) sentence describing the full screening period.	To gain consistency and further clarify the criteria for the two screening-visit time periods across several sections of the protocol.
	additional)↓ xβ)Δ≥’ ×-≥≤)µΔ×’)≠–≥) sentence describing recommended testing of stool cultures before rescreening participants with prior screen failure due to positive results.	To correct and gain consistency between recommendations made in Section 5.4. and in Section 8.2.10.
8.1.1. Daily Electronic Diary Measures	Wording added to indicate that 2 diary measures have different minimal completion requirements.	To clarify this difference
8.1.2.1. Normal Number of Stools	Added text regarding the specific periods of time referred in this questionnaire, and the importance for site personnel to explain time periods and questions to the participants. Also added reference to Section 10.6.	To further clarify and emphasize the importance of site personnel β)Δ×‘≥)„) ensuring participantβ understanding of the wording and time periods used in this questionnaire.
8.2.10 Screening Stool Testing	Stool Culture Corrected and expanded the wording for testing stool cultures in participants undergoing rescreening, after resolution of prior screen failure due to positive stool-culture results.	To correct and gain consistency with related wording and recommendations in Section 5.4., and to also further clarify the rescreen testing requirements in Section 8.2.10.
	C difficile toxin testing Corrected and expanded wording for *C difficile* testing in participants undergoing rescreening, after resolution of prior screen failure due to positive *C difficile* results.	To correct and gain consistency with related wording and recommendations made in Section 5.4., and to also further clarify the rescreen testing requirements in Section 8.2.10
9.3.2. Primary Endpoint Analysis	Sentence reworded to state the minimum required days (4), instead of the maximum missing days (3). The rewording did not change the meaning of the sentence.	To align wording to increase consistency with other areas or the protocol, and to minimize misunderstanding.

Section # and Name	Description of Change	Brief Rationale
10.12. Appendix 12: Optional Continued Access Period 10.12.1 Overview	Added the phrase and accessible8 and parenthetical reference to Section 10.12.7 to the sentence about approval and worldwide commercial availability of mirikizumab.	To connect and align content of the Appendix 12 Overview Section (10.12.1).with the more detailed content of the Discontinuation Section (10.12.7).
10.12.7. Discontinuation of Study Intervention and Participant Discontinuation from the Study	Added examples to the criterion including local access of mirikizumab The word ⸸ ×Δ≤⸸ –<>)x<<>)in statement regarding continuous access of mirikizumab	To further clarify and describe the meaning of local access

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Multicenter, Phase 3b, Open-Label, Single-Arm Study to Investigate Bowel Urgency and its Relationship with Other Outcome Measures in Adults with Moderately to Severely Active Ulcerative Colitis Treated with Mirikizumab

Brief Title:

A Study to Investigate Bowel Urgency in Adults with Moderately to Severely Active Ulcerative Colitis Treated with Mirikizumab

Regulatory Agency Identifier Numbers:

IND: 125444

EU trial number: 2022-502393-16-00

Rationale:

Study I6T-MC-AMBZ (AMBZ) is a Phase 3b, open-label, single-arm study to investigate the relationship of bowel urgency with other outcome measures in participants with moderately to severely active Ulcerative Colitis (UC) treated with mirikizumab.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
To assess the improvement in bowel urgency severity at Week 12.	Change from baseline in bowel urgency severity (UNRS) score at Week 12.
Secondary	
To assess the improvement in bowel urgency severity at Week [redacted].	[redacted]
To assess the improvement in [redacted]	[redacted]

Objectives	Endpoints
To assess the improvement in CCI [redacted]	[redacted]
To assess the proportion of participants achieving clinical remission and a UNRS score CCI [redacted].	[redacted]
To assess the proportion of participants achieving clinical response and clinically meaningful change in bowel urgency severity.	[redacted]
To assess the association between CCI [redacted]	[redacted]
To assess associations between bowel urgency measures and QoL/functional outcome measures and UC symptom measures.	[redacted]

Objectives	Endpoints
	CCI [redacted]

Abbreviations: QoL = quality of life; UC = ulcerative colitis; UNRS = urgency numeric rating scale.

Estimand

The primary clinical question of interest is:

What is the mean change from baseline in Urgency Numeric Rating Scale (UNRS) at Week 12 CCI [redacted]

Overall Design

Study AMBZ is a multicenter, open-label, single-arm Phase 3b study to investigate bowel urgency and its relationship with other outcome measures in participants with moderately to severely active UC treated with mirikizumab over a CCI -week period.

The study will have 4 study periods:

Period I (CCI days)

Participants must complete all Visit 1 screening activities within CCI days prior to Visit 2. The screening endoscopy must occur within CCI days prior to Visit 2.

Period II (CCI weeks)

Participants will receive CCI mg mirikizumab CCI [redacted]

Period III (CCI weeks)

Participants will receive CCI mg mirikizumab CCI [redacted]

Note: Participants planning to participate in continued access must complete self-administration training during at least 2 visits between Visits 6 and 9.

Upon completion of all Visit 10 activities, eligible participants may enter the Continued Access Period.

Period IV

Participants who meet the following criteria should enter posttreatment follow-up, including completion of Visit 801:

CCI [redacted]

An optional continued access will be provided for eligible participants following the completion of Period III.

Brief Summary:

Study AMBZ is designed to broadly investigate bowel urgency (severity, CCI), and to evaluate the relationship between CCI and other outcome measures.

Study Population:

In general, an individual may take part in the study if they

- Are ≥18 years and ≤80 years of age at the time of informed consent
- Have an established diagnosis of UC of ≥3 months before Visit 2 (Week), which includes documented endoscopic evidence of UC and a histopathology report that supports a diagnosis of UC

  Participants with rectal sparing on the Visit 1 screening endoscopy must have documentation of rectal involvement from a prior endoscopy and histopathology report to confirm UC diagnosis
- Have moderately to severely active UC as defined by a modified Mayo score (MMS) of CCI with a centrally read endoscopic CCI . The scores must be based on data from the screening endoscopy performed CCI days before Visit 2
- Have current bowel urgency, defined as an UNRS score of CCI during screening
- Have demonstrated an inadequate response, loss of response, or intolerance to conventional or biologic/JAK inhibitor/S1P receptor modulator (biologic/JAK/S1P) therapy for UC

In general, an individual may not take part in the study if they

- Have a current diagnosis of Crohn's disease or inflammatory bowel disease-unclassified formerly known as indeterminate colitis, or ulcerative proctitis, disease limited to the rectum, that is, distal to the recto-sigmoid junction, which lies approximately 10 to 15 cm from anal verge.
- Have a history of the following bowel, intestinal or intra-abdominal surgeries:
  - extensive colonic surgery for UC or for other reasons, such as subtotal colectomy, or are likely to require surgery for the treatment of UC during the study,

    Participants who had limited colonic surgery for UC, such as a segmental resection, may be allowed in the study after discussion with the medical monitor.
  - any small bowel or colonic surgery within 6 months prior to Visit 2, or
  - any non-intestinal intra-abdominal surgery within 3 months prior to Visit 2
- Have evidence of toxic megacolon, intra-abdominal abscess, or stricture/stenosis within the small bowel, colon, or rectum

- Have received CCI for any indication, including investigational use.
- Have discontinued CCI due to loss of response, inadequate response, or intolerance:

  Exception: if discontinuation was due to other reasons, such as a change of insurance or well controlled disease, and the duration of exposure was ≤1 year. Consultation with the medical monitor should occur to establish eligibility.

Number of Participants:

Approximately 160 participants will be assigned to study intervention.

Intervention Groups and Duration:

All enrolled participants will receive mirikizumab.

Period II (CCI weeks): Participants receive CCI mg mirikizumab CCI.

Period III (CCI weeks): Participants receive CCI mg mirikizumab CCI.

Ethical Considerations of Benefit/Risk:

Given both the efficacy and safety data from the Phase 3 adult studies in UC and data from other mirikizumab clinical studies completed to date, as well as safety data in ongoing studies of adults with UC, the participants receiving mirikizumab in Study AMBZ have the potential for clinical benefit with an acceptable safety profile.

Data Monitoring Committee: No

[a] Participants who are eligible for continued access should move directly from Visit 10 to Visit 501, on the same day, if possible. Visit 801 should not be performed.

[b] Optional Continued Access Period is described in Section 10.12.

1.3. Schedule of Activities (SoA)

Period I

Completion of the Visit 1 screening activities requires more than 1 day.

Period II

Visit 3 is a telephone visit. All safety assessments should be performed by telephone.

Period III

Upon completion of all Visit 10 activities, eligible participants may enter the Continued Access Period. These participants will move directly from Visit 10 to Visit 501 of the Continued Access Period if they meet requirements detailed in Section 10.12.

Period IV

Visit 801, a telephone visit, should be performed CCI days after the participant's last visit, either Visit 10 or the ED visit.

Visit 801 may be performed onsite when onsite activities are required or at investigator's discretion.

Early discontinuation (ED) visit

Required for all participants who discontinue mirikizumab treatment prior to Visit 10.

Unscheduled visits (UV)

May occur as needed, on any day without regard to visit interval. Required activities are indicated in the SoA. Additional procedures may be performed at the investigator's discretion.

	I	II				III							IV	Comments
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**ED**	**UV**	**801**	Dosing visits: complete all visit activities before administration of mirikizumab.
Weeks from treatment assignment	CCI													
Study day														
Visit interval tolerance (days)														
Visit location	O	O	T	O	O	O	O	O	O	O	O	O	T	O = Onsite, T = Telephone
Informed consent	X													The informed consent form (ICF) must be signed before any protocol-specific activities are performed. See Section 10.1.3.
Inclusion and exclusion criteria, review and confirm eligibility	X	X												Confirm before Visit 2 assignment and administration of first dose.
Demographics	X													Includes year of birth, sex, race, and ethnicity (where permissible).
Preexisting conditions and medical history	X													Collect all ongoing conditions; relevant surgical or medical history.
Prespecified medical history (UC and history of interest)	X													Collect additional data for UC and comorbidities of interest.
Prior treatments for UC	X													
Substance use including alcohol, caffeine, tobacco, nicotine	X					X				X	X		X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	Refer to Section 6.8.
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	See Sections 8.3.1 and 8.3.3.

	I	II				III							IV	Comments
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**ED**	**UV**	**801**	Dosing visits: complete all visit activities before administration of mirikizumab.
Weeks from treatment assignment	CCI													
Study day														
Visit interval tolerance (days)														
Visit location	O	O	T	O	O	O	O	O	O	O	O	O	T	O = Onsite, T = Telephone
Pre-endoscopy instructions and reminders	X				X				X					Includes diary compliance, dates, and bowel preparation/procedure
Physical Evaluation														
Height	X													
Weight	X	X				X				X	X			
Vital signs	X	X		X	X	X	X	X	X	X	X	X	X‡	‡ optional per investigator discretion. See Section 8.2.2.
Physical examination	X													See Section 8.2.1.
Symptom-directed physical assessment		X		May perform at any visit, per investigator discretion						X	X	X	X‡	‡ optional per investigator discretion. See Section 8.2.1.
Evaluate for EIMs	X	X		May perform at any visit, per investigator discretion						X	X			See Section 8.2.1.
Tuberculosis (TB) evaluation		X				X		X		X	X			Risk factors and symptoms of active TB. See Section 8.2.7.
Chest X-ray	X													For instructions and exceptions, see Section 8.2.7.1.
12-lead ECG (local)	X													See Section 8.2.3.
Participant Diary (Electronic)														
Diary dispensed	X													Explain use of device and each measure. See Section 8.1.1.

	I	II				III							IV	Comments
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**ED**	**UV**	**801**	Dosing visits: complete all visit activities before administration of mirikizumab.
Weeks from treatment assignment	CCI													
Study day														
Visit interval tolerance (days)														
Visit location	O	O	T	O	O	O	O	O	O	O	O	O	T	O = Onsite, T = Telephone
Diary compliance check, retraining as needed	X↓	X	X	X	X	X↓	X	X	X	X↓	X			X↓: Site personnel must ensure diary completed on 4 or more (≥4) of 7 days prior to bowel preparation at V1, V6, and V10. See Section 8.1.1.
Diary returned										X	X			
Patient-Reported Outcomes (Electronic tablet)														
CCI	X													CCI
CCI				X	X	X				X	X			
CCI		X				X		X		X	X			
CCI		X				X		X		X	X			

	I	II				III							IV	Comments
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**ED**	**UV**	**801**	Dosing visits: complete all visit activities before administration of mirikizumab.
Weeks from treatment assignment	CCI													
Study day														
Visit interval tolerance (days)														
Visit location	O	O	T	O	O	O	O	O	O	O	O	O	T	O = Onsite, T = Telephone
CCI		X				X		X		X	X			CCI
		X				X				X	X			
		X				X				X	X			
		X				X				X	X			
		X				X				X	X			
Clinician-Administered Assessments														
CCI [redacted] Baseline/Screening	X													Complete on electronic tablet, by site staff trained on C-SSRS. See Section 8.2.6.1.

	I	II				III							IV	Comments
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**ED**	**UV**	**801**	Dosing visits: complete all visit activities before administration of mirikizumab.
Weeks from treatment assignment	CCI													
Study day														
Visit interval tolerance (days)														
Visit location	O	O	T	O	O	O	O	O	O	O	O	O	T	O = Onsite, T = Telephone
Physician's Global Assessment (PGA)		X				X				X	X			Complete on electronic tablet. See Section 8.1.3.
Laboratory Tests and Sample Collections														
Hematology	X	X		X	X	X		X		X	X	X‡	X‡	‡ Optional per investigator discretion
Clinical chemistry	X	X		X	X	X		X		X	X	X‡	X‡	‡ Optional per investigator discretion
Urinalysis	X													
Serum pregnancy	X													For WOCBP. See Section 8.2.5.
Urine pregnancy (local)		X		X	X	X	X	X	X	X	X			WOCBP; negative test required prior to dosing at marked visits. See Section 8.2.5.
Follicle Stimulating Hormone (FSH)	X‡	X‡												‡ Optional per investigator discretion , to confirm postmenopausal status. See Section 8.2.5.
Tuberculosis (TB) Testing	X									X$^{\Delta}$				QuantiFERON®-TB Gold; central or local laboratory. See Section 8.2.7. $^{\Delta}$ Visit 10: Perform only if necessary, per local requirements.
HIV screening test	X													

	I	II				III							IV	Comments
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**ED**	**UV**	**801**	Dosing visits: complete all visit activities before administration of mirikizumab.
Weeks from treatment assignment	CCI													
Study day														
Visit interval tolerance (days)														
Visit location	O	O	T	O	O	O	O	O	O	O	O	O	T	O = Onsite, T = Telephone
Hepatitis C virus (HCV) screening tests	X													See Section 8.2.8.2.
Hepatitis B virus (HBV) screening tests	X													See Section 8.2.8.1.
HBV DNA						X		X			X	X		Only if positive serology at screening. See Section 8.2.8.1.
Immunogenicity (ADA) samples: predose		X												
Immunogenicity (ADA) samples		In the event of CCI [redacted] related event- Collect PK and ADA samples												Collect PK and ADA samples as detailed in Section 10.2.
Pharmacokinetic (PK) samples														
Stool Sample Collection and Testing														
Dispense stool collection kit	X				X				X					V1 = 2 kits: Stool culture/*C difficile* and fecal calprotectin V5/V9 = 1 kit: fecal calprotectin See Section 8.2.10.

	I	II				III							IV	Comments
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**ED**	**UV**	**801**	Dosing visits: complete all visit activities before administration of mirikizumab.
Weeks from treatment assignment	CCI													
Study day														
Visit interval tolerance (days)														
Visit location	O	O	T	O	O	O	O	O	O	O	O	O	T	O = Onsite, T = Telephone
Stool culture CCI oxin	X													Instruct participant to collect their stool sample as soon as possible during screening/V1, to allow for receipt of test results prior to V1 endoscopy. The test results must be negative at screening. See Section 8.2.10.
CCI		X				X				X				Instruct participant to collect their stool sample as follows: V2: After V1 endoscopy and before V2 dosing. V6/V10: 3 or less (≤3) days prior to day of bowel prep
Endoscopy Procedures and Sample Collection														
CCI	X					X				X				See Section 8.1.5. Note: For eligibility, diary must be completed for 4 or more (≥4) of the 7 days prior to bowel preparation for endoscopy

	I	II				III							IV	Comments
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**ED**	**UV**	**801**	Dosing visits: complete all visit activities before administration of mirikizumab.
Weeks from treatment assignment	CCI													
Study day														
Visit interval tolerance (days)														
Visit location	O	O	T	O	O	O	O	O	O	O	O	O	T	O = Onsite, T = Telephone
Stored Samples														
CCI	X					X				X				See Sections 8.7 and 8.1.5.4.
		X				X				X				
Registration and Dosing														
Register visit with IWRS	X	X	X	X	X	X	X	X	X	X	X		X	
Assign Treatment with IWRS		X												
Dispense mirikizumab via IWRS		X		X	X	X	X	X	X					See Section 6.1.
Administer mirikizumab		X		X	X	X	X	X	X					See Section 6.1.
Self-Administration Training														
Provide training on self-administration						X*	X*	X*	X*					*Completion of training required for Continued Access Period. See Section 6.1.1.

Abbreviations: ADA = anti-drug antibody DNA = deoxyribonucleic acid; ECG = electrocardiogram; ED = early discontinuation; EIM = extraintestinal manifestation; HIV = human immunodeficiency virus; IWRS = interactive web-response system; UC = ulcerative colitis; UV = Unscheduled Visit; V = visit; WOCBP = woman of childbearing potential.

2. Introduction

2.1. Study Rationale

Study I6T-MC-AMBZ (AMBZ) is a Phase 3b, open-label, single-arm study to investigate the relationship of bowel urgency with other outcome measures in participants with moderately to severely active UC treated with mirikizumab.

2.2. Background

Disease state

UC is a chronic relapsing and remitting disease characterized by inflammation, ulceration, and bleeding in the colon and rectum. Symptoms include diarrhea; RB; bowel urgency; and tenesmus, a feeling of incomplete evacuation of the rectum after defecation, even though there is no remaining stool to expel. UC has a relapsing remitting course, meaning that many individuals have intermittent disease flares that are interspersed with periods of remission.

Treatment goals

Treatment goals in UC traditionally include induction of remission, typically within a 6- to 12-week time frame, and maintenance of remission in the longer term as assessed over 52 weeks of continuous treatment in clinical studies.

In both clinical practice and clinical studies, clinical response and clinical remission are assessed by a combination of improvement in the endoscopic appearance of the mucosa and healing of ulcers and patient-reported outcomes, including a reduction in SF and a resolution of RB (Levesque et al. 2015). Control of intestinal inflammation in UC is associated with a reduction in corticosteroid use, risk of hospitalization, colectomy and, in the longer term, UC-associated dysplasia and colorectal cancer.

Importance of bowel urgency

More than 80% of individuals with UC experience bowel urgency (Petryszyn et al. 2018; Nóbrega et al. 2018; Newton et al. 2019; Dulai et al. 2020) and 50% experience bowel urgency at least once a day (Petryszyn et al. 2018). More than 40% of individuals experience bowel urgency, even when SF and RB measure scores are 0 (Hibi et al. 2020). An estimated 36% to 54% of individuals with UC report having a deferral time (make it to the bathroom on time) of less than 5 minutes and nearly 18% have less than 2 minutes. In severe cases, individuals have less than 30 seconds to make it to the bathroom. These data demonstrate that bowel urgency has a significant negative impact on the QoL, and the functional ability of individuals with UC.

The American College of Gastroenterology clinical guidelines specifically highlight the need to evaluate urgency of defecation when diagnosing and assessing disease severity, driving a growing need to characterize this endpoint for clinical practice. Regulatory bodies are also interested in defining and validating patient-reported outcomes beyond SF and RB, with bowel urgency being one of the most relevant symptoms to patients (Danese et al. 2019).

Despite its significant impact, robust examination of bowel urgency has only recently been incorporated into clinical investigations and is now increasingly considered an emerging endpoint in clinical studies.

Mirikizumab

Mirikizumab (LY3074828) is a humanized immunoglobulin G4 monoclonal antibody that binds to the p19 subunit of IL-23, a cytokine associated with mucosal inflammation (Croxford et al. 2014; Gheita et al. 2014; Globig et al. 2014; El-Bassat et al. 2016).

Preclinical and clinical data to date support the development of mirikizumab as a treatment for moderately to severely active UC.

A detailed description of the chemistry, pharmacology, nonclinical and clinical efficacy, and safety of mirikizumab is provided in the IB.

See Section 4.3 for results from the Phase 3 studies in participants with moderately to severely active UC.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of mirikizumab may be found in the IB.

2.3.1. Risk Assessment

Risks due to Common Study Procedures		
Potential Risks of Clinical Significance	**Summary of Data/ Rationale for Risk**	**Mitigation Strategy**
Risk associated with the endoscopic procedures including bleeding and colonic perforation.	These risks are considered rare but are recognized risks for endoscopic procedures. (Rabeneck et al. 2008; Arora et al. 2009)	Trained and experienced endoscopists will be performing endoscopic assessments.
Blood collection volumes may exceed usual standard of care volume for a single visit.		Blood volumes are calculated for every visit and where potentially problematic, sample collections may be eliminated based on prioritization guidance.

Evaluation of safety data from mirikizumab clinical studies examining psoriasis, UC, and CD, shows a safety profile consistent with the anti-IL-23 p19 antibody class.

2.3.2. Benefit Assessment

At the time of this benefit/risk assessment, mirikizumab has demonstrated efficacy in

Phase 3, placebo-controlled studies in adults with
- psoriasis (Papp et al. 2020), and
- UC (U [x≥,,β)≥≠)x‘. 2022)

Phase 2 studies in adults with
- psoriasis (Reich et al. 2019)
- UC (Sandborn et al. B=AHK)U [x≥,,β)≥≠)x‘. 2019), and
- CD (Sands et al. 2019, 2020).

The potential benefits from participation in this study include

clinical remission
reduced bowel urgency
clinical response
endoscopic remission
symptomatic remission, and
improvement in endoscopic histologic inflammation.

2.3.3. Overall Benefit Risk Conclusion

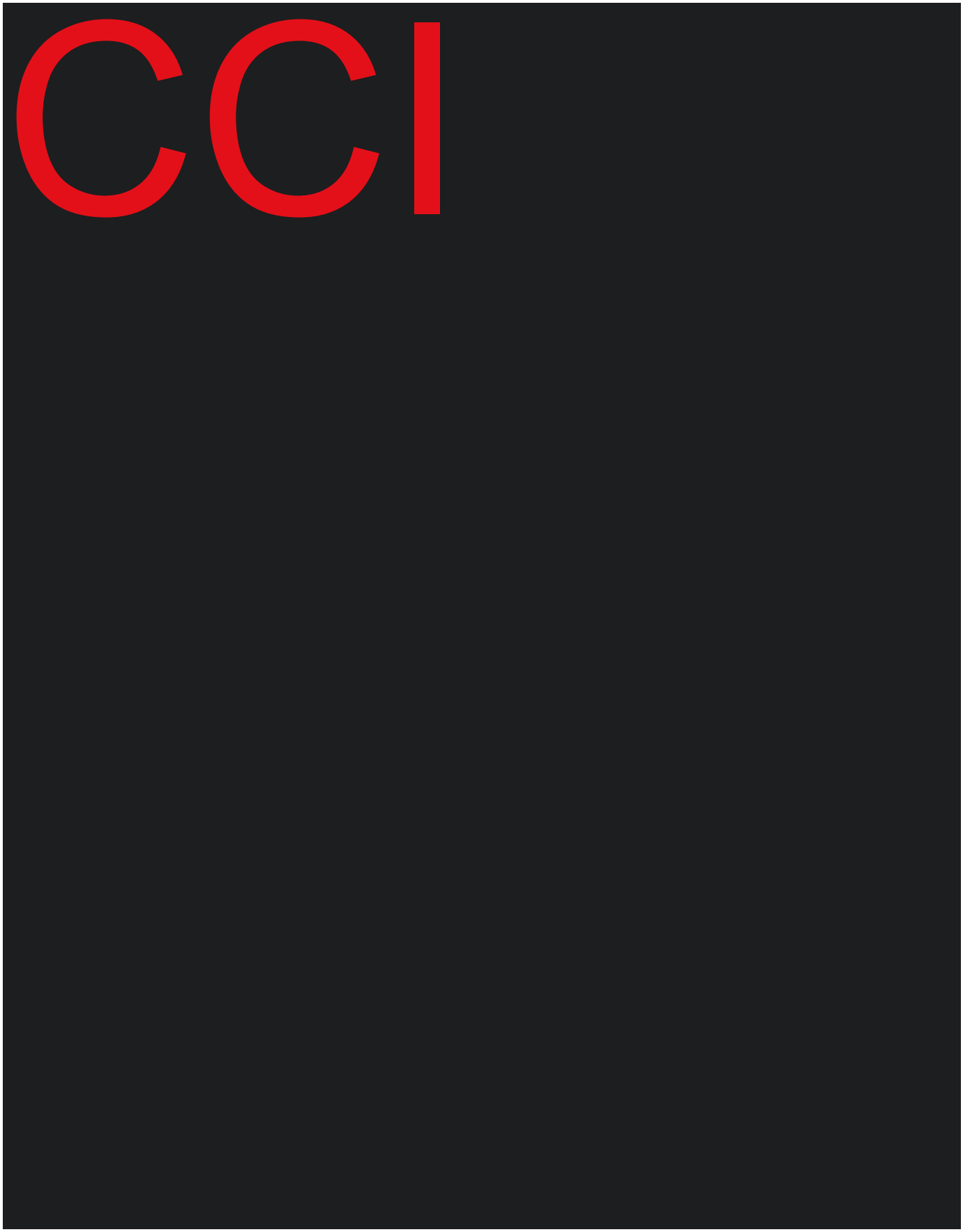
Given both the efficacy and safety data from the Phase 3 adult studies in UC and data from other mirikizumab clinical studies completed to date, as well as safety data in ongoing studies of adults with UC, the participants receiving mirikizumab in Study AMBZ have the potential for clinical benefit with an acceptable safety profile.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
To assess the improvement in bowel urgency severity at Week 12.	Change from baseline in bowel urgency severity (UNRS) score at Week 12.
Secondary	
To assess the improvement in bowel urgency severity at Week [redacted].	[redacted]
To assess the improvement in [redacted]	
To assess the improvement in [redacted]	
To assess the proportion of participants achieving clinical remission and a UNRS score [redacted].	
To assess the proportion of participants achieving clinical response and clinically meaningful change in bowel urgency severity.	

To assess the association between CCI .	CCI
To assess associations between bowel urgency measures and QoL/functional outcome measures and UC symptom measures.	
Exploratory	
CCI	

Abbreviations: QoL = quality of life, UC = ulcerative colitis, UNRS = urgency numeric rating scale.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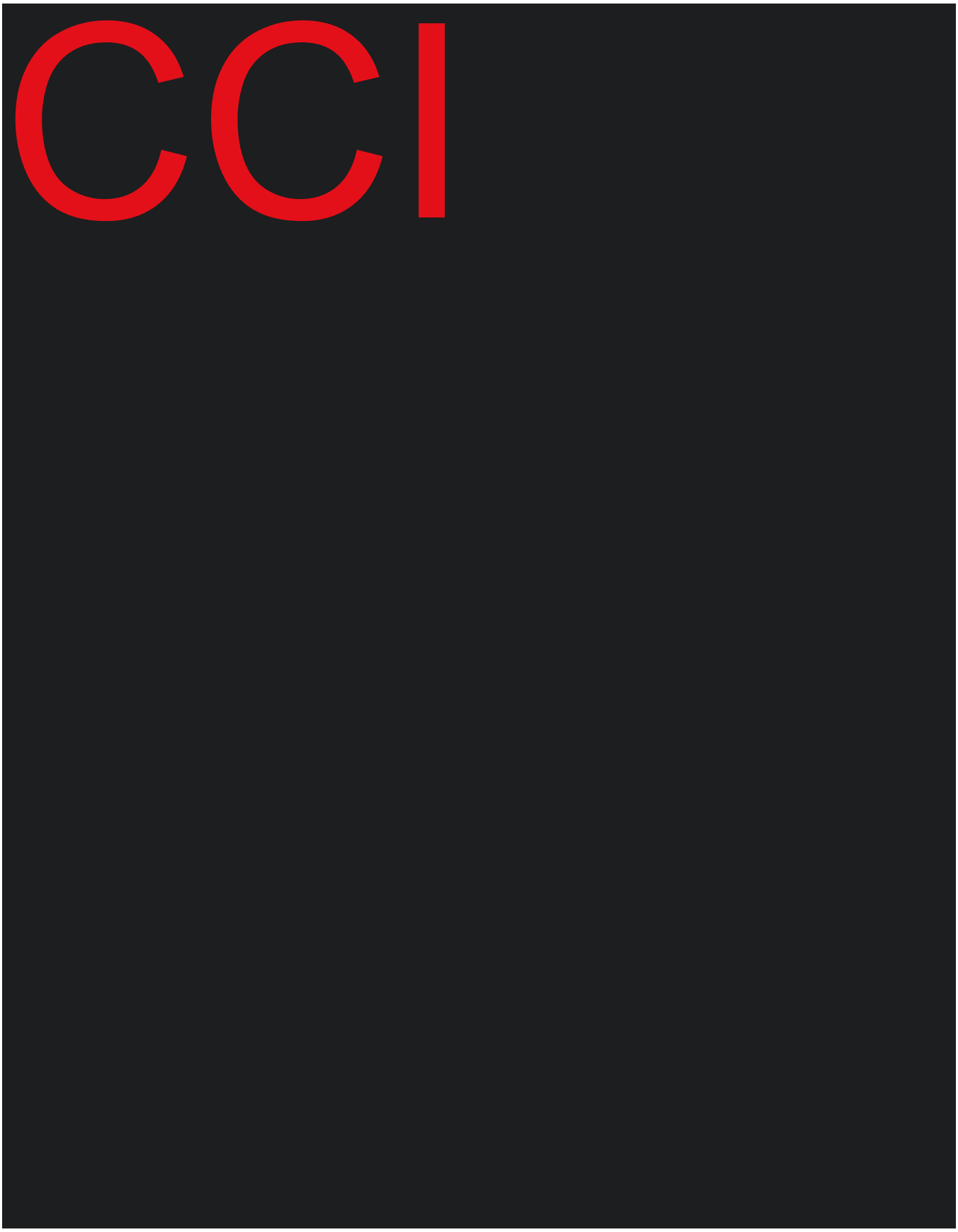

4. Study Design

4.1. Overall Design

This is a multicenter, open-label, single-arm Phase 3b study to investigate bowel urgency and its relationship with other outcome measures in participants with moderately to severely active UC treated with mirikizumab over a [redacted]-week period.

Design

The study will have 4 study periods:

Period I ([redacted] days)

Participants must complete all Visit 1 screening activities within [redacted] days prior to Visit 2. The screening endoscopy must occur within [redacted] days prior to Visit 2.

Period II ([redacted] weeks)

Participants will receive [redacted] mg mirikizumab [redacted].

Period III ([redacted] weeks)

Participants will receive [redacted] mg mirikizumab [redacted].

Note: Participants planning to participate in continued access must complete self-administration training during at least 2 visits between Visits 6 and 9 (see Section 6.1.1). Upon completion of all Visit 10 activities, eligible participants may enter the Continued Access Period.

Period IV

Participants who meet the following criteria should enter posttreatment follow-up, including completion of Visit 801:

[redacted]

An optional continued access will be provided for eligible participants following the completion of Period III. See Section 10.12.

See [redacted] Section 1.3 for the SoA.

4.2. Scientific Rationale for Study Design

Study AMBZ is designed to broadly investigate bowel urgency (severity, [redacted]), and to evaluate the relationship between the components of bowel urgency and other outcome measures.

In Studies I6T-MC-AMAN and I6T-MC-AMBG, improvement in bowel urgency severity was reported as early as Week 2 after the first induction dose of mirikizumab, and this improvement became statistically significant compared to placebo at Week 12 of induction dosing. The mirikizumab treatment group continued to have incremental improvement in bowel urgency severity through Week 20 (Week 8 of SC mirikizumab maintenance dosing) and then plateaued

for the remainder of the maintenance period. These results support the use of a [redacted]-week mirikizumab [redacted] induction period and a [redacted]-week mirikizumab [redacted] dosing period in this study.

Primary and secondary endpoints

See Section 2.2 for the background rationale for the primary endpoint.

The bowel urgency endpoint (UNRS) in Studies AMAC, AMAN and AMBG was constructed in alignment with FDA guidance to assess mean change of severity. Mean change from baseline in UNRS was added as a gated endpoint to the LUCENT clinical program based on results of the binary analysis of bowel urgency in the Phase 2 Study AMAC.

The results from the LUCENT clinical program suggest that while the mean change in bowel urgency severity is a relevant, differentiating endpoint at the population level, there is a need to further characterize bowel urgency with [redacted]. In addition to investigating a broader characterization of bowel urgency in UC, providing a better understanding of the association between bowel urgency and other clinical outcomes would further advance the scientific understanding of urgency and inform the clinical community.

Collection of demographic information

In this study, collection of demographic information includes race and ethnicity (where permissible). The scientific rationale is based on the need to assess variable response of the endpoints based on race or ethnicity. This question can be answered only if all the relevant data are collected.

4.3. Justification for Dose

The induction and maintenance dose levels and regimens in Study AMBZ were based on analyses of PK, safety, and efficacy data from the following studies of mirikizumab in participants with moderate to severe UC:

- AMAC: Phase 2 study with a 12-week IV induction and ≤92-week SC maintenance
- AMAN (LUCENT-1): Phase 3 induction study with a 12-week IV treatment duration
  - Active dosing regimen: 300 mg mirikizumab IV Q4W, and
- AMBG (LUCENT-2): Phase 3 maintenance study with a 40-week SC treatment duration.
  - Active dosing regimen: 200 mg mirikizumab SC Q4W.

Study AMAN was a Phase 3, randomized, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of mirikizumab over a 12-week induction period. Responders to mirikizumab induction treatment in AMAN were re-randomized to receive blinded mirikizumab 200 mg or placebo subcutaneously Q4W for 40 weeks in the AMBG study.

Study AMBG was a Phase 3, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of mirikizumab 200 mg SC Q4W in maintaining treatment response after 52 weeks of continuous study intervention treatment.

Efficacy results from Studies AMAN and AMBG

Studies AMAN and AMBG demonstrated that both the induction and maintenance dosing regimens provided clinically meaningful and statistically significant efficacy.

Study AMAN demonstrated that mirikizumab induction dosing of 300 mg mirikizumab IV Q4W was consistently superior to placebo in the treatment of moderately to severely active UC for all primary and major secondary endpoints.

Study AMBG demonstrated that 200 mg mirikizumab SC Q4W was superior to placebo at achieving the primary endpoint of clinical remission and all major secondary endpoints at Week 40, which was representative of 52 weeks of continuous treatment.

In both the induction and maintenance studies, the mirikizumab treatment groups were consistently superior to placebo across clinical, symptomatic, QoL, endoscopic, and histologic measures.

CCI [redacted]

Safety results from Studies AMAN and AMBG

The proportion of participants with TEAEs was similar between mirikizumab and placebo groups during both AMAN and AMBG studies.

The frequency of SAEs and discontinuations of study treatment due to AEs were numerically lower in the mirikizumab group compared to placebo in both studies.

More detailed information about the safety and dosing rationale for mirikizumab may be found in the IB.

4.4. End of Study Definition

The end of the study is defined as the date of last visit for the last participant in the study globally.

A participant is considered to have completed the main study if the participant has completed study periods I-III and all required procedures for Visit 801 or Visit 501 as outlined in Sections 1.3 and 10.12.3, respectively.

5. Study Population

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

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Age

1. Are ≥18 years and ≤80 years of age at the time of signing the informed consent.

Type of participant and disease characteristics

2. Have an established diagnosis of UC for ≥3 months before Visit 2 (Week [redacted]), which includes documented endoscopic evidence of UC and a histopathology report that supports diagnosis of UC (see Section 8.1.5.4).

   Participants with rectal sparing on the Visit 1 screening endoscopy must have documentation of rectal involvement from a prior endoscopy and histopathology report to confirm UC diagnosis.

3. Have moderately to severely active UC as defined by a MMS of [redacted] with a centrally read [redacted]. The scores must be based on data from the screening endoscopy performed ≤14 days before Visit 2 (see Section 8.1.5.4).
4. Have current bowel urgency, defined as an UNRS score of [redacted] or more [redacted] during screening (see Section 9.3.2).
5. Have evidence of UC extending proximal to the rectum.
6. Participants with a history of UC for [redacted] years have had a surveillance colonoscopy with biopsies completed within [redacted] prior to Visit 2, with documented negative results for colorectal dysplasia and cancer.

   Participants with primary sclerosing cholangitis, regardless of duration of UC diagnosis, have had a surveillance colonoscopy with biopsies completed within [redacted] year prior to Visit 2, with documented negative results for colorectal dysplasia and cancer.

   For participants who do not have documented negative results for colorectal dysplasia and cancer from a surveillance colonoscopy with biopsies completed as above, the investigator should perform a colonoscopy with biopsies as the endoscopic procedure at Visit 1 to meet this inclusion criteria and other study requirements. A documented negative result is needed prior to Visit 2 to meet this inclusion criterion. See detailed requirements in Section 8.1.5.2.

   Surveillance biopsies should be collected and sent to a local laboratory for testing and documentation of results.

Sex and contraceptive/barrier requirements

7. Are male or female and agree to adhere to the contraception requirements for the study.

   Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For the contraception requirements of this protocol, see Section 10.4.

Informed consent

8. Are capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Prior medication use

9. Have met conditions for either conventional-failure or biologic/JAK inhibitor/S1P receptor modulator (biologic/JAK/S1P) failure stated in **9a** OR **9b**. Documentation of dose, frequency, route of administration, and duration of use for the prior failed treatment is required.

9a. Conventional-failed participants

A conventional-failed participant is one who had an inadequate response to, a loss of response to, or an intolerance to at least 1 of the conventional medications described in the table below

Conventional Medication	Criteria for Inadequate Response, Loss of Response, or Intolerance
Corticosteroid	Corticosteroid-refractory colitis defined as signs or symptoms of active UC despite taking oral prednisone, or equivalent oral corticosteroid, at doses of 30 mg/day for 2 weeks. Exception: budesonide MMX and beclomethasone dipropionate gastro-resistant prolonged-release tablet are not included in this category.
	Corticosteroid-dependent colitis defined as an inability to taper or reduce corticosteroid dose below the equivalent of prednisone 10 mg/day within 3 months of starting corticosteroids without a return of signs or symptoms of active UC, or a relapse 3 months after completing a course of corticosteroids.
	History of intolerance of corticosteroids defined as AEs including, but not limited to cataracts T β—„„. . β syndrome hyperglycemia hypertension osteopenia/osteoporosis, or neuropsychiatric AEs, including insomnia
Immunomodulator	Signs or symptoms of persistently active UC despite 3 months treatment with 1 of the following: oral AZA 4 A:E)' .;".;≤x 5)or 6-MP 4 =:ŒE)' .;".;≤x 5 oral AZA or 6-MP within a therapeutic range as judged by thioguanine metabolite testing, or a combination of a thiopurine and allopurinol within a therapeutic range as judged by thioguanine metabolite testing.
	History of intolerance to at least 1 immunomodulator listed above defined as AEs including, but not limited to

	• nausea/vomiting • abdominal pain • pancreatitis • liver function test abnormalities, and • lymphopenia/blood dyscrasias

Additionally, CCI [redacted]

CCI [redacted]

9b. Biologic/JAK/S1P-failed participants

A biologic/JAK/S1P-failed participant is one who had an inadequate response to, a loss of response to, or an intolerance to 1 of the medications listed below.

Medications used to qualify the participant for entry into this category must be approved in the US, UK, or European Union for the treatment of UC. Investigators must be able to document an adequate course of the medication.

Biologic/JAK/S1P-failed Categories	Criteria for Inadequate Response, Loss of Response, or Intolerance
Anti-TNF for example, adalimumab, golimumab, infliximab **JAK inhibitor** for example, tofacitinib, upadacitinib **Anti-integrin** vedolizumab only **S1P receptor modulator** for example, ozanimod	Signs and symptoms of persistently active disease despite completion of the induction dosing regimen that is indicated in the relevant product label.
	Recurrence of signs and symptoms of active disease after prior clinical benefit during approved maintenance dosing.
	History of intolerance, 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.

Note: Participants who discontinue these therapies for reasons other than stated above do not qualify for criterion 9b.

CCI [redacted]

Participants previously exposed to investigational therapies for the treatment of UC must still meet conditions stated in **9a** OR **9b**.

10. If participants are receiving 1 of these permitted therapies, they should continue the stable dose regimen during Study Periods I and II, as detailed in Section 10.10.
    - Oral 5-aminosalicylic acid and sulfasalazine therapy if the prescribed dose has been stable for CCI prior to the screening endoscopy.
    - Oral corticosteroid therapy (prednisone ≤20 mg/day or equivalent, or budesonide extended-release ≤9 mg/day tablets [budesonide MMX], or beclomethasone dipropionate [gastro-resistant, prolonged-release tablet] 5 mg/day) if the prescribed dose has been stable for CCI before the screening endoscopy.
    - AZA, 6-MP, and methotrexate if the prescribed dose has been stable for CCI before the screening endoscopy.
11. Agree to abstain from recreational or medicinal marijuana use during the study.

Study procedures

12. Are willing and able to complete the scheduled study assessments and procedures, including venous access sufficient to allow blood sampling, endoscopy procedures, and completion of daily diary entries and study site questionnaires.
13. Have clinically acceptable central laboratory results during screening, as defined in the CCI

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

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Gastrointestinal exclusion criteria

14. Have a current diagnosis of
    - CD
    - inflammatory bowel disease-unclassified, formerly known as indeterminate colitis, or
    - ulcerative proctitis, disease limited to the rectum, that is, distal to the recto-sigmoid junction, which lies approximately 10 to 15 cm from anal verge.
15. Have an inherited immunodeficiency syndrome or a monogenic cause of UC-like colonic inflammation.
16. Have a history of the following bowel, intestinal or intra-abdominal surgeries
    - extensive colonic surgery for UC or for other reasons, such as subtotal colectomy, or are likely to require surgery for the treatment of UC during the study.
      - Participants who had limited colonic surgery for UC, such as a segmental resection, may be allowed in the study after discussion with the medical monitor.
    - any small bowel or colonic surgery within [redacted] months prior to Visit 2, or
    - any non-intestinal intra-abdominal surgery within [redacted] months prior to Visit 2.
17. Have evidence of toxic megacolon, intra-abdominal abscess, or stricture/stenosis within the small bowel, colon, or rectum.

Adenoma, dysplasia, and gastrointestinal cancer

18. Have any history or current evidence of cancer of the gastrointestinal tract.
19. Have any current sporadic adenoma without dysplasia (adenomatous polyps occurring proximal to known areas of colitis), that has not been removed. If completely removed, this criterion would no longer apply.
20. Have any history or current evidence of colonic dysplasia, including
    - polypoid or non-polypoid lesion(s) of colonic mucosa in an area which is endoscopically visible or invisible, and
    - histopathology report of "indefinite for dysplasia," low-grade dysplasia, or high-grade dysplasia.

Prohibited medications

21. Have received any medication prohibited within the required screening washout period, as described in Section 10.11.
22. Have received [redacted] for any indication, including investigational use.
23. Have discontinued [redacted] due to loss of response, inadequate response, or intolerance:

    Exception: if discontinuation was due to other reasons, such as a change of insurance or well controlled disease, and the duration of exposure was [redacted] year. Consultation with the medical monitor should occur to establish eligibility.

24. Have failed >3 [redacted].
    Note: originator and biosimilar count as 1 therapy (for example, [redacted] biosimilar).

Infectious disease exclusion criteria

25. Have active TB (Section 8.2.7).
26. Have or have had LTBI that has not been treated with a complete course of appropriate therapy as defined by the WHO or the US CDC, unless such treatment is underway (Section 8.2.7).
27. Have received any live vaccine (that is, live attenuated) within 3 months prior to Visit 2, or intend to receive a live attenuated vaccine during the study. See Section. 6.8.3.
28. Have received a BCG vaccination or treatment within [redacted] months prior to Visit 2 or intend to receive BCG vaccination or treatment during the study.
29. Have HIV infection.
30. Have a current infection with HBV, that is, positive for HBsAg and/or PCR positive for HBV DNA (see Section 8.2.8).
31. Have a current infection with HCV, that is, positive for HCV RNA (see Section 8.2.8).

    Exception: Participants with a previous HCV infection that was successfully treated with antiviral therapy are not excluded.

32. Have *Clostridioides difficile* or other intestinal infection within [redacted] days of screening endoscopy, or test positive at screening for *C difficile* or for other intestinal pathogens. Participants with a confirmed diagnosis of cytomegalovirus-associated colitis should have adequate treatment and resolution of symptoms at least [redacted] months prior to screening endoscopy.
33. Have a current or recent acute, active nonserious extraintestinal infection for which signs or symptoms are present, or if current treatment is not completed [redacted] weeks prior to screening.
34. Have had any of the following types of infection within [redacted] days prior to Visit 1, or develops any of these infections before Visit 2:
    - Serious: requiring hospitalization, IV or equivalent oral antibiotic treatment, or both.
    - Opportunistic: see Section 10.8.
      Note: Herpes zoster is considered active and ongoing until all vesicles are dry and crusted over.
    - Chronic: defined as duration of symptoms, signs, or treatment of 6 weeks or longer.
    - Recurring: including, but not limited to, herpes simplex, herpes zoster, recurring cellulitis, and chronic osteomyelitis.

    Note: Participants with only recurrent mild and uncomplicated orolabial herpes, or genital herpes, or both may be discussed with the medical monitor and considered for enrollment if other study eligibility criteria are met.

35. Have serious, opportunistic, or chronic/recurring extraintestinal infections who are not adequately treated and off antibiotics for [redacted] days without recurrence of symptoms prior to Visit 1.

36. Have evidence of active/infectious herpes zoster infection or primary varicella zoster infection [redacted] weeks prior to Visit 1. Infections are considered active until all vesicles are crusted over.

Other exclusion criteria

37. Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
38. Are Eli Lilly and Company employees or employees of third-party organizations involved with the study.
39. 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.
40. Have previously completed or withdrawn from this study or any other study investigating mirikizumab after receiving study intervention. This criterion does not apply to participants undergoing rescreening procedures.
41. Have had extra-abdominal surgery and have not recovered fully following surgery,

43. Have lymphoma, leukemia, or any malignancy within 10 years prior to Visit 2.
    Exceptions:
    - Basal cell or squamous epithelial carcinoma of the skin that has been adequately treated without recurrence evidence of metastatic disease for at least [redacted] year prior to Visit 2.
    - Cervical carcinoma in situ that has been adequately treated without evidence of recurrence within [redacted] years of prior to Visit 2.
44. Have a history or presence of an underlying disease, or surgical, physical, or medical condition that, in the opinion of the investigator, would potentially affect participant safety within the study or interfere with the interpretation of data.
45. Have a known hypersensitivity to any component of mirikizumab or monoclonal antibodies.
46. Have a solid organ transplant or hematopoietic stem cell transplantation.

47. Have a blood transfusion in the last [redacted] days prior to hematology blood sample collection.
48. Are pregnant, lactating, or planning pregnancy (females only) while enrolled in the study or within [redacted] weeks [redacted] or [redacted] weeks [redacted] after receiving the last dose of study intervention.
49. Have used either recreational or medicinal marijuana within 2 weeks prior to screening endoscopy.
50. Have current or history of chronic alcohol abuse or illicit drug abuse within 1 year before Visit 1.
51. 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.

5.3. Lifestyle Considerations

Study participants should not donate blood or blood products during the study or for up to 16 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 (Sections 5.1, 5.2 and 10.4).

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and any SAE related to study procedures.

5.4.1. Allowed Rescreening of Participants after Initial Screen Failure

Individuals who have failed screening because of the following inclusion/exclusion criteria detailed in Section 5 may be rescreened when the reason for screen failure has resolved: Criterion 2 to 6, 9 to 13, 16, 19, 21, 26 to 28, 32 to 36, 39, 41, 43, 44, 47 to 50.

Participants may be rescreened up to 2 times, for a maximum total of 3 screening visits. The interval between rescreening visits should be at least 4 weeks unless a shorter interval has been agreed upon with the medical monitor. Each time rescreening is performed the individual must sign a new ICF and be assigned a new identification number.

Participants who fail screening because they are unable to complete their endoscopy within 14 days prior to Visit 2 or were unable to complete all visit procedures within the required screening window of ≤28 days prior to Visit 2, may repeat screening procedures sooner than 4 weeks between screen failure and rescreening. These participants are not required to repeat HIV or TB testing, CXR, stool cultures or *C difficile* testing if results were normal or negative during prior screening and done within the prior 3 months. However, *C difficile* retesting should be reconsidered if there is a suspicion of infection.

Participants who fail screening because of exclusion criterion 32 may be rescreened once when the reason for screen failure has resolved. It is recommended that the investigator first confirm the participant has a negative *C difficile* stool toxin/stool culture/stool ova parasite (as applicable) before performing rescreening investigations (see Section 8.2.10).

Requests to rescreen participants for eligibility criteria other than those listed above must be discussed with the medical monitor prior to rescreening.

5.4.2. Allowed Retesting of Screening Procedures

The screening procedures below may be retested once within the screening period at the discretion of the investigator:

- Screening hematology and chemistry blood tests: where 1 or more results are outside the acceptable range for inclusion in the study but may be within the acceptable range for inclusion on retesting, due to test-retest variability.
- Stool testing: if there is a technical difficulty in performing or reporting the *C difficile* or stool culture assays.
- Retesting or confirmatory testing with CCI Gold test in selected participants as part of screening for LTBI (see Section 10.9 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 reader is unable to determine the centrally read Mayo ES (for example, failure of the recording equipment).

Retesting of all other screening procedures within the screening period must be discussed with the medical monitor prior to retesting.

5.5. Criteria for Temporarily Delaying Enrollment of a Participant

This section is not applicable for this study.

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any medicinal products or medical device(s) intended to be administered to/used by a study participant according to the study protocol.

In this study, the study intervention is mirikizumab.

6.1. Study Intervention(s) Administered

All enrolled participants will receive mirikizumab.

Detailed instructions for mirikizumab administration, CCI will be provided separately by the sponsor or designee.

Sites must have resuscitation equipment, emergency medications, and appropriately trained personnel available during the CCI monitoring period.

Administration of mirikizumab should always be done after all other visit assessments are completed, as specified in SoA (see Section 1.3).

Returned study intervention should not be re-dispensed to the participants.

This table provides information about mirikizumab administration in this clinical study.

Intervention Name	Mirikizumab	
Study Period	II	III
Dosage Level(s)	CCI mg CCI	CCI mg CCI
Route of Administration	CCI	CCI via CCI mL CCI
Administration	• onsite • by authorized study personnel only • maximum rate of 10 mg/min by CCI over no less than 30 min.	• onsite • by authorized study personnel, or via self-administration by participant or caregiver, as indicated in the SoA (Section 1.3)
Participant Monitoring	CCI hour following CCI administration. Note: Longer monitoring is allowed when required by investigator practice or local standard of care	According to investigator practice or local standard of care
Authorized as Defined by EU Clinical Trial Regulation	Not authorized in EU	Not authorized in EU

Abbreviations: EU = European Union; CCI SoA = Schedule of Activities; CCI

Packaging and labeling

Study intervention, mirikizumab, will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice. Study intervention will be labeled as appropriate for country requirements.

6.1.1. Self-Administration Training

In this protocol, self-administration is defined as the [redacted] of [redacted] mg mirikizumab [redacted] by the participant or caregiver.

Completion of self-administration training is required for eligibility in the Continued Access Period.

It is recommended that self-administration training starts at Visit 6 (Week [redacted]). Training must occur during at least 2 visits and start no later than Visit 8 (Week [redacted]) for participants planning to complete self-administration training. See SoA in Section 1.3.

During self-administration, the site staff should use the Study Drug Administration Training Log to train participants on the completion of the SDAL.

After completion of self-administration training at 2 or more visits, trained participants may self-administer [redacted] mg mirikizumab [redacted] and complete the SDALs at any remaining dosing visits. At these visits, the site staff should observe the self-administration of mirikizumab and review the completion of the SDAL [redacted]. If deviations in self-administration procedures or in SDAL completion are identified, the site staff should take corrective actions, including retraining as appropriate.

6.2. Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, and administer study intervention. Exception: participants or caregivers may administer mirikizumab injections at dosing visits during or following self-administration training.

All study intervention 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 study personnel.

The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Assignment to Study Intervention

All participants will be centrally assigned to mirikizumab using an interactive web-response system. Before the study is initiated, the log in information and directions for the interactive web-response system will be provided to each site.

6.4. Blinding

This is an open-label study and all participants will receive mirikizumab. There is no blinding.

6.5. Study Intervention Compliance

Period II: [redacted] dosing

[redacted] mg mirikizumab [redacted] must be administered under medical supervision by the investigator or designee. The date and time of each dose administered will be recorded in the source documents and will be provided to the sponsor as requested.

Period III: [redacted] dosing

[redacted] mg mirikizumab [redacted] must be administered by authorized study personnel or self-administered by the participant or caregiver, per protocol training procedures. The date and time of each dose administered should be recorded in the source documents and provided to the sponsor as requested.

6.6. Dose Modification

Dose modifications are not permitted in this study.

6.7. Treatment of Overdose

There is no known antidote for mirikizumab.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.
- Initiate supportive treatment according to the participant's clinical signs and symptoms.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities (hematology and chemistry), as well as vital signs and oxygen saturation.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted.

6.8. Prior and Concomitant Therapy

Section 10.10 provides the list of permitted medications with dose stabilization guidance.

Section 10.11 provides the list of prohibited medications.

Section 6.8.1 provides corticosteroid taper instructions for participants taking oral corticosteroids.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Continued use of nonprescription herbal supplements/medicines that are taken specifically for the treatment of UC should be discussed with the medical monitor.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

All participants should maintain their usual medication regimens for concomitant conditions or diseases throughout the study, unless those medications are specifically prohibited (Section 10.11).

Stable doses of permitted UC medications, other than oral corticosteroids, should be continued, unless dose modification is required due to AEs, or dose modification is otherwise specified in Section 10.10. Other medications may be allowed if they are approved by the medical monitor.

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

Reporting of prior or concomitant therapy

Any medication or vaccine, including over-the-counter or prescription medicines, bowel preparations, vitamins, and herbal supplements; or other specific categories of interest, that the participant is receiving at the time of enrollment or receives during the study must be recorded in the concomitant medication CRF, along with:

- Reason for use
- Dates of administration including start and end dates, and
- Dosage information including dose and frequency for concomitant therapy of special interest.

6.8.1. Corticosteroid Use and Taper

Local administration of corticosteroids, for example, intranasal, inhaled, and intra-articular, is allowed if required for the management of preexisting conditions and AEs.

Periods I and II

For participants who enter the study on corticosteroid therapy, the prescribed dose must have been stable for at least 2 weeks before the screening endoscopy. The prescribed dose should remain stable for the duration Study Periods I and II.

Period III

For participants who enter the Study Period III on corticosteroids, tapering of corticosteroid therapy may be initiated at Visit 6 (Week CCI).

The investigator should use clinical judgment of the benefit/risk of steroid tapering for each individual participant as corticosteroids should be tapered as soon as possible following the recommended tapering regimen below or as preferred per local practice.

The recommended tapering schedule for oral corticosteroids (other than budesonide extended-release tablets [budesonide MMX]) is as follows:

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

The tapering schedule for oral budesonide MMX (≤9 mg/day) is to CCI of tablets from daily to every other day for CCI, followed by every third day for CCI, and then discontinue.

The recommended tapering schedule for participant receiving oral beclomethasone dipropionate (gastro-resistant prolonged-release tablet) [redacted] mg/day is to reduce tablets to [redacted] mg every other day for CCI, and then discontinue.

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

CCI are needed, consult the medical monitor.

In situations where the steroid tapering is paused, the tapering regimen (as described above) should be CCI, if possible.

6.8.2. Prohibited Medications

Administration of prohibited medications for the treatment of UC, approved or investigational, constitutes treatment failure. Use of such medications should not be withheld if, in the opinion of the investigator, failure to prescribe them would compromise participant safety. Participants who require a prohibited medication to treat their UC must be discontinued from study intervention, complete an ED visit, and a posttreatment follow-up visit.

A participant who requires a prohibited medication for a non-UC indication should be discussed with the medical monitor.

Section 10.11 provides the list of prohibited medications and details.

6.8.3. Vaccine Administration During the Study

Prohibited vaccines

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

Live attenuated vaccines such as measles, mumps, rubella, or varicella are prohibited during the study and for 3 months after the last dose of study intervention. Use of emergency vaccinations (such as rabies or tetanus vaccinations) is allowed with no timing restriction.

Allowed vaccines

Use of non-live (killed, inactivated, subunit, or RNA-based) vaccinations is allowed for all participants; however, their efficacy with concomitant mirikizumab is unknown. If a permitted non-live vaccine is needed, it is recommended that study intervention not be administered on the same day as a vaccination.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.9.

7.1. Discontinuation of Study Intervention

When necessary, a participant may be permanently discontinued from mirikizumab. If so, the participant will discontinue mirikizumab and will remain in the study to complete procedures for an ED visit, if applicable, and posttreatment follow-up, as shown in the SoA.

A participant should be permanently discontinued from study intervention (mirikizumab) if

the participant becomes pregnant during the study

in the opinion of the investigator, the participant should permanently discontinue the study intervention for safety reasons

the participant has a lack of clinical benefit or disease worsening and

- requires treatment with medication(s) at doses higher than those specified in Sections 10.10 and 10.11.

  or

- requires treatment with prohibited medications specified in Section 10.11.

the participant undergoes surgery for active UC

the participant has a systemic hypersensitivity reaction (Section 7.1.3)

the participant has a diagnosis of the following during the study:

- malignancy (except for successfully treated basal or squamous cell skin carcinoma), or
- intestinal dysplasia

the participant develops HIV infection.

the participant develops active TB or has untreated LTBI (Section 8.2.7).

HBV or HCV: the participant tests positive for HBV DNA (see Section 8.2.8.1) or tests positive for HCV RNA (Section 8.2.8.2)

Note: The HBV DNA result is to be confirmed if initial test result is positive but below the level of quantification (Section 8.2.8.1).

Prior to discontinuation of any immunomodulatory and/or immunosuppressive therapy due to hepatitis, including study intervention, it is recommended that the participant is to be referred to, evaluated, and managed by a specialist physician with expertise in evaluation and management of viral hepatitis.

The timing of discontinuation from study intervention relative to the initiation of any antiviral treatment for hepatitis is to be based on the recommendation of the consulting specialist physician, in conjunction with the investigator, and aligned with medical guidelines and standard of care.

7.1.1. Suicidal Ideation or Behavior

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

- the participant scores a 3 for Item 12 (thoughts of death or suicide) on the CCI at any time in the study, or
- the participant reports suicidal ideation or suicidal behaviors during the study.

A psychiatrist or appropriately trained professional may assist in the decision to discontinue the participant or assist in preparing a safety monitoring plan for the participant should they continue in the study.

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7.1.3. Hypersensitivity Reactions

If the investigator determines that a systemic hypersensitivity reaction has occurred related to study intervention administration, the participant may be permanently discontinued from the study intervention, and the sponsor's designated medical monitor should be notified. If the investigator is uncertain about whether a systemic hypersensitivity reaction has occurred and whether discontinuation of study intervention is warranted, the investigator should consult the medical monitor.

7.1.4. Temporary Discontinuation

Temporary withholding of study intervention is required if the participant meets any of the following infection-related criteria during the study.

Criteria for temporary discontinuation of study intervention	Next steps
Infection-related criteria	
Serious or opportunistic infections, as defined in Section 5.2	Withhold until resolution of all acute clinical signs and symptoms, and completion of all appropriate anti-infective treatment. If participant is diagnosed with LTBI, see Section 8.2.7.
A participant diagnosed with LTBI during the study	Permanently discontinue from study intervention unless the participant is a candidate for LTBI treatment, and is treated for LTBI as follows: ○ Study intervention is temporarily held for at least the CCI weeks of LTBI treatment. ○ After receiving at least [redacted] weeks of appropriate LTBI therapy (as per WHO or US CDC guidelines), if there is no evidence of hepatotoxicity (ALT/AST must remain ≤2 times ULN) or other treatment intolerance, study intervention may be resumed. ○ The participant must complete appropriate LTBI therapy to remain eligible to receive study intervention.
HBV DNA results that are reported as positive, or as detecting HBV DNA, but HBV DNA is below the level of quantification	Contact medical monitor. Repeat HBV DNA testing as soon as is feasible. If HBV DNA is confirmed as positive, then study intervention must be permanently discontinued.
Hematology Laboratory Criteria	
• Platelet count < 50.0 x 10^9/L • WBC <2.0 x 10^9/L (leukopenia) • Absolute Neutrophil Count <1.0 x 109/L (< 1.0 × 103/µL or < 1.0 GI/L) (neutropenia) • Lymphocyte count <500 cells/uL (<0.5 x 10^3/µL or <0.5 GI/L) (lymphopenia)	Contact medical monitor. Discuss timing of repeat hematology laboratory panel and term for withholding intervention.

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study:

- at any time at the participant's own request for any reason or without providing any reason
- at the request of the participant's designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons

if enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study

if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

At the time of discontinuing from the study, if possible, the participant should complete procedures for an ED visit and posttreatment follow-up, if applicable, as shown in the SoA (see Section 1.3). If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

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 or designee 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 are summarized in the SoA.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator should maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

8.1.1. Daily Electronic Diary Measures

Participants must use an electronic diary to complete these patient-reported measures daily.

1. Urgency NRS

The investigator should monitor electronic diary compliance throughout the study and provide retraining to participants as needed.

For this study, ‘stool’ is defined as a trip to the toilet when the participant has a bowel movement; or passes blood alone; or passes blood and mucus; or passes mucus only.

If the participant is not compliant with CCI

8.1.1.1. Urgency NRS

Urgency NRS is a patient-reported, single-item measure of 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”.

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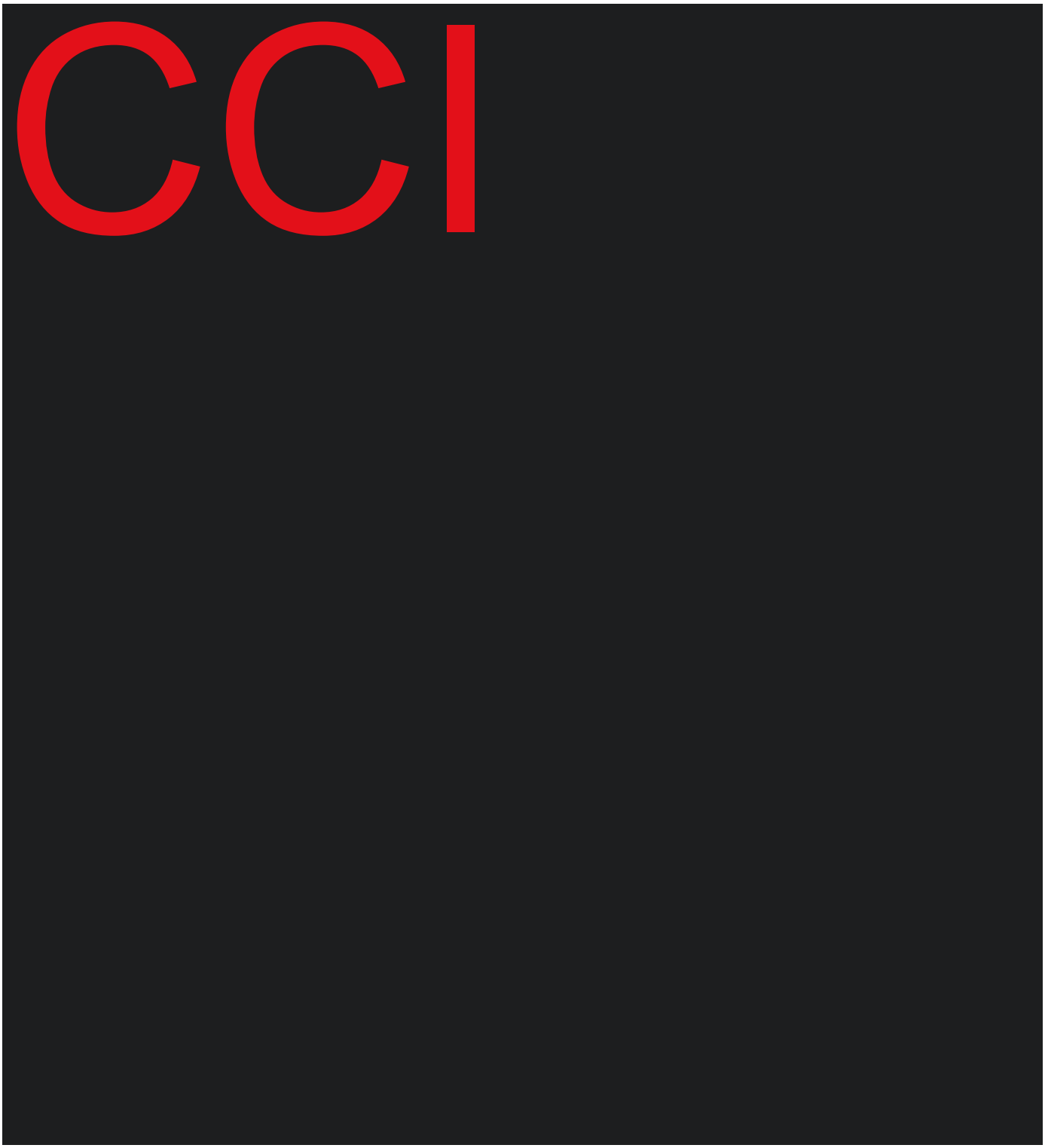
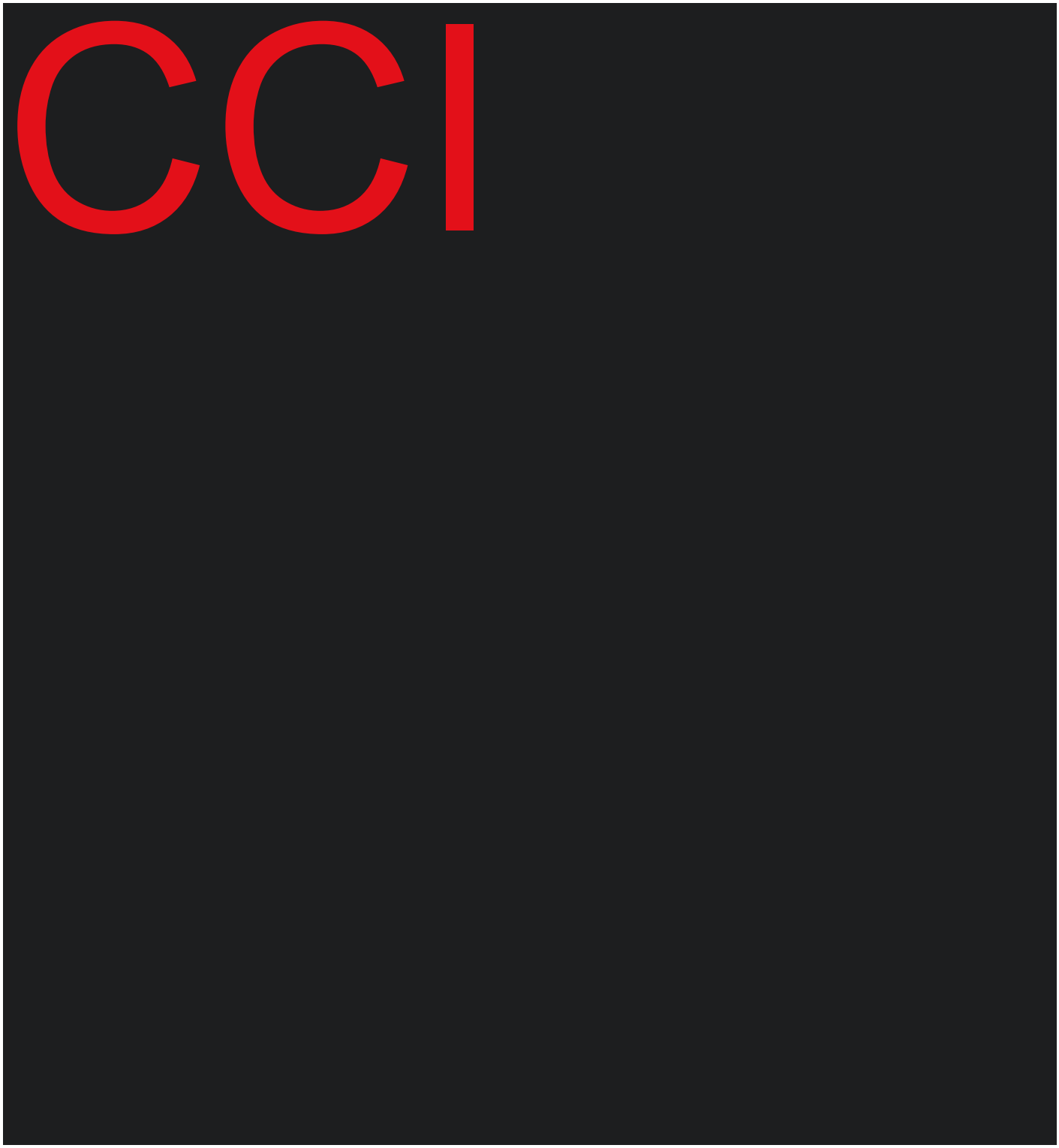
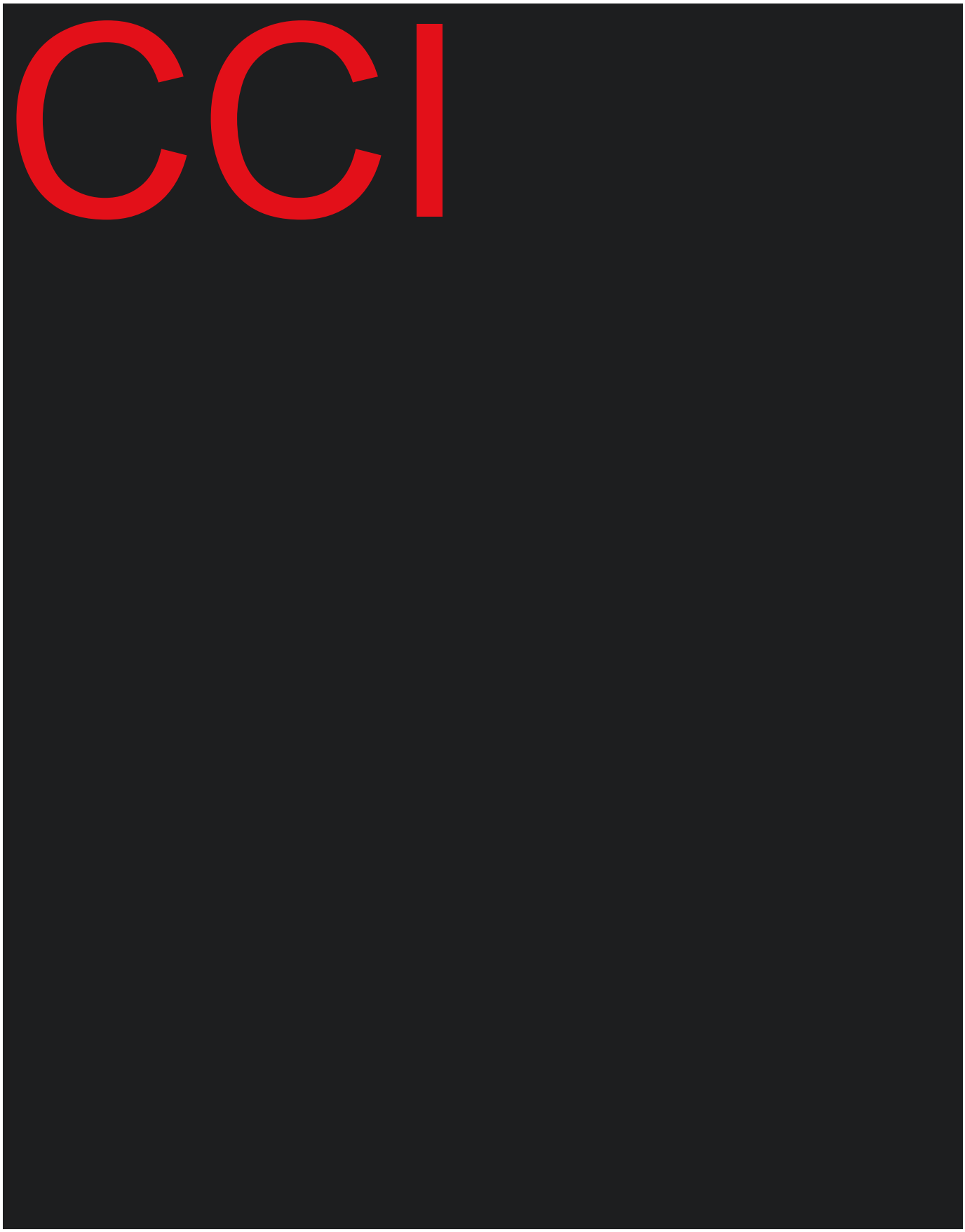


8.1.2. Patient-reported Outcomes on the Electronic Tablet

The following patient-reported measures will be completed using an electronic tablet at onsite visits, as designated in the SoA.





8.1.3. Physician's Global Assessment (PGA)

The PGA is a physician-reported measure that summarizes the investigator's assessment of the participant's UC disease activity on a 4-point scale (see Section 10.6). Consistent with regulatory guidance, the PGA will not be used as an efficacy assessment in this study.

8.1.4. Mayo Score

The Mayo score (adapted from Schroeder et al. 1987) is a composite instrument reported by participants and the physician and is comprised of the following 4 subscores:

- SF subscore (described below)
- RB subscore CCI
- ES (described below), and
- PGA (see Section 8.1.3).

The SF subscore is the number of stools reported in a 24-hour period, relative to the Normal Number of Stools for that participant in the same period, on a 4-point scale.

The ES is a physician-reported measure that indicates the worst appearance of the mucosa on flexible sigmoidoscopy or colonoscopy, on a 4-point scale. Determination of the ES is further detailed in Section 10.6. Consistent with current clinical practice and regulatory advice, the ES excludes friability from the definition of an ES of 1. Also consistent with best clinical study practice, endoscopy scores will be determined from blinded central readers.

The local endoscopy score is collected on paper and should be transcribed immediately, no more than 24 hours after reading, in the CRF. The entry of the local endoscopy is critical to initiate the blinded central reading process.

The Mayo score is CCI If the participant is not compliant CCI for at least CCI days in the CCI -days prior to bowel preparation, the Mayo score cannot be calculated.

Scoring

Each subscore is scored on a 4-point scale, ranging from 0 to 3, to give a maximum Mayo score of 12. See Section 10.6. for more details about the Mayo scoring system.

The following permutations of the Mayo score will be used in this study:

- MMS: a sum of the Mayo SF, RB, and ES, giving a maximum MMS of 9
- Partial Mayo score: a sum of the Mayo SF, RB, and PGA, giving a maximum partial Mayo score of 9

8.1.5. Endoscopy

Standard procedures

Flexible sigmoidoscopy is the standard endoscopic procedure for assessment of endoscopic disease activity in this study, except when a full colonoscopy is indicated.

A colonoscopy can be performed instead of flexible sigmoidoscopy within this study for surveillance, or for other clinically indicated reasons, per investigator discretion (see Section 8.1.5.2).

8.1.5.1. Study-required Endoscopies

Endoscopies will be used to determine the Mayo ES at the time points described in the SoA (Section 1.3).

Visit 1 screening

It is highly recommended that the investigator confirm the participant meets other screening criteria for inclusion in the study before performing the Visit 1 screening endoscopy (see Sections 5.1 and 5.2).

Visit 6

The investigator should ensure the participant is compliant with electronic diary daily completion, particularly during the 7 days prior to bowel preparation.

Visit 10

The investigator should ensure the participant is compliant with electronic diary daily completion, particularly during the 7 days prior to bowel preparation.

For participants otherwise eligible for the Continued Access Period, the Visit 10 endoscopy must be completed prior to initiating Visit 501 (see Section 10.12).

8.1.5.2. Surveillance Colonoscopy Requirements

Requirements for a surveillance colonoscopy with biopsies for colorectal dysplasia and cancer, with documented negative results, are as follows:

- Participants with a history of UC for [redacted] years are to have had a surveillance-colonoscopy with biopsies completed within the past [redacted] years prior to Visit 2.
- Participants with primary sclerosing cholangitis, regardless of duration of UC diagnosis, are to have had a surveillance colonoscopy with biopsies completed within the [redacted] year prior to Visit 2.

If a potential participant has not had a surveillance colonoscopy with biopsies, as described above, or does not have the required documentation of negative results for colorectal dysplasia and cancer, the investigator should perform a colonoscopy with biopsies as the endoscopic procedure at Visit 1 to meet surveillance eligibility criteria and study requirements.

Surveillance biopsies should be collected and sent to a local laboratory for testing and documentation of results.

Participants should remain up-to-date with their surveillance colonoscopy requirement during the study, including the Continued Access Period if relevant. If needed for continued eligibility, colonoscopy with biopsies should be the endoscopic procedure at Visit 10 (Week [redacted]) to meet both surveillance eligibility criteria and study requirements.

8.1.5.3. Procedural Requirements for Endoscopies

Endoscopist qualifications

The endoscopist must be a licensed physician who is qualified by education, training, and experience to perform endoscopies.

Investigators may delegate endoscopy to other qualified individuals.

Anyone performing endoscopy must receive training from the sponsor or designee in the determination and calculation of the Mayo ES.

Video procedures

All study endoscopies and endoscopic procedures should be video recorded using a storage medium provided by the sponsor or designee. The video images must be sent for independent central reading. An endoscopy video instruction manual from the central reading laboratory will outline the standard study procedures used to capture and transmit video recordings of endoscopic procedures throughout the study.

The central readers will determine the Mayo ES at each endoscopy in a blinded manner.

Disagreement between the site readers and central readers will be resolved using an established adjudication process.

The central reading laboratory must provide the final Mayo ES to the sites prior to Visit 2 for determination of the MMS to confirm study eligibility (see Section 5.1).

8.1.5.4. Endoscopic Biopsies

Eligibility requirements

A histopathology report supporting the diagnosis of UC must be available in the source documents prior to study enrollment, to satisfy the inclusion criteria for this study.

If a histopathology report is not available, the investigator may obtain additional biopsies for this purpose at the screening endoscopy and send these to the local histopathology laboratory.

Study endoscopic biopsies

Biopsies will be obtained at each endoscopy to support assessment of the exploratory histopathology endpoints and their association with gene expression in this study and, where permitted by local regulations and ERBs, for the assessment of exploratory biomarkers.

Endoscopic Biopsy Sample Collection	
Sample number, segment, and purpose	N = CCI biopsy samples collected per endoscopy (Visits 1, 6, and 10) • CCI (for exploratory biomarker analyses) • CCI (for exploratory biomarker analyses)
Sample segment and area, by visit	Visit 1: • within the defined segment CCI collect from worst affected area Visits 6 and 10 CCI • within the defined segment CCI collect from worst affected area, even if area within the segment is not the same as Visit 1/screening. • if no affected area is visible within the defined segment, collect from same general area as screening.

In rare circumstances, the investigator may consider it unsafe to collect all required biopsies. In this situation, fewer biopsies may be collected.

Biopsies will be sent to the central study laboratory for processing. A detailed biopsy reference guide from the central reading laboratory will outline the procedures to be used for biopsy collection, secure specimen transfer, processing, slide preparation, and digitization of slides for histopathologic scoring. These results will not be made available to study sites.

8.1.6. Histopathology Scoring Instrument

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

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examination

The physical examination should include evaluation of the heart, lungs, abdomen, peripheral lymph nodes and visual examination of the skin, and exclude pelvic, rectal, and breast examinations unless clinically indicated.

Symptom-directed physical assessments should be performed as specified in the SoA to evaluate specific symptoms reported by the participant.

A physical examination may be repeated at the investigator's discretion at any time a participant presents with physical complaints.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Extraintestinal manifestations

Review of extraintestinal manifestations will be performed at the time points described in the SoA (Section 1.3). Extraintestinal Manifestations include

ankylosing spondylitis
aphthous stomatitis
arthralgia
autoimmune hepatitis
cholelithiasis
deep vein thrombosis
episcleritis
erythema nodosum
iritis
osteopenia
osteoporosis
pancreatitis
peripheral arthritis
primary sclerosing cholangitis
pyoderma gangrenosum
nephrolithiasis
sacroiliitis
skin vasculitis, and
uveitis

8.2.2. Vital Signs

Measurements of vital signs (body temperature, blood pressure, and pulse rate) should be conducted at the study visits specified in the SoA. Measure vital signs with the participant in the seated position with feet on the floor, after sitting quietly for at least 5 minutes.

Any clinically significant findings from vital sign measurement that result in a diagnosis and that occur after the participant receives the first dose of mirikizumab should be reported as an AE via CRF.

8.2.3. Electrocardiograms

Collect the screening ECG at least 30 minutes prior to blood sample collections. The participant should be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during the ECG.

If deemed clinical necessary, ECGs may be obtained at additional times.

ECGs should be interpreted by the investigator or qualified designee at the study site as soon after the time of ECG collection as possible, and ideally while the participant is still present, to determine whether the participant meets the study entry criteria and for immediate participant management, if any clinically relevant findings are identified.

8.2.4. Clinical Safety Laboratory Tests

See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.

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

- The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a source document agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study including the CCI post-treatment follow-up period should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the medical monitor and sponsor notified.
    - All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.
- If laboratory values from non-protocol specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator (for example, SAE or AE or dose modification), then report the information as an AE.
- 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.

8.2.5. Pregnancy Testing

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

Female participants of childbearing potential should undergo a urine pregnancy test, performed locally, at visits indicated in the SoA through Week CCI. The urine pregnancy test must be "negative" within 24 hours prior to administration of mirikizumab at every study visit.

Urine pregnancy testing may be performed at additional time points during the treatment period 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 10.4. FSH levels can be optionally obtained during screening or during the study, at the discretion of the investigator to determine postmenopausal status (see Section 1.3).

8.2.6. Suicidal Ideation and Behavior Risk Monitoring

Suicide ideation and behavior will be assessed at screening with the administration of the CCI . Depressive symptomology will be assessed with the CCI during the study, at visits specified in the SoA (Section 1.3).

These assessments are described below, and further information is provided in Section 10.7.

Participants should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of study intervention. Participants who experience signs of suicidal ideation and behavior should undergo a risk assessment. All factors contributing to suicidal ideation and behavior should be evaluated and consideration should be given to discontinuation of the study intervention.

8.2.7. Tuberculosis Testing and Monitoring

Screening

During screening, all participants will be assessed for risk factors, symptoms, and signs of TB with all of the following:

- Thorough history to determine the lifetime risk factors for TB infection, for TB progression, and for symptoms or signs of active TB.
- Signs of previous or active TB by means of

- Thorough physical examination for signs of active TB, including measurement of body temperature and assessment of peripheral lymph nodes.
- A high-quality CXR (PA, including a lateral view if needed) interpreted and reported by a radiologist or pulmonologist (see Section 8.2.7.1).

All participants with no history of LTBI or active TB, and no history of positive Mantoux tuberculin skin test using purified protein derivative or positive *Mycobacterium tuberculosis* [redacted], must have an [redacted] for *M tuberculosis,* using [redacted] gold test. For details about these tests, see Section 10.9.

Participants diagnosed with LTBI

Guidance when participants are diagnosed with LTBI during screening

Participants diagnosed with LTBI are excluded (Section 5.2) unless they are candidates for LTBI treatment, are treated for LTBI, and the following criterion are met:

- After receiving at least 4 weeks of appropriate LTBI therapy (as per WHO or the United States CDC guidelines), there is no evidence of hepatotoxicity (ALT/AST must remain ≤2 times ULN) or other treatment intolerance. In this case, the participant may be rescreened (Section 5.4) and is not excluded due to LTBI.

Guidance when participants are diagnosed with LTBI during the study

- The participant must continue and complete appropriate LTBI therapy to remain eligible to continue to receive study intervention (Sections 7.1 and 7.1.4)

Monitoring during the study

For all participants, monitoring for TB will be continuous throughout the study. At a minimum, each participant will have the following documented at least every 3 months

- thorough history to determine any risk factors for TB infection and for TB progression, symptoms, or signs of active TB, and
- thorough physical examination that includes assessment for signs of active TB, including measurement of body temperature and assessment of peripheral lymph nodes.

8.2.7.1. Chest Imaging

Collect a high-quality CXR (PA view and, if needed, a lateral view), interpreted and reported by a radiologist or pulmonologist as specified in the SoA (Section 1.3).

Exception: Participants do not need to have a CXR at screening if, in the opinion of the investigator, both of these 2 conditions are met:

- a 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.

For each participant, the CXR films, images, or a radiology report must be available to the investigator for review before the participant is assigned treatment.

Note: Results of a chest computed tomography scan or other imaging study similar to a CXR ’ x)y≥) β≥≤)-„,β≠≥x≤)×μ)≠–≥)To i)μ×Δ)k S)≥- x‘ x≠–×„,8)-„,)z×„,β ‘≠x≠–×„,)↓. -≠–)≠–≥)β○×„,β×Δβ)’ ≥≤-zx‘) monitor.

8.2.8. Hepatitis B and C Testing and Monitoring

8.2.8.1. Hepatitis B Testing and Monitoring

As specified in the SoA (Section 1.3), initial testing for HBV infection includes HBsAg and anti-HBc.

If HBsAg is positive, the participant is excluded.
If HBsAg is negative and anti-HBc is negative, the participant is not excluded.
If HBsAg is negative and anti-HBc is positive, further testing for HBV DNA is required.

- If the screening HBV DNA is positive, the participant is excluded.
- If the screening HBV DNA is negative, the participant is not excluded. Repeat testing for HBV DNA is required at least every 3 months during the study.

Management of enrolled participants with detectable HBV DNA during the study

If HBV DNA is detected, study intervention will be temporarily withheld or permanently discontinued, as described in Section 7.1, and the participant should receive appropriate follow-up medical care.

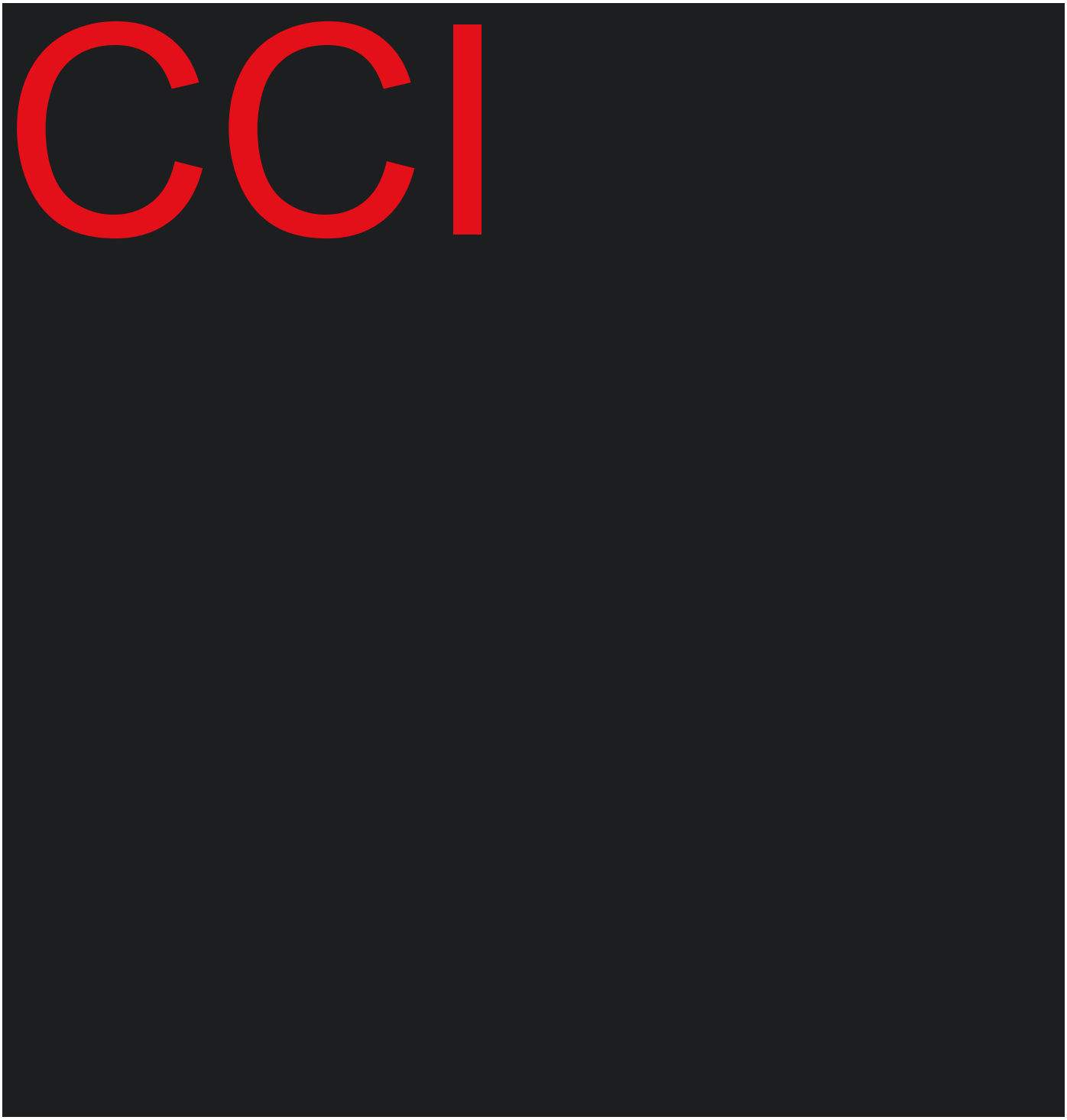
8.2.8.2. Hepatitis C Testing

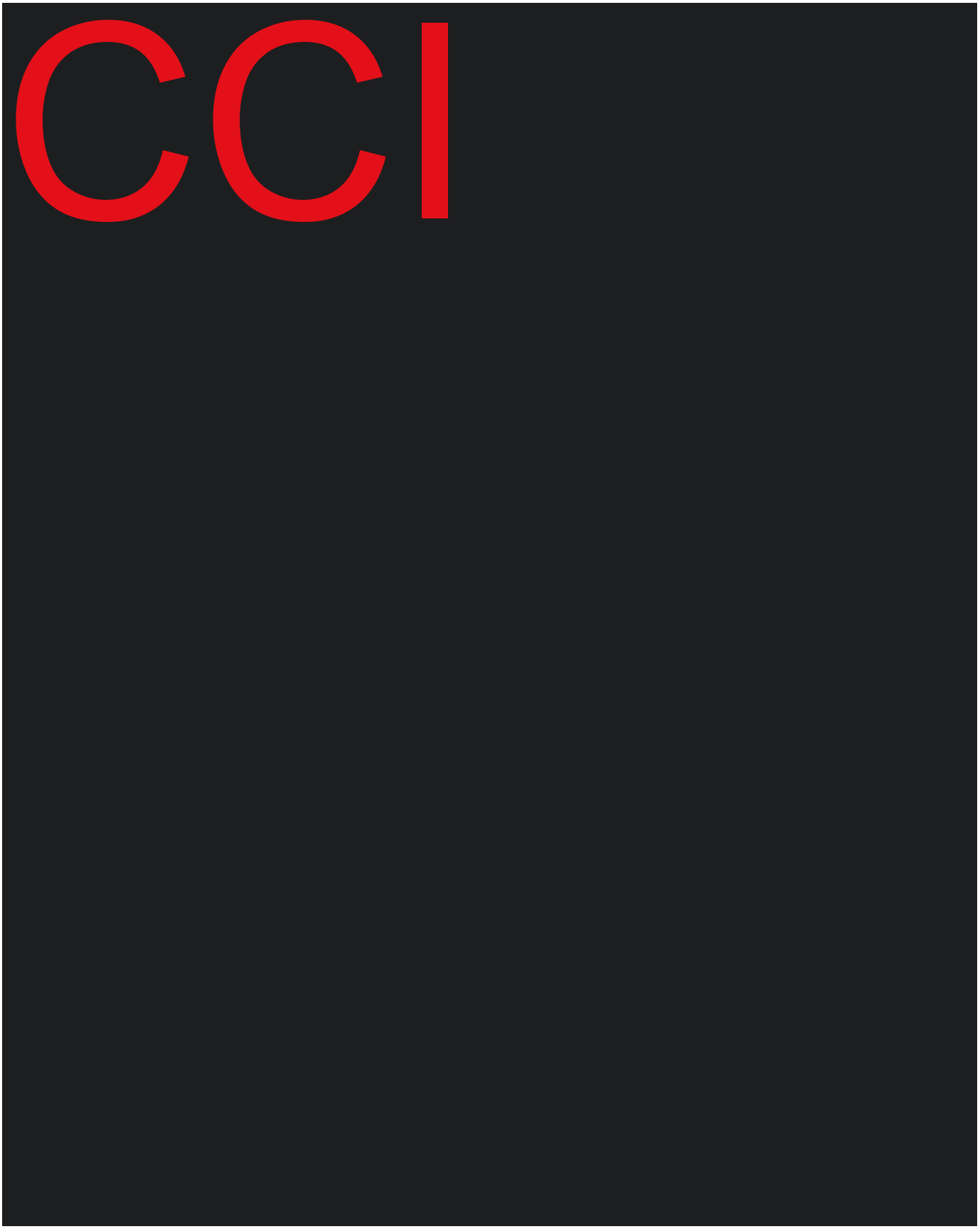
As specified in the SoA (Section 1.3), initial testing for HCV infection includes testing for anti-HCV.

If anti-HCV is positive, a test for circulating HCV RNA is required.
If HCV RNA test is negative, the participant is not excluded.
If HCV RNA test is positive, the participant is excluded (see Section 5.2).

Participants who have had HCV infection and have been successfully treated, defined as a sustained virologic response (HCV RNA by PCR negative for at least 24 weeks following treatment completion) are not excluded on the basis of HCV as long as HCV RNA test is negative at screening.

If HCV RNA is detected during the study, the study intervention will be discontinued (Section 7.1), and the participant should receive appropriate follow-up medical care.





8.2.10. Screening Stool Testing

Stool culture

Participants must have a negative stool culture from which no enteric pathogens are isolated to participate in the study.

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.

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 CCI days, or
  - if antibiotics were not prescribed, CCI days or more has elapsed since resolution of acute symptoms and signs associated with the underlying intestinal infection.

To confirm that the reason for screen failure (positive stool culture) has resolved, it is recommended that the investigator performs a local stool culture test before rescreening. Upon rescreen (Visit 1), a negative stool culture result from the central lab is required to meet this eligibility criterion.

Additional local stool culture/testing is allowed at the investigator's discretion or based on country requirements.

***C difficile* toxin testing**

This assay tests for the presence of *C difficile* toxin protein, followed by a confirmatory test for *C difficile* toxin gene expression in the stool sample.

Participants should test negative for *C difficile* to receive mirikizumab. Retesting is allowed within the same screening period if there is a technical difficulty in performing or reporting the *C difficile* assays, or if in the judgment of the investigator, the participant's symptoms or signs are not consistent with *C difficile* infection.

Participants who test positive at screening for *C difficile* can be rescreened once for the study, once they have been adequately treated and off antibiotics for [redacted] 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 [redacted] days after completing their therapy.

To confirm that the reason for screen failure (positive *C difficile*) has resolved, it is recommended that the investigator performs a local *C difficile* test before rescreening. Upon rescreen (Visit 1), a negative *C difficile* result from the central lab is required to meet this eligibility criterion.

8.3. Adverse Events, Serious Adverse Events, and Product Complaints

The definitions of the following events can be found in Section 10.3, Appendix 3:

- AEs
- SAEs
- PCs

These events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet these definitions and remain responsible for following up events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7.1).

Care will be taken not to introduce bias when detecting events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about event occurrences.

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 8.3.3) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). For PCs, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Section 10.3.

8.3.1. Timing and Mechanism for Collecting Events

This table describes the timing, deadlines, and mechanism for collecting events.

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	Signing of the ICF	Participation in study has ended	As soon as possible upon site awareness	AE CRF	N/A
Serious Adverse Event					
SAE and SAE updates prior to start of study intervention **and** deemed reasonably possibly related to study procedures	Signing of the ICF	Start of intervention	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE and SAE updates after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE[a] after ○xΔ‡z–⊖x„ǂβ) study participation has ended **and** the investigator becomes aware	After ○xΔ‡z–⊖x„ǂβ) study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	16 weeks after the last dose	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	PC form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	PC form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed PC form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	PC form	

AE = adverse event; CRF = case report form; ICF = informed consent form; N/A = Not applicable; PC = product complaint; SAE = serious adverse event

[a] Serious adverse events should not be reported unless the investigator deems them to be possibly related to study treatment or study participation.

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive mirikizumab.

After learning of a pregnancy in the female partner of a study participant, the investigator will

- obtain a consent to release information from the pregnant female partner directly, and
- within 24 hours after obtaining this consent will record pregnancy information on the appropriate form and submit it to the sponsor.

The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than CCI weeks following the estimated delivery date. Any termination of the

pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than CCI weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at CCI weeks gestational age) or still birth (occurring at CCI weeks gestational age) is always considered to be an SAE and will be reported as such.

Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in protocol Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention. If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

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

8.3.3. Adverse Events of Special Interest

The AESIs for this program may include but are not limited to:

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

8.4. Pharmacokinetics

In the event of a potential systemic drug hypersensitivity reaction or CCI related event, venous blood samples approximately CCI each 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. The actual date and time (24-hour clock time) of each sampling will be recorded. 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.

The sample retention is described in Section 10.1.12.

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

Genetics are not evaluated in this study.

8.7. Biomarkers

Whole blood, stool, and endoscopic biopsy tissue samples for exploratory biomarker research will be collected at the times specified in the SoA (Section 1.3) where local regulations allow. See Section 8.1.5.4 for details on endoscopic biopsy tissue samples.

Exploratory biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics, 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 CCI

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

Sample retention is described in Section 10.1.12.

8.8. Immunogenicity Assessments

In the event of a potential CCI or an CCI reaction and at visits and times specified in SoA (Section 1.3), venous blood samples will be collected to determine antibody production against mirikizumab. Additional samples may be collected at the final visit from participants who discontinued mirikizumab or were withdrawn from the study due to a CCI event or an CCI reaction.

Antibodies may be further characterized for their ability to neutralize the activity of mirikizumab.

To interpret the results of immunogenicity, a venous blood PK sample will be collected at the same time points to determine the concentrations of mirikizumab.

Sample retention is described in Section 10.1.12.

9. Statistical Considerations

The SAP will be finalized prior to first participant visit, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.1. Statistical Hypothesis

The primary objective is to assess the improvement from baseline in UNRS in participants treated with mirikizumab at Week [redacted]. No formal hypothesis testing will be performed on the primary endpoint.

9.1.1. Multiplicity Adjustment

Multiplicity control is not applicable for this study.

9.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Population	Description
Full Analysis Set	All participants who are assigned to treatment and receive at least 1 (partial or complete) dose of study treatment
Safety Analysis Set	All participants who are assigned to treatment and receive at least 1 (partial or complete) dose of study treatment

9.3. Statistical Analyses

9.3.1. General Considerations

Statistical analysis of this study will be the responsibility of the sponsors or their designees.

Handling of missing, unusable, and spurious data will be addressed prospectively in the overall statistical methods described in the protocol and in the SAP, where appropriate. Any change to the data analysis methods in the protocol will require an amendment only if it changes a principal feature of the protocol. Additional exploratory analyses of the data will be conducted as deemed appropriate.

When reported, descriptive statistics will include the number of participants; mean, standard deviation, median, minimum, and maximum for continuous measures; frequency counts and percentages for categorical measures; and estimates and 95% confidence intervals for correlation coefficients.

9.3.2. Primary Endpoint Analysis

As described in Section 3, the primary endpoint is change from baseline in UNRS score at Week [redacted]. The UNRS score at each time point (baseline and Week [redacted]) will be summarized as a continuous measure for each participant as the average daily diary score over a [redacted]-day period. The difference between the UNRS score at Week [redacted] and at baseline will be calculated for each participant and averaged. Diary data from at least [redacted] of the [redacted] days from the specified period are

required to calculate the average UNRS score and change from baseline, otherwise these endpoints will be considered missing. Further details regarding the primary estimand are described in Section 3.

CCI [redacted]

9.3.3. Secondary Endpoint Analysis

Secondary endpoints and estimands are presented in Section 3. Descriptive summaries and confidence intervals will be provided for continuous and binary secondary endpoints as indicated in Section 9.3.1. Further details regarding endpoint definitions and analysis methods will be described in the SAP.

9.3.4. Exploratory Analysis

Exploratory endpoints are presented in Section 3. Details of the analyses of these endpoints, as well as additional exploratory analyses, will be described in the SAP or additional supplemental SAP, as appropriate.

9.3.5. Safety Analyses

Safety will be assessed by describing the following: including, but not limited to, AEs, laboratory analytes, vital signs, participant characteristics, and AESIs (Section 8.3.3).

The AEs will be coded according to the MedDRA. A TEAE is defined as an event that first occurred or worsened in severity after baseline. The MedDRA Lowest Level Terms 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. TEAEs (all and by maximum severity), SAEs, including deaths, and AEs that lead to treatment discontinuation will be summarized and analyzed by MedDRA system organ class and PT or by PT alone.

Laboratory and vital sign measurements will be summarized using boxplot displays and treatment-emergent shifts to low/high tables. Further analyses may be performed as deemed necessary. Potential AESIs will be identified by 1 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.

This study also includes assessment of tolerability and acceptability of the CCI [redacted] dose regimen through the summarization of AEs reported as CCI [redacted] reactions and pain, as well as treatment discontinuations as defined in the SAP. Reports of CCI [redacted] pain will include the assessment of severity (mild, moderate, or severe). Data from these assessments will be reviewed regularly throughout the study by the medical team as part of the trial level safety reviews.

All safety analyses will be fully detailed in the SAP.

9.3.6. Other Analyses

9.3.6.1. Subgroup Analyses

Subgroup analyses for selected endpoints in Section 3 may be conducted. Subgroups to be evaluated may include CCI [redacted] A detailed description of the subgroup variables and analyses will be provided in the SAP.

Analyses specifically requested by regulatory agencies will be identified and implemented as deemed appropriate.

9.3.6.2. Pharmacokinetic Analyses

No pharmacokinetic analysis will be conducted for this study.

9.4. Interim Analysis

No interim analyses are planned for this study. However, if needed for regulatory interactions or publication purposes, an interim analysis may be performed after completion of Period II.

9.5. Sample Size Determination

Approximately 160 participants will be assigned to study intervention. The sample size was determined by considering the precision of the estimated correlation between endpoints. Simulations were performed for both binary and continuous measures where the true correlation varied between CCI [redacted] The average half width of the 95% confidence intervals for the correlations at Week CCI [redacted] varied between CCI [redacted] under considered assumptions for an overall sample size of 160. The average half width of the 95% confidence intervals varied between CCI [redacted] for endpoints during the maintenance period under the assumption that CCI [redacted] of participants could discontinue early from the study.

Additionally, the proposed sample size of 160 participants is considered sufficient to have CCI [redacted] power to detect a significant (non-zero) change from baseline in UNRS at Week CCI [redacted] (primary endpoint).

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 ICH Good Clinical Practice (GCP) Guidelines, and

applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, 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.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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 study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity

Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or ǂ–≥)„– ≥∫ʼn . xǂ×Δβ representative will explain the nature of the study, including the risks and benefits, to the potential participant and answer all questions regarding the study.

Potential participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection 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 was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

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 and is kept on file.

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

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or tissue samples 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 ǂ–≥)○xΔ‾z ○x„ǂ β 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 who will be required to give consent for their data to be used as described in the informed consent. This is done by the site personnel through the informed consent process.

The participant must be informed through the informed consent by the site personnel that their 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.

The sponsor has processes in place to ensure data protection, information security, and data integrity, including data transfer, unauthorized access, disclosure, dissemination, alteration, or loss of information or personal data. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach. The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. These processes are compliant with General Data Protection Regulation (GDPR) data privacy regulations and the European Clinical Trial Regulation (CTR) (articles 56, 57, 58).

10.1.5. Committees Structure

Clinical event committee

An independent Clinical Event Committee with membership external to the sponsor will be responsible for cerebro-cardiovascular event adjudication. The committee will include experts with appropriate expertise in cardiovascular medicine.

The Clinical Event Committee charter will contain the final membership and detailed event definitions used for adjudication.

10.1.6. Dissemination of Clinical Study 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.

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete dataset would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

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 data 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, statistical analysis plan, clinical study report, and 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.vivli.org.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically, for example, laboratory data. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must review and confirm that data entries are accurate and complete throughout the duration of the study, by physically or electronically signing the CRF, as instructed by the sponsor. All completed CRFs must be signed prior to archival.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.

Quality tolerance limits will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study, and important excursions from the quality tolerance limits and remedial actions taken will be summarized in the clinical study report.

Monitoring details describing strategy (for example, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques, are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (for example, contract research organizations).

The sponsor or designee will perform monitoring to confirm that data transcribed into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the clinical trial agreement (CTA) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

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

Data capture system

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

An EDC will be used in this study for the collection of CRF 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 CRF.

Additionally, clinical outcome assessment data (participant-focused outcome instrument) and other data, such as SDAL, will be collected by the participant, via a paper source document, and will be transcribed by the authorized study personnel into the EDC system.

Additionally, electronic clinical outcome assessment data (participant-focused outcome instrument) will be directly recorded by the participant or investigator site personnel, into an instrument, for example, handheld smart phone or tablet). The electronic clinical outcome assessment 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 system(s) 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 system(s). Prior to decommissioning, the investigator will receive or access an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in ǂ–≥)z≥„ǂΔ‘)- ≥„≤×Δβ)≤xǂxyxβ≥)ββ ββ’ , and reports will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Sponsor data warehouse.

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

10.1.8. 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 –„- ≥ββ. xǂ×Δβ)ββǂ≥:

Data reported on or entered in the CRF and 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.

Definition of what constitutes source data can be found in Section 10.1.7.

10.1.9. Study and Site Start and Closure

First act of recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open.

Study or site termination

The sponsor ×Δβ○×„β×Δβdesignee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to

For study termination

discontinuation of further study intervention development
For site termination

failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines

inadequate recruitment (evaluated after a reasonable amount of time) of participants by the investigator, and

total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

In xzz×Δ≤x„z≥)↓ ⊣–)⊧–≥)β○×„β×Δβ)○ y‘–zx⊧–×„)○×‘–z– , the results of this study will be submitted for publication by a peer-reviewed journal.

10.1.11. Investigator Information

Researchers with appropriate education, training, and experience, as determined by the sponsor, will participate as investigators in this clinical trial.

10.1.12. Sample Retention

Sample retention 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 become(s) commercially available for ulcerative colitis.

Sample Type	Custodian	Retention Period after Last Participant Visit[a]
Exploratory biomarkers	Sponsor or Designee	CCI
Pharmacokinetic	Sponsor or Designee	
Immunogenicity	Sponsor or Designee	

[a] Retention periods may differ locally.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed by the Lilly-designated laboratory or by the local laboratory as specified in the table below.

In circumstances where the sponsor approves local laboratory testing in lieu of central laboratory testing (in the table below), the local laboratory must be qualified in accordance with applicable local regulations.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Investigators must document their review of the laboratory safety results.

Clinical Laboratory Tests	Comments
Hematology	Assayed by Lilly-designated laboratory
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs - red blood cells)	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Leukocytes (WBCs - white blood cells)	
Absolute neutrophil count (segmented and bands) (calculated)	
Absolute count of	
Neutrophils, segmented	
Neutrophils, bands (if detected)	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBC and WBC)	
Clinical Chemistry	Assayed by Lilly-designated laboratory
Sodium	
Potassium	
Chloride	
Bicarbonate	
Total bilirubin	
Direct bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	

Clinical Laboratory Tests	Comments
Gamma-glutamyl transferase (GGT)	
Blood urea nitrogen (BUN)	
Creatinine	
Creatine kinase (CK)	
Uric acid	
Total protein	
Albumin	
Calcium	
Glucose	
Cholesterol	
Urinalysis	Assayed by Lilly-designated laboratory
Specific gravity	
pH	
Protein	
Glucose	
Ketones	
Blood	
Nitrite	
Urine leukocyte esterase	
Hormones (female)	
Urine pregnancy	Evaluated locally
Serum pregnancy	Assayed by Lilly-designated laboratory
Follicle stimulating hormone (FSH)	Assayed by Lilly-designated laboratory
HIV, hepatitis serology, and TB	
HIV testing:	
HIV antibody	Assayed by Lilly-designated laboratory
HIV RNA	Assayed by Lilly-designated laboratory
Hepatitis C Virus (HCV) testing:	
HCV antibody	Assayed by Lilly-designated laboratory
HCV RNA	Assayed by Lilly-designated laboratory
Hepatitis B Virus (HBV) testing:	
Hepatitis B core antibody (Anti-HBc)	Assayed by Lilly-designated laboratory
Hepatitis B surface antigen (HBsAg)	Assayed by Lilly-designated laboratory
HBV DNA	Assayed by Lilly-designated laboratory. Performed only for participants who test positive for Anti-HBc
Tuberculosis (TB) testing:	
CCI Gold test	Assayed by Lilly-designated laboratory (preferred) or if available, by local laboratory
Pharmacokinetic samples	Assayed by Lilly-designated laboratory
Mirikizumab concentration	
Immunogenicity samples	Assayed by Lilly-designated laboratory
Anti-mirikizumab antibodies	

Clinical Laboratory Tests	Comments
CCI	
Stool Samples	Assayed by Lilly-designated laboratory. Additional local testing (for example, for ova and parasites) is allowed at the investigator's discretion
Stool Culture	
Clostridioides difficile (C difficile) testing	Assayed by Lilly-designated laboratory. Confirmed by a test for *C difficile* toxin gene expression
Fecal calprotectin	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites
Exploratory biomarker storage samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites

CCI

10.2.1. Laboratory Samples to be Obtained at the Time of a Systemic Hypersensitivity Event

Purpose of collecting samples after a systemic hypersensitivity event

The samples listed in this appendix are not collected for acute study participant management.

The sponsor will use the laboratory tests results from these samples to characterize hypersensitivity events across the clinical development program.

When to collect samples after a systemic hypersensitivity event occurs

Collect the samples listed below if a systemic hypersensitivity event is suspected. The timing should be as designated in the table, assuming the participant has been stabilized.

Obtain follow-up predose samples at the next regularly scheduled laboratory sample collection (ideally prior to the next dose after the event) to assess post-event return to baseline values.

Timing	Laboratory Test[a]
Collect from CCI hour after the start of the event. ● Note: The optimal collection time is from CCI hr after the start of event.	CCI
Collect only if not already collected on the same day as the event. ● Note: If collecting, collect up to CCI hr after the start of the event.	

Abbreviation: CCI

[a] All samples for hypersensitivity testing will be assayed by Lilly-designated laboratory. Results will not be provided to the study site. If samples are not collected or are collected outside the specified time period, this will not be considered a protocol deviation.

What information to record

Record the date and time when the samples are collected.

Allowed additional testing for participant management

The investigator may perform additional tests locally, if clinically indicated, for acute study participant management.

10.3. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE definition

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Events meeting the AE definition

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, and vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease).

Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition.

New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

Medication error, misuse, or abuse of study intervention, including signs, symptoms, or clinical sequelae.

Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy measures. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition

Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe ŧ–x,,)≥ ○≥z≠≥)µ×Δ)ŧ–≥)○xΔŧ z ○x,,ŧ β)z×,,≤ŧ ×,,:

The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the ○xΔŧ z ○x,,ŧ β)z×,,≤ŧ ×,,:

Medical or surgical procedure, for example, endoscopy and appendectomy: the condition that leads to the procedure is the AE.

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:

Results in death

Is life-threatening

- The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the ○– β-z-x,, β)×μμ-z≥)×Δ)× ǂ○xǂ-≥,,ǂ)β≥ǂǂ-,,. .:)T×’ ○‘-zxǂ-×,,β)ǂ–xǂ)×ccur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

Results in persistent disability/incapacity

- k–≥)ǂ≥Δ’)≤-βxy-‘ǂ-)’ ≥x,,β)x)β yβǂx,,ǂ-x‘)≤-βΔ ○ǂ-×,,)×μ)x)○≥Δβ×,, β)xy-‘ǂ-)ǂ×)z×,,≤ zǂ) normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma, for example, sprained ankle, which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect

- Abnormal pregnancy outcomes, for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy, are considered SAEs.

Other situations

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood

dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Product Complaints

Product complaint

A PC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also PCs:

- deficiencies in labeling information, and
- use errors for device or drug-device combination products due to ergonomic design elements of the product.

PCs related to study interventions used in clinical trials are collected to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.

Investigators will instruct participants to contact the site as soon as possible if he or she has a PC or problem with the study intervention so that the situation can be assessed.

An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.

10.3.4. Recording and Follow-Up of AE and/or SAE and Product Complaints

AE, SAE, and product complaint recording

When an AE/SAE/PC occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE/PC [illegible] medical records, in accordance with [illegible] information is reported on the appropriate CRF page and PC information is reported on the Product Complaint Form.

Note: An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.

[illegible] records to Sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for PCs.

There may be instances when copies of medical records for certain cases are requested by Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor or designee.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs or symptoms) will be documented as the AE/SAE.

Assessment of intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the pre-defined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

[redacted]

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB in their assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor or designee.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor or designee

to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

10.3.5. Reporting of SAEs

SAE reporting via paper form

Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the sponsor.

Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

Contacts for SAE reporting can be found in SAE paper form.

10.3.6. Regulatory Reporting Requirements

SAE regulatory reporting

Prompt notification by the investigator to the sponsor of an SAE 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. Investigator safety reports will be prepared for SUSARs according to local regulatory requirements and sponsor policy. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

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.

Consistent with the EU CTR (536/2014), the sponsor has procedures that will be followed for the identification, recording, and expedited reporting of SUSARs. Upon an ‗„- ≥[β‡ . .x‡×Δβ)Δ≥○×Δ‡)×μ)x„)j RV8)‡—≥)|β○×„β×Δ)↓ —‘)≥- x‘ x‡≥)‡—≥)≤x‡x8) „z‘ ≤—. .). confirmation of relatedness and assessment of expectedness. The sponsor will submit any qualifying reports to the EudraVigilance database within the required time frame. Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and will be forwarded to investigators as necessary.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
Women of childbearing potential (WOCBP)	Adult females are considered WOCBP unless they are WNOCBP.
Women not of childbearing potential (WNOCBP)	Females are considered WNOCBP if they • have a congenital anomaly, such as Müllerian agenesis • are infertile due to surgical sterilization, or • are postmenopausal. Examples of surgical sterilization include total hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Postmenopausal state	The postmenopausal state is defined as a woman: • at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note or • aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy[a], who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a follicle stimulating hormone CCI or • 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or • aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy. [a] Women should not be taking medications during amenorrhea, such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea.

10.4.2. Contraception Guidance

WOCBP and WNOCBP may participate in this trial. See Section 10.4.1 for definitions and additional requirements related to contraception.

WOCBP who are completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship as their preferred and usual lifestyle:

	G
agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males	use periodic abstinence methods ○ calendar ○ ovulation ○ symptothermal, or ○ post-ovulation declare abstinence just for the duration of a trial, or use the withdrawal method

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or NOT in a same-sex relationship as their preferred and usual lifestyle, must do the following:

Topic	**Condition**
Pregnancy testing	Have a negative serum test result at screening. At each dosing visit, have a negative urine test result within 24 hours prior to treatment exposure. See the protocol SoA for subsequent pregnancy testing requirements.
Contraception	Agree to use 1 highly effective method of contraception, or a combination of 2 effective methods of contraception. These forms of contraception must be used for the duration of the study.

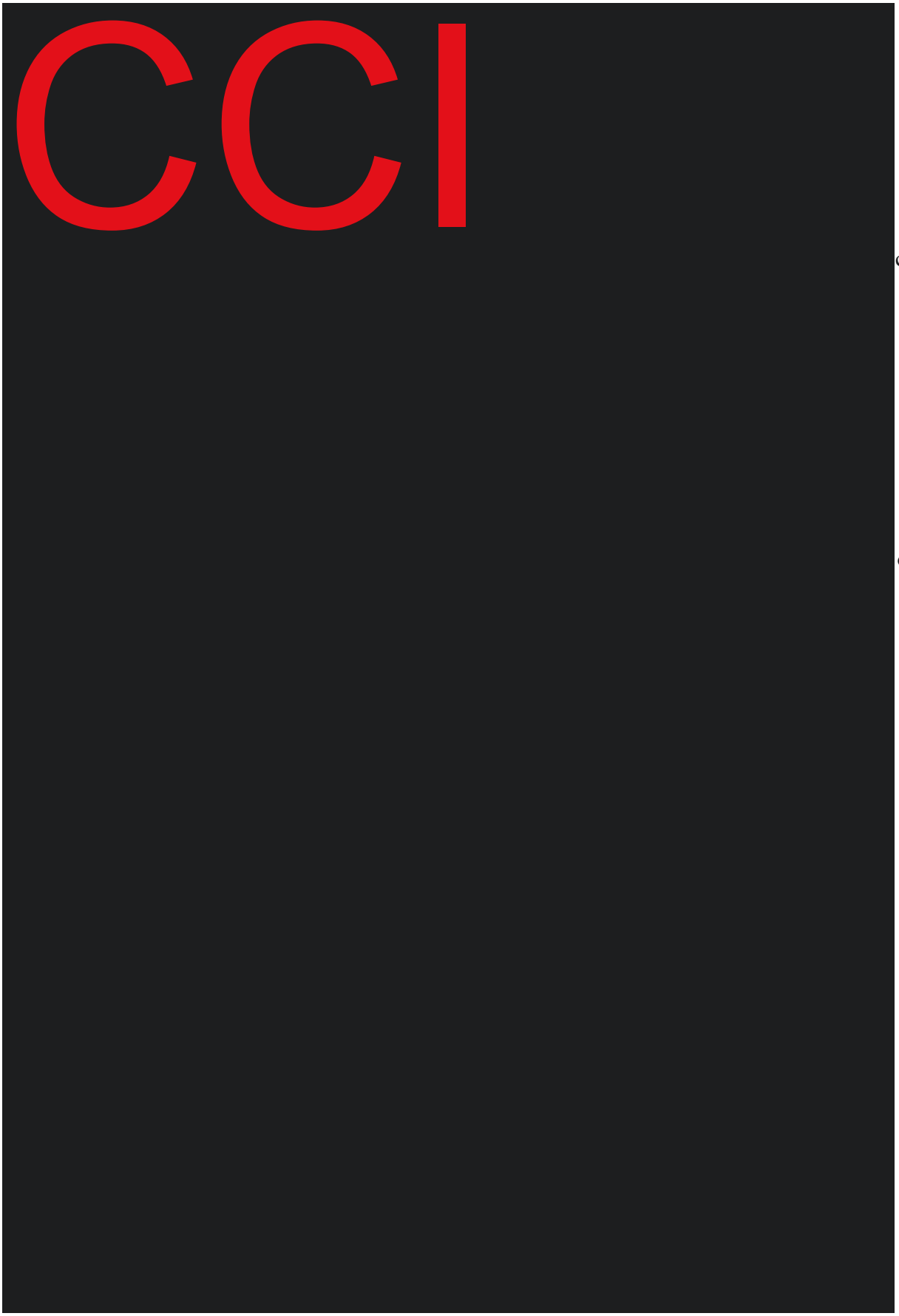
Examples of different forms of contraception:

Methods	Examples
Highly effective contraception (less than 1% failure rate)	female sterilization combination oral contraceptive pill progestin-only contraceptive pill (mini-pill) implanted contraceptives injectable contraceptives contraceptive patch (only women <198 pounds or 90 kg) total abstinence (in compliance with local requirements) vasectomy (if only sexual partner) fallopian tube implants (if confirmed by hysterosalpingogram) combined contraceptive vaginal ring, or intrauterine devices
Effective contraception	male or female condoms with spermicide diaphragms with spermicide or cervical sponges barrier method with use of a spermicide o condom with spermicide o diaphragm with spermicide, or o female condom with spermicide
Ineffective forms of contraception whether used alone or in any combination	spermicide alone periodic abstinence fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) withdrawal postcoital douche, or lactational amenorrhea

Guidance for all men

Males may participate in this trial.

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



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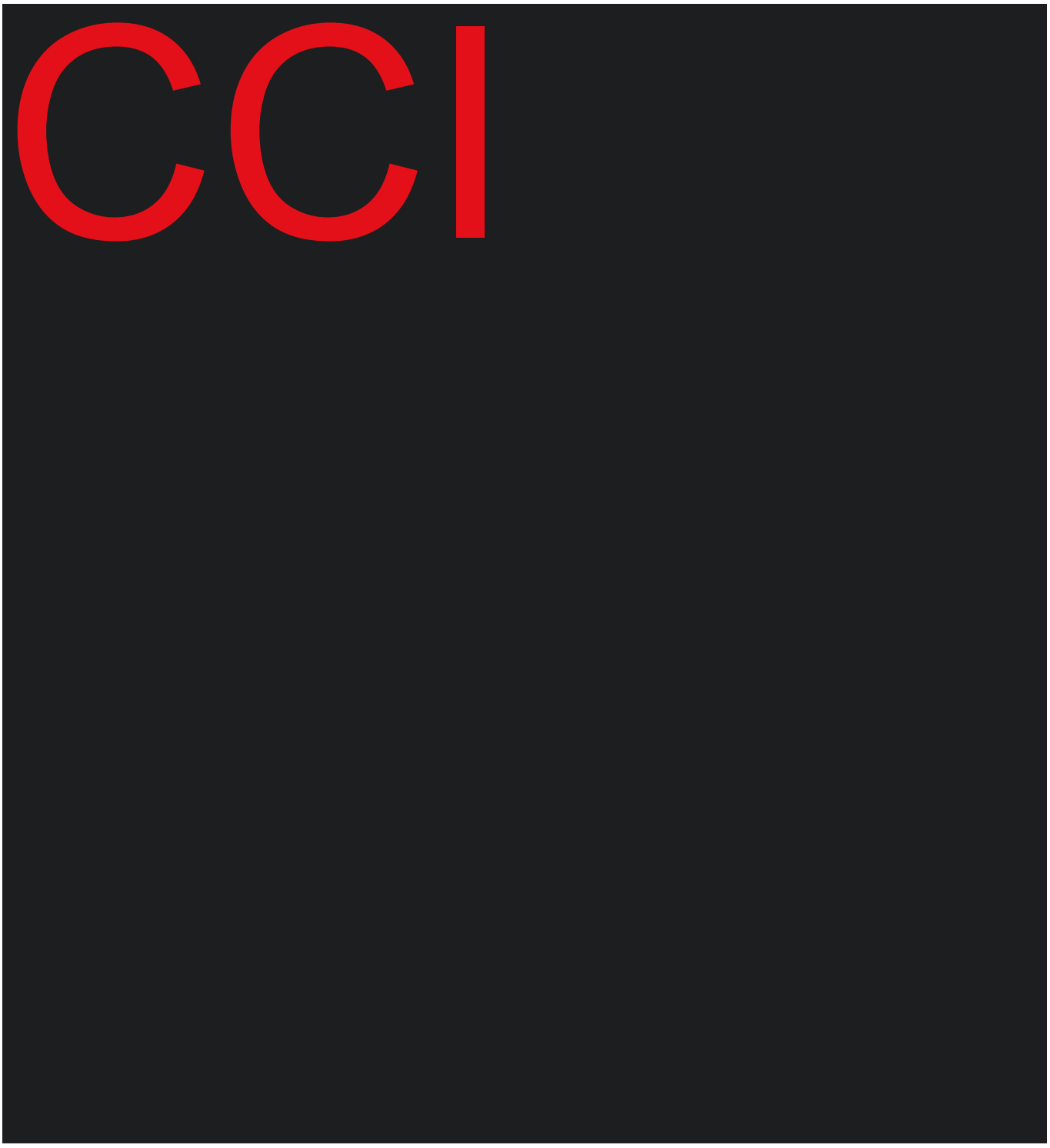
10.6. Appendix 6: Mayo Scoring System

This table describes the Mayo Scoring System for the assessment of UC disease activity.

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

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

Source: Adapted from Schroeder et al. (1987).



10.8. Appendix 8 Examples of Infections That May Be Considered Opportunistic in the Setting of Biologic Therapy

This table lists examples of infections that may be considered opportunistic in the context of biologic therapy. This table is provided to aid the investigator in recognizing infections that may be considered opportunistic. This list is not exhaustive. For data analysis, infections will be categorized by Lilly as opportunistic according to the article by CCI .

Examples of infections that may be considered opportunistic in the setting of biologic therapy

Parasitic
CCI [redacted]

Source: Based on CCI [redacted].

10.9. Appendix 9: Tuberculosis Testing

This table describes recommendations for performing and interpreting TB tests. It also provides recommendations on TB retesting.

TB test type	How to perform the test	How to interpret the test	When to retest
CCI [redacted] *M tuberculosis*	Ensure that specimen handling, transport, timing, and laboratory procedures meet all requirements per package insert.	Results are provided by the laboratory assaying the test.	The investigator may discuss retesting with the sponsor's designated medical monitor if ● the investigator suspects a false-positive CCI [redacted] Gold test result in a participant with no increased risk of TB infection during lifetime, and ● there is no evidence of prior or current TB on physical examination and/or on CXR interpreted by radiologist and/or pulmonologist (investigator assessment by history and physical examination, and with documented CXR report).

Abbreviation: CXR = chest X-ray.

10.10. Appendix 10: Permitted Concomitant Medications/Therapies

Drug Class (examples) – Comments by Study Period	Screening and Washout	Treatment	
	I	II	III
Oral 5-ASAs (mesalamine, balsalazide, olsalazine) and sulfasalazine for UC • if participant is on a stable prescribed dose [CCI] weeks before screening endoscopy	If continuing stable screening dose, prescribed dose must remain stable until Visit 6 (Week [CCI])		May continue with stable dose encouraged
Oral corticosteroids for UC • prednisone [CCI] mg/day or equivalent, or • extended-release budesonide tablets (budesonide MMX) [CCI] mg/day, or • beclomethasone dipropionate [CCI] mg/day (gastro-resistant, prolonged-release tablet) • if participant on stable prescribed dose [CCI] weeks before screening endoscopy	If continuing stable screening dose, prescribed dose must remain stable until Visit 6 (Week [CCI])		Tapering of dose may begin at Visit 6 (Week [CCI]). See Section 6.8.1
Corticosteroids for non-UC indications	Stable doses encouraged • continued use/regimen to treat adrenal insufficiency • locally administered use, e.g., inhaled, intranasal, intra-articular, topical, and • single doses, oral or IV, as premedication for mirikizumab administration in participants with prior mirikizumab/other biologic administration reactions		
Oral AZA, 6-MP, MTX for UC indication • if participant on stable prescribed dose [CCI] weeks before screening endoscopy	If continuing stable screening dose, prescribed dose must remain stable throughout the study unless modifications are needed due to AEs related to the medication		
Topical JAK inhibitors and calcineurin inhibitors	As needed		
Antidiarrheals (loperamide, diphenoxylate with atropine)	Stable doses encouraged		
Low-dose or baby aspirin ([CCI] mg)	Daily use of a stable dose for cardiovascular prophylaxis		
Non-live vaccines (killed, inactivated, subunit, or RNA-based)	If a non-live vaccine is needed, it is recommended that study intervention not be administered on the same day of the vaccination		
Complementary alternative medicine for non-UC indications (dietary or herbal supplements, vitamins, probiotics)	Stable regimen and doses encouraged. Other nonprescription medicines in this category may be permitted following discussion with the medical monitor		

Abbreviations: 5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; AE = adverse event; AZA = azathioprine; IV = intravenous; JAK = Janus kinase; MMX = Multi matrix colonic delivery technology; MTX = methotrexate; UC = ulcerative colitis.

10.11. Appendix 11: 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 intervention and completes the ED visit.

Drug Class (examples) – Comments by Study Period	**Screening and Washout**	**Treatment**	
	I	**II**	**III**
Biologics, JAK inhibitors, Immunomodulators			
Anti-TNF antibodies (adalimumab, golimumab, infliximab)	DC CCI prior to screening endoscopy	Prohibited	
CCI [redacted]	DC CCI prior to screening endoscopy. See Section 5.2.	Prohibited	
Anti-integrin antibodies (vedolizumab)	DC CCI prior to screening endoscopy	Prohibited	
JAK inhibitors, oral (tofacitinib, upadacitinib)	DC CCI prior to screening endoscopy	Prohibited	
CCI [redacted]	DC CCI prior to screening endoscopy	Prohibited	
Immunomodulators for UC: oral AZA, 6-MP, MTX	Initiation or increase above the stable dose at screening is prohibited during the study		
Immunomodulatory medications, oral or IV: cyclosporine, mycophenolate mofetil, thalidomide, tacrolimus. Other immunomodulatory medications should be discussed with medical monitor prior to use	DC CCI prior to screening endoscopy	Prohibited	
Corticosteroids			
Rectally administered corticosteroids, enemas or suppositories	DC CCI prior to screening endoscopy	Prohibited	
Oral corticosteroids for UC	Initiation or increase above the stable oral dose at screening is prohibited during the study		
Oral budesonide standard formulation - Note: this is not budesonide MMX	DC CCI prior to screening endoscopy	Prohibited	
IV corticosteroids for UC	DC CCI prior to screening endoscopy	Course of IV corticosteroids prohibited	
Systemic corticosteroids for non-UC indication, oral or IV. Allowed exceptions: See Section 10.10.	DC CCI prior to screening endoscopy	Prohibited	

Drug Class (examples) – Comments by Study Period	Screening and Washout	Treatment	
	I	II	III
Other			
Rectally administered 5-ASA therapies - enemas, suppositories	DC CCI prior to screening endoscopy	Prohibited	
Agents depleting B or T cells (alemtuzumab, rituximab, visilizumab)	DC CCI prior to screening endoscopy	Prohibited	
Any investigational therapy, biologic or non-biologic	DC CCI or [redacted] half-lives, whichever is longer, prior to screening endoscopy	Prohibited	
Rectally administered investigational preparations for UC (arsenic)	DC CCI prior to screening endoscopy	Prohibited	
Interferon therapy	DC CCI prior to screening endoscopy	Prohibited	
Leukocyte apheresis, leukapheresis (Adacolumn)	DC CCI prior to screening endoscopy	Prohibited	
BCG vaccination	Not CCI prior to Visit 2	Prohibited, also CCI after last dose of mirikizumab	
Live or attenuated vaccines (for measles, mumps, rubella, or varicella). See Section 6.8.3.	Not CCI prior to Visit 2	Prohibited, also CCI after last dose of mirikizumab	
Nonprescription complementary alternative medicines for UC indication (dietary/herbal supplements, vitamins, probiotics)	Prohibited during study. May consult with medical monitor		
Medicinal and recreational marijuana	DC CCI prior to screening endoscopy	Prohibited	

Abbreviations: 5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; AZA = azathioprine; BCG = Bacillus Calmette-Guerin; DC = discontinue; IL= interleukin; IV = intravenous; JAK = Janus kinase; M = month; MMX = multi matrix colonic delivery technology; MTX = methotrexate; S1P = Sphingosine-1-phosphate; TNF = tumor necrosis factor; UC = ulcerative colitis; W = weeks.

10.12. Appendix 12: Optional Continued Access Period

10.12.1. Overview

The Continued Access Period is offered to sites with eligible study participants who complete AMBZ Study Periods I to III.

The duration of the Continued Access Period will differ by participant and country.

Efficacy data will not be collected during the Continued Access Period. Participants will continue to be followed for safety throughout their participation in this Continued Access Period.

Study activities and procedures described in this appendix are in addition to the requirements of the main AMBZ protocol, unless otherwise specified. Some information from the main AMBZ protocol is repeated for clarity.

[a] Participants who are eligible for Continued Access should move directly from Visit 10 to Visit 501, on the same day, if possible. Visit 801 should not be performed.

10.12.3. Schedule of Activities for Continued Access Period

Throughout this appendix, "self-administration" refers to CCI of mirikizumab by the participant or caregiver**.**

All visits

Self-administration of mirikizumab CCI mg CCI is required at all visits, regardless if the visit is onsite, or telehealth or remote. All activities should be completed prior to self-administration of mirikizumab, unless otherwise stated below.

Continued Access Treatment (Visit 501 to last dosing visit)

Visit 501 activities should occur on the same day as Visit 10 of Study Period III.

Complete all Visit 10 activities before starting Visit 501 activities and dosing.

If Visit 10 and Visit 501 do not occur on same day, Visit 501 activities may need to be repeated, as detailed in the continued access period SoA.

If Visit 10 and Visit 501 occur more than 2 weeks apart, the following laboratory tests must be repeated: hematology, clinical chemistry, and HBV DNA.

Extended continued access visits (ECAV)

After Visit 507 (Week CCI), ECAV continue until criteria for the final visit occurs.

Visits ECAVa, ECAVb, and ECAVc occur every CCI weeks.

Visit ECAVa and ECAVb represent telehealth or remote visits that occur every CCI weeks, and follow an onsite visit.

Visit ECAVc represents the quarterly onsite visit.

Visit numbers will be registered sequentially after Visit 507. This table provides an example of the visit structure that will continue until the final visit.

Visit Number	Visit ID	Weeks from Visit 2
507	507	CCI
ECAVa	508	
ECAVb	509	
ECAVc	510	
ECAVa	511	
ECAVb	512	
ECAVc	513	

Discontinuation (DC) visit

All participants who discontinue mirikizumab treatment after Visit 501 should complete this DC Visit.

Continued Access Period follow-up (weeks)

Visit 901

All participants will complete this visit following their DC visit or at the end of their participation in the Continued Access Period of the study.

Visit 901 may be performed onsite when onsite activities are required or at investigator's discretion.

Unscheduled visits

Unscheduled visits may occur as needed, on any day without regard to visit interval. Required activities are indicated in the SoA. Additional procedures may be performed at the investigator's discretion.

AMBZ Continued Access Period														Comments
Visit number	**501**	**502**	**503**	**504**	**505**	**506**	**507**	**ECA Va**	**ECA Vb**	**ECA Vc**	**DC**	**UV**	**V901**	ECAV = extended continued access visit DC = discontinuation visit
CCI														CCI
Visit conduct	**O**	**T**	**T**	**O**	**T**	**T**	**O**	**T**	**T**	**O**	**O**	**O**	**T**	O = onsite; T = telehealth/remote visit ⸸ = If Visit 10 and Visit 501 do not occur on same day, these activities must be repeated ⸸⸸= If Visit 10 and Visit 501 occur >2 weeks apart, these laboratory tests must be repeated
Informed consent	X													ICF must be signed before any continued access-specific activities are performed.
Inclusion and exclusion criteria	X													Review and confirm specific inclusion and exclusion criteria before V501 activities and dosing.
Substance use, including alcohol, caffeine, tobacco, nicotine											X			
Concomitant medications	X⸸	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events (AEs)	X⸸	X	X	X	X	X	X	X	X	X	X	X	X	See Sections 8.3.1 and 8.3.3.
Physical evaluation														
Weight	X⸸			X			X			X	X			
Vital signs	X⸸			X			X			X	X			See Section 8.2.2.
Symptom-directed physical assessment	X⸸			X			X			X	X			See Section 8.2.1.
Evaluate for EIMs	X⸸			X			X			X	X			See Section 8.2.1.

Tuberculosis (TB) evaluation	X‡			X			X			X	X			TB risk factors; symptoms of active TB. See Section 8.2.7.
Participant education														
Self-administration retraining	X													Complete at the investigator's discretion. See Section 10.12.6.
Laboratory tests														
Hematology	X‡‡			X			X			X	X	X‡	X‡	‡ Optional per investigator discretion.
Clinical Chemistry	X‡‡			X			X			X	X	X‡	X‡	‡ Optional per investigator discretion.
Urine pregnancy (local)	X‡	X	X	X	X	X	X	X	X	X	X		X	Must be performed, with negative result available, prior to dosing at each visit, for WOCBP.
Follicle stimulating hormone (FSH)	X													Optional, perform as needed to confirm postmenopausal status in female participants. See Section 8.2.5.
HBV DNA	X			X			X			X	X			Only required for participants with positive HBV serology at screening. See Section 8.2.8.
Pharmacokinetic (PK) samples	Collect PK and ADA samples in the event of a potential systemic drug hypersensitivity reaction [redacted] reaction.													Collect PK and ADA samples as detailed in Section 10.2.
Immunogenicity (ADA) samples														
Endoscopy Procedures														
Endoscopy	Not required, may perform per investigator's discretion.													If performed, conduct local read.
Registration and dosing														
Register visit with IWRS	X	X	X	X	X	X	X	X	X	X	X		X	
Dispense mirikizumab via IWRS	X			X			X			X				
Self-administer mirikizumab	X	X	X	X	X	X	X	X	X	X				

Provide self-administration materials for remote dosing	X			X			X			X				Materials include mirikizumab; SDALs; and ancillary supplies, including urine pregnancy tests for WOCBP.
Review SDALs and mirikizumab [redacted] cartons	X			X			X			X				See Section 10.12.6.

ICF = Informed consent form; IWRS = interactive web response system; SDAL = Study Drug Administration Log; V= Visit; WOCBP = women of childbearing potential

10.12.4. Overall Design

Transition of participants from the main study to continued access

A participant will

- complete all AMBZ Visit 10 activities, including the Visit 10 study endoscopy with biopsies, and
- complete Visit 501 of the Continued Access Period.
    - If a potentially eligible participant does not meet all inclusion and exclusion criteria at Visit 501, that participant should enter the posttreatment follow-up period of the main study protocol and complete Visit 801 as indicated in Section 1.3.
    - If a potentially eligible participant meets all inclusion and exclusion criteria at Visit 501, that participant should continue visits and procedures according to the SoA in Section 10.12.3.

10.12.5. Study Population

The inclusion and exclusion criteria in this section are specific to this Continued Access Appendix.

The inclusion and exclusion criteria stated in Section 5 do not apply to participant eligibility for continued access, unless that criterion is re-stated below.

10.12.5.1. Inclusion Criteria

Participants are eligible to enter the Continued Access Period only if all the following criteria apply.

Informed consent

52. Are capable of giving signed informed consent to take part in the continued access period, prior to any procedures specific to Continued Access Period being completed.

Participant and disease characteristics

53. Have completed AMBZ Study Periods I to III, including
    - all Visit 10 activities, including the endoscopy with biopsies
    - administration of at least CCI mg mirikizumab CCI doses, without early termination of mirikizumab in Study Period III
    - self-administration training, or demonstrate willingness and ability to complete training and/or retraining, and
    - in the opinion of the investigator, would continue to derive benefit from treatment with mirikizumab
54. Have the ability to complete Visit 501, including the first dose of mirikizumab of the Continued Access Period, on the same day as Visit 10, or within approximately 4 weeks after Visit 10.

- It is strongly recommended that no more than [redacted] weeks occur between Visit 9 of Period III and Visit 501 of the Continued Access Period. Participants requiring a longer duration for entry into the Continued Access Period, but not to exceed approximately [redacted] weeks, must be discussed on an individual basis with the medical monitor.

55. Are up-to-date with surveillance colonoscopy requirement per Section 8.1.5.2, with documented negative results for colorectal dysplasia and cancer. If needed, a colonoscopy with biopsies should be the endoscopic procedure performed at Visit 10 (Week [redacted]).
56. Are willing and able to complete the scheduled visit activities for the Continued Access Period, including self-administration of mirikizumab (by participant or caregiver). Also, in the opinion of the investigator, are able to reliably perform remote, self-administration procedures and related required documentation.

Sex and contraceptive/barrier requirements

57. Agree to adhere to the contraception requirements specified in Section 10.4.

10.12.5.2. Exclusion Criteria

Participants are excluded from the Continued Access Period if any of the following criteria apply:

Gastrointestinal exclusion criteria

58. Have been diagnosed with CD, inflammatory bowel disease-unclassified, formerly known as indeterminate colitis.
59. Have had bowel resection or other surgery for the treatment of UC or are likely to require surgery for the treatment of UC during the Continued Access Period.
60. Have had evidence of toxic megacolon, intra-abdominal abscess, or stricture or stenosis within the small bowel or colon prior to Visit 501 of the Continued Access Period.
61. Have evidence of cancer of the gastrointestinal tract prior to Visit 501 of the Continued Access Period.
62. Have evidence of current sporadic adenoma without dysplasia (adenomatous polyps occurring proximal to known areas of colitis), that has not been removed. If completely removed prior to Visit 501, this exclusion criterion would no longer apply.
    Note: Once removed, the participant may be eligible for the Continued Access Period, after confirming no dysplasia or malignancy on local histology report; and the maximum roll-over period to enter the Continued Access Period has not been exceeded.
63. Have current evidence of colonic dysplasia prior to Visit 501, including
    - polypoid or non-polypoid lesion(s) of colonic mucosa in an area which is endoscopically visible or invisible, and
    - histopathology report of "indefinite for dysplasia," low-grade dysplasia, or high-grade dysplasia.

Infectious disease exclusion criteria

64. Have been diagnosed with a clinically important infection including, but not limited to, hepatitis B, hepatitis C, HIV/AIDS, and active tuberculosis (TB) prior to Visit 501 of the Continued Access Period.
65. Have detectable hepatitis B virus (HBV) DNA detected at any time prior to Visit 501 of the Continued Access Period.
66. Have been diagnosed with LTBI prior to Visit 501 of the Continued Access Period and are not willing to comply with completing TB treatment as appropriate.
67. Intend to receive a Bacillus Calmette-Guerin (BCG) vaccination or live attenuated vaccine(s) during the Continued Access Period.

Other exclusion criteria

68. Have been diagnosed with a condition, underwent a surgical procedure, received prohibited treatment, or experienced a laboratory abnormality that met criteria for permanent discontinuation from mirikizumab treatment prior to Visit 501 of the Continued Access Period. See Section 7.1.
69. Currently meet temporary discontinuation of study intervention criteria (see Section 7.1.4). Note: Once resolution of the condition or appropriate treatment is met, the participant may be eligible for the Continued Access Period if the maximum roll-over period to enter the Continued Access Period has not been exceeded.
70. Have initiated a new prohibited medication (see Section 10.11) prior to Visit 501 of the Continued Access Period.
71. Have had evidence of alcohol dependence or illicit drug abuse prior to Visit 501 of the Continued Access Period.
72. Have had the presence of a hepatic or hematologic laboratory abnormality prior to Visit 501 of the Continued Access Period, that would require permanent discontinuation from mirikizumab treatment. See Section 7.1.
73. Have an underlying disease, or surgical, physical, or medical condition that, in the opinion of the investigator, would potentially affect participant safety within the continued access period.
74. Have a known systemic hypersensitivity to any component of mirikizumab, or have experienced an acute systemic hypersensitivity event with previous mirikizumab treatment administration, that precludes mirikizumab treatment.
75. Are pregnant or planning pregnancy (females only) while enrolled in the continued access period, or within CCI weeks after receiving the last dose CCI dose of mirikizumab.
76. Became part of the investigator site personnel directly affiliated with this study or their immediate families prior to Visit 501 of the Continued Access Period.
77. Became a Lilly employee or an employee of third-party organizations involved with the study prior to Visit 501 of the Continued Access Period.
78. Have 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.

79. Are unsuitable for inclusion in the continued access period in the opinion of the investigator or sponsor for any reason that may compromise the subject's safety.

10.12.6. Study Intervention

All participants enrolled in the Continued Access Period will self-administer CCI mg mirikizumab CCI [redacted].

Administration of mirikizumab should always be done after completion of all other visit activities, as specified in SoA (Section 10.12.3).

At all telehealth or remote dosing visits, self-administration of mirikizumab should be performed immediately following completion of the telephone-portion of the visit.

If self-administration is not possible at a visit, the study site staff may administer the dose at the study site and provide source documentation for the reason. If self-administration is not possible for repeated visits, study site should contact the medical monitor.

Reporting requirements

All required self-administration dosing information must be documented on the relevant SDALs for each visit. Deviations from the prescribed dosing regimen should be documented by the participant on the SDAL and recorded by site staff in the CRF.

Following review of the completed SDALs, and returned mirikizumab CCI cartons, including any unused CCI, if the site staff identifies any deviations from correct procedures, incomplete doses administered, PCs, and/or CCI concerns from participant, appropriate corrective actions, including retraining, should be completed.

Treatment compliance

Compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting unused syringes, review of SDALs, and documented in the source documents.

If a participant is noncompliant with self-administration procedures, the investigator should determine the reason for noncompliance and educate or manage the participant as appropriate to improve compliance.

If, in consultation with the medical monitor, the noncompliance is deemed to be significant such that it affects the safety of the participant or the evaluation of the safety data during the Continued Access Period, the participant should be discontinued from the Continued Access Period.

10.12.7. Discontinuation of Study Intervention and Participant Discontinuation from the Study

In addition to the study intervention discontinuation requirements in Section 7.1, the following also apply to the continued access period:

CCI [redacted]

Following discontinuation from mirikizumab during the continued access period, the participant should complete both the discontinuation visit and Visit 901, as indicated in the Continued Access Period SoA (Section 10.12.3).

10.12.8. Safety Assessments

During the Continued Access Period, all AEs, SAEs, and mirikizumab exposure will be reported on the CRF. SAEs will also be reported to the sponsor. In the event that an SAE occurs, the sponsor may request additional information to evaluate the reported SAE.

Investigators will perform any other standard procedures, and tests needed to treat and evaluate participants; however, the choice and timing of the tests will be at the investigator's discretion. The sponsor will not routinely collect the results of these assessments.

See Sections 10.12.1, and Sections 8.2 and 8.3 for more details.

10.12.9. Permitted Concomitant Medications/Therapies during Continued Access

Note: At the discretion of the investigator, any permitted concomitant medication may have the dose modified, be discontinued, or be re-started during the Continued Access Period. If there are any questions on these permitted medications, please contact the medical monitor.

Drug Class (examples)	Comments
Oral corticosteroids or oral budesonide (standard or extended-release formulation [budesonide MMX]) for UC • prednisone CCI mg/day or equivalent • budesonide MMX CCI mg/day, or • beclomethasone dipropionate CCI mg/day (gastro-resistant prolonged-release tablet)	Short courses of corticosteroids, including budesonide, are permitted with tapering to begin as soon as clinically feasible, with a goal of discontinuing within 3 months. Participants who require increasing doses and repeated courses or are intolerant to tapering of corticosteroids should be considered for treatment discontinuation and termination from the Continued Access Period
Corticosteroids for non-UC indications	Permitted as follows: • continued use to treat adrenal insufficiency • locally administered use, e.g., inhaled, intranasal, intraarticular, and topical • single doses (oral or IV) corticosteroids as premedication for miri self-administered CCI and • limited use for acute conditions per investigator discretion
Rectally administered corticosteroids (enemas or suppositories)	Permitted with the goal of tapering as soon as clinically feasible or discontinuing within 3 months. Participants who require continuous use of steroid enemas or suppositories or are intolerant to tapering should be considered for treatment discontinuation and early termination from the Continued Access Period
Immunomodulators for UC (oral AZA, 6-MP, or methotrexate)	Permitted
Oral 5-ASAs (mesalamine, balsalazide, olsalazine) and sulfasalazine for UC	Permitted
Rectally administered 5-ASAs (enemas or suppositories)	Permitted
Topical JAK inhibitors and calcineurin inhibitors	Permitted
Antidiarrheals (loperamide, diphenoxylate with atropine)	Permitted
Low-dose or baby aspirin (75 to 162.5 mg)	Daily use for cardiovascular prophylaxis permitted
Non-live vaccines (killed, inactivated, subunit, or RNA-based)	Permitted
Complementary alternative medicine for UC and non-UC indications	Permitted

(dietary/herbal supplements, vitamins, probiotics)	

Abbreviations: 5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; AZA = azathioprine; IV = intravenous; JAK = Janus kinase; MMX = Multi-matrix system; UC = ulcerative colitis.

10.12.10 Prohibited Concomitant Medications/Therapies during Continued Access

This section outlines medications that are prohibited during the continued access period of the study. Use of the medications in this table is allowed at the discretion of the investigator after a participant discontinues study intervention and completes the DC visit.

Drug Class (examples)	Continued Access Period Comments and Guidelines
Biologics, JAK inhibitors, Immunomodulators	
Anti-TNF antibodies (adalimumab, golimumab, infliximab)	Prohibited
CCI [redacted]	Prohibited
Anti-integrin antibodies (vedolizumab)	Prohibited
CCI [redacted]	Prohibited
Small-molecule S1P receptor modulator (ozanimod)	Prohibited
Immunomodulatory medications, oral or IV: Cyclosporine, mycophenolate mofetil, thalidomide, tacrolimus. Other immunomodulatory medications should be discussed with medical monitor prior to use	Prohibited
Corticosteroids	
Oral corticosteroids for UC	Initiation or increase above the oral dose at screening is prohibited
IV corticosteroids for UC	Course of IV corticosteroids prohibited
Systemic corticosteroids for non-UC indication, oral or IV Allowed exceptions: See Section 10.12.9.	Prohibited
Other	
Agents depleting B or T cells (alemtuzumab, rituximab, visilizumab)	Prohibited
Any investigational therapy, biologic or non-biologic	Prohibited
Rectally administered investigational preparations for UC (arsenic)	Prohibited
Interferon therapy	Prohibited
Leukocyte apheresis, leukapheresis (Adacolumn)	Prohibited
Bacillus Calmette-Guerin (BCG) vaccination	Use prohibited, also CCI after last dose of mirikizumab
Live or attenuated vaccines (for measles, mumps, rubella, or varicella. See Section 6.8.3.)	Use prohibited, also CCI after last dose of mirikizumab

Abbreviations: DC = discontinue; IL= Interleukin; IV = intravenous; M = month; S1P = Sphingosine-1-phosphate; TNF = tumor necrosis factor; UC = ulcerative colitis.

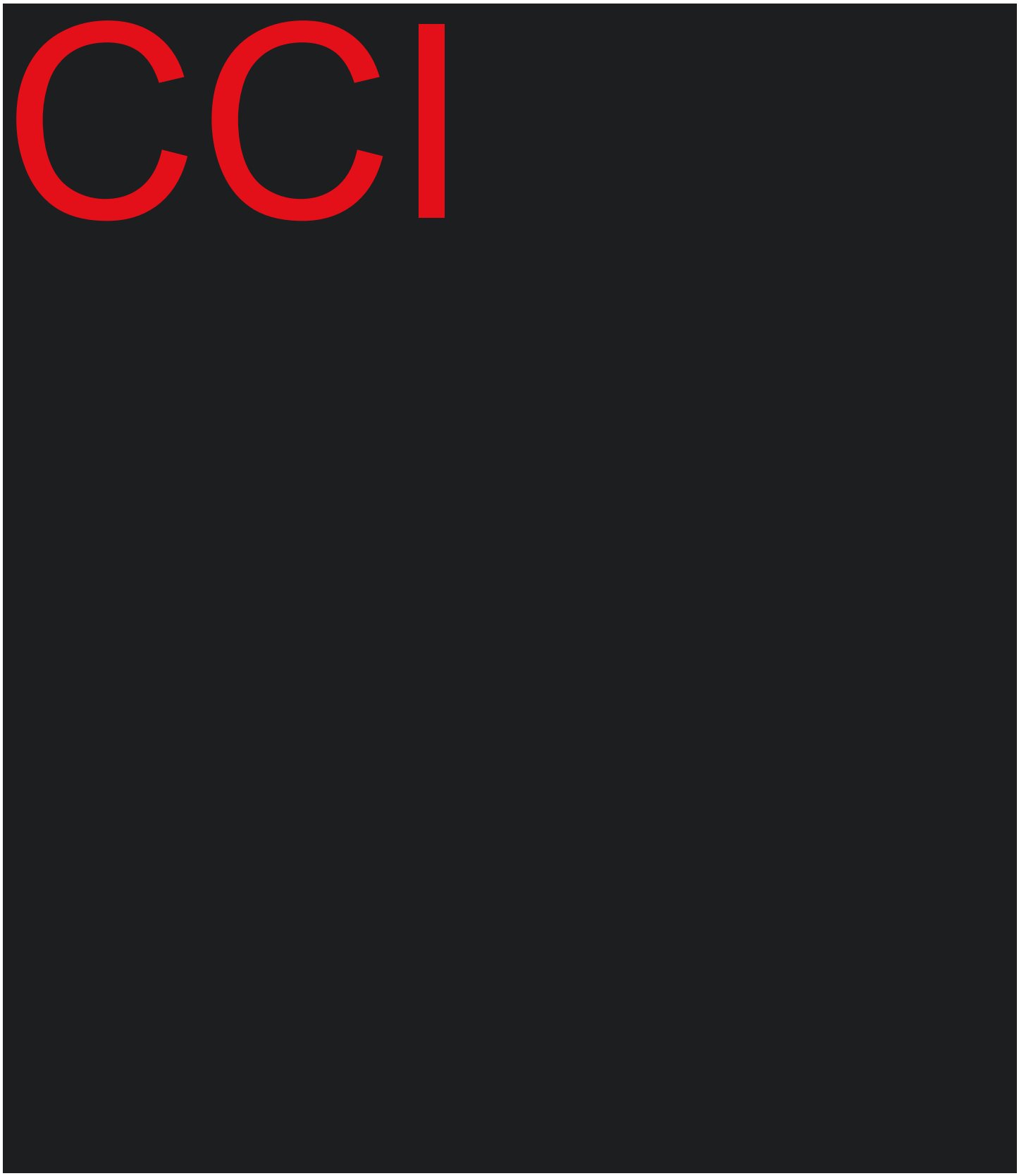
10.13. Appendix 13: Country-specific Requirements

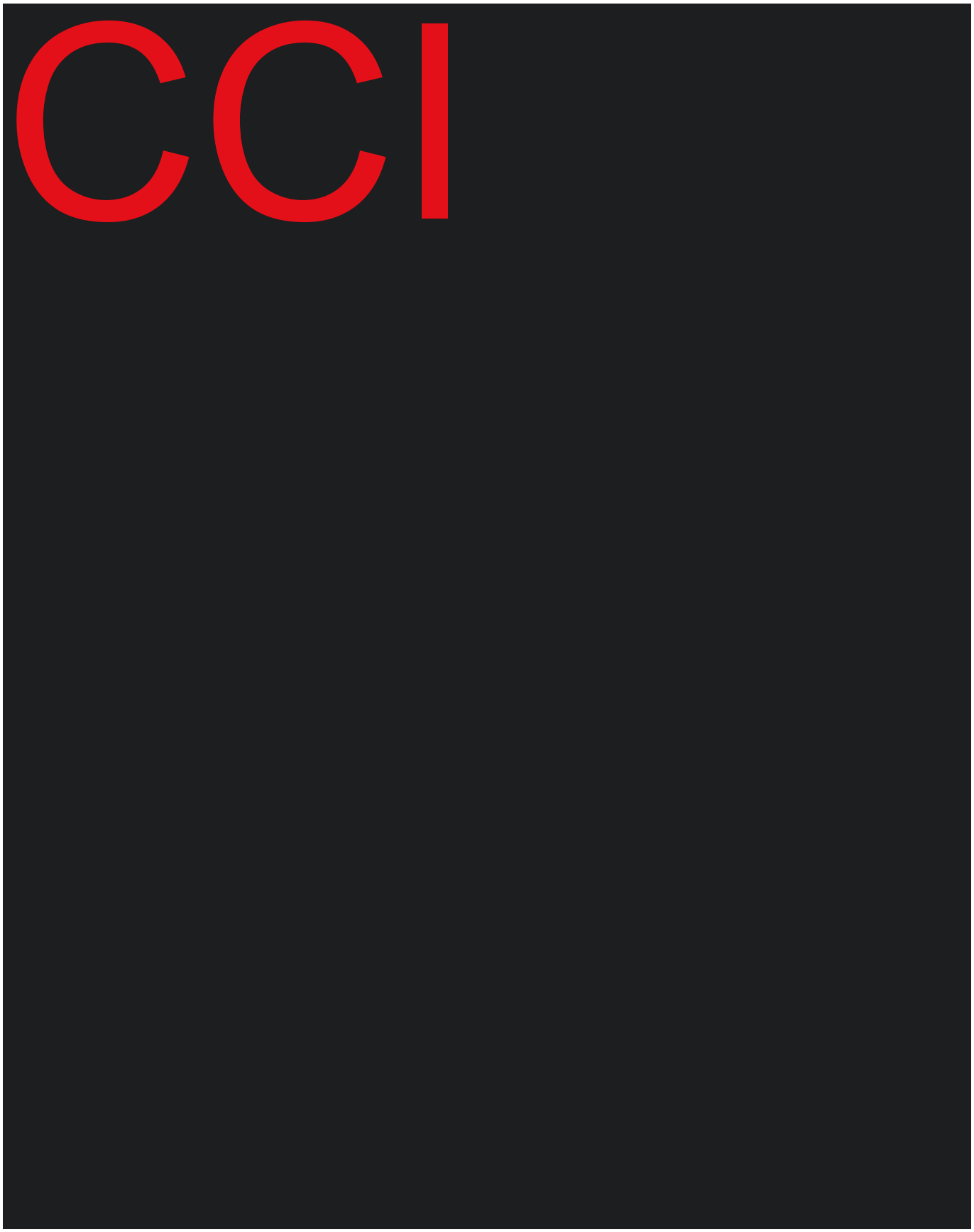
For sites in EU member states

This appendix is not applicable at this time.

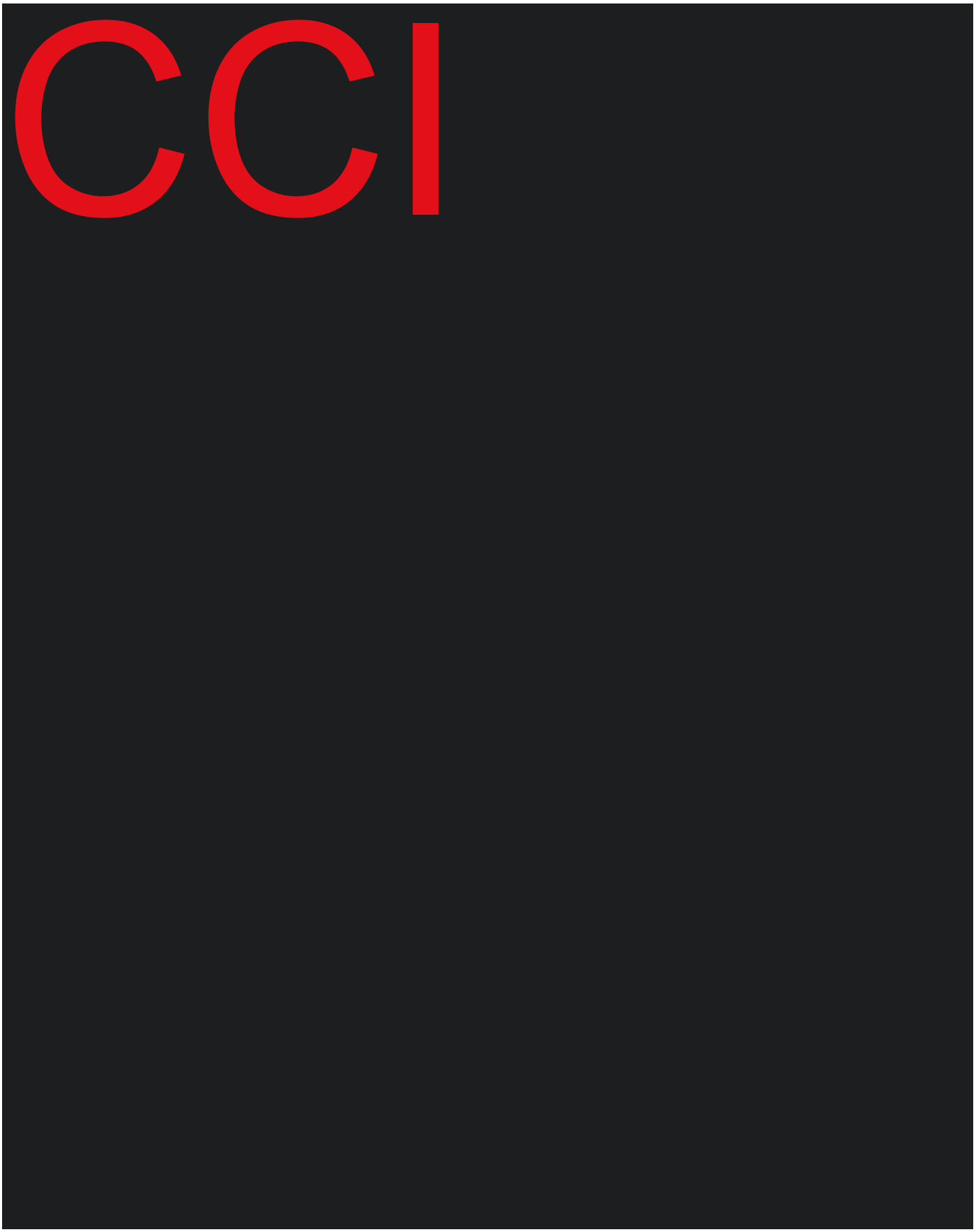
For sites outside of EU member states

Country-specific requirements, if any, will be described in a separate protocol addendum.






CCI


CCI

10.15. Appendix 15: Abbreviations and Definitions

Term	Definition
6-MP	6-mercaptopurine
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Anti-HBc	Antibodies to hepatitis B core antigen
AST	aspartate aminotransferase
authorized IMP	*Applicable to the EU only*: a medicinal product authorized in accordance with Regulation (EC) No 726/2004 or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labeling of the medicinal product, which is used as an investigational medicinal product
AZA	azathioprine
BCG	Bacillus Calmette-Guerin
C difficile	*Clostridioides difficile*
CD	TΔx–„ β)≤⊣β≥xβ≥
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
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

Term	Definition
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant
CRP	clinical research physician: individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer
CCI	[redacted]
CTA	Clinical Trial Agreement
CTR	Clinical Trial Regulation
CXR	Chest X-ray
D.Bil	Direct bilirubin
Device deficiencies	equivalent to product complaint
ECAV	extended continued access visit
ECG	electrocardiogram
ED	early discontinuation
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 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
ERB	Ethical Review Board
ES	endoscopic subscore
FSH	follicle stimulating hormone
CCI	[redacted]
GCP	good clinical practice
GGT	gamma-glutamyl transferase
HBsAg	hepatitis B surface antigen
HBV	hepatitis B Virus

Term	Definition
HCV	hepatitis C Virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
CCI	[redacted]
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IL	interleukin
IMP	Investigational Medicinal Product (see also "investigational product") A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial
informed consent	A process by which a participant voluntarily confirms their 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
INR	international normalized ratio
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 or locked
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. See also "IMP"
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web-response system
JAK	Janus Kinase
LTBI	latent tuberculosis infection

Term	Definition
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involves a failure to uphold 1 or more of the 5 "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core 5 rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, and protocol), or • shared use of cartridges or prefilled pens, or both
Misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
MMS	Modified Mayo Score
MMX	multi matrix colonic delivery technology
MTX	methotrexate
NRS	numeric rating scale
PA	posterior–anterior
Participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PC	product complaint
PCR	polymerase chain reaction
PGA	Physician's Global Assessment
CCI	[redacted]
[redacted]	[redacted]
PK	Pharmacokinetics
PRO/ePRO	patient-reported outcomes or electronic patient-reported outcomes
PT	Prothrombin Time

Term	Definition
Q4W	once every 4 weeks
CCI [redacted]	[redacted]
QoL	quality of life
RB	rectal bleeding
RNA	ribonucleic acid
S1P	Sphingosine-1-phosphate
SAE	serious adverse event
SAP	statistical analysis plan
SC	Subcutaneous
Screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study
SDAL	Study Drug Administration Log
SF	stool frequency
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TBL	total bilirubin level
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment
TNF	tumor necrosis factor
UC	ulcerative colitis
ULN	upper limit of normal
UNRS	urgency numeric rating scale
UV	unscheduled visit
WBC	white blood cell
WHO	World Health Organization

Term	Definition
WNOCBP	women not of childbearing potential
WOCBP	women of childbearing potential
CCI [redacted]	[redacted]

10.16. Appendix 16: 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]

Overall Rationale for the Amendment:

The purpose of this amendment is to clarify the surveillance colonoscopy requirements and to update protocol wording to align with current regulatory requirements.

Minor editorial changes are not included in this table.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities	Removed the 'X' indicator for CCI [redacted] at ED visit.	To align with the analysis strategy.
5.1. Inclusion Criteria	Criterion 6: Added specific surveillance colonoscopy criteria to clarify the requirements for eligibility prior to Visit 2.	To clarify the surveillance colonoscopy requirements.
6. Study Intervention(s) and Concomitant Therapy	Reworded the definition of study intervention.	To improve alignment with regulatory definitions.
8.1.5.2. Surveillance Colonoscopy Requirements	Added specific surveillance colonoscopy criteria to clarify the requirements for eligibility prior to Visit 2; and removed subsection on minimum colonoscopy biopsy procedural requirements.	To maintain consistency with revisions in Section 5.1, and to allow for regional differences in biopsy requirements for surveillance colonoscopies in participants with moderately to severely active UC.
10.1.4. Data Protection	Added statements to clarify methods for protection of personal data and handling of data security breach.	To address an EU CTR (536/2014) requirement.
10.3.6. Regulatory Reporting Requirements	Added a description of the reporting of SUSARs.	To address an EU CTR (536/2014) requirement.
10.12.1. Overview (of Appendix 12: Optional Continued Access Period)	Clarified that the Continued Access Period may be stopped if sponsor discontinues plans for seeking regulatory approval "in any markets" rather than "within the participant's country."	To maintain consistency with statement in Section 10.12.7.
10.12.3. Schedule of Activities for Continued Access Period	Removed the footnote indicator on HBV DNA cell for Visit 501.	To correct a typographical error.
10.12.5.1. Inclusion Criteria (of Appendix 12: Optional Continued Access Period)	Revised Criterion 55.	To maintain consistency with other sections of the protocol.

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