I6T-MC-AMBU(c) Clinical Protocol

A Multicenter, Open-Label PK Study of Mirikizumab in Pediatric Patients with Moderately to Severely Active Ulcerative Colitis (SHINE-1)

NCT04004611

Approval Date: 23-Oct-2021

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A Multicenter, Open-Label PK Study of Mirikizumab in Pediatric Patients with Moderately to Severely Active Ulcerative Colitis
SHINE-1

EUDRA CTA: 2019-001298-96

Confidential Information

Mirikizumab (LY3074828)

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Document ID: VV-CLIN-008288

Amendment (c) Electronically Signed and Approved by Lilly on date provided below.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment b	*30-Apr-2021*
Amendment a	*26-Aug-2019*
Original Protocol	*24-Apr-2019*

Amendment c

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The primary purpose of this amendment is to modify dosing instructions for the ≥20-40 kg participants during the maintenance period. Each participant will receive one injection of a 1 mL prefilled syringe instead of two 0.5 mL injections for SC maintenance dosing.

Section # and Name	Description of Change	Brief Rationale
Section 2. Schedule of Activities	Updated notes for endoscopy with biopsies procedure	Clarified that a medical consult is necessary to omit endoscopy at the ETV visit
Section 1 Synopsis and Section 4. Objectives and Endpoints	CCI [redacted]	CCI [redacted]
Section 5.1 Overall Design	Figure AMBU.1 Study design	Updated the study design figure to reflect the updated language in section 7.1 (see below)
Section 7.1 Treatments Administered, Table AMBU.3. Treatment Regimens: Week 12 Clinical Responders	Updated enrollment initiation criteria for the ≤40 kg cohort receiving 10 mg/kg dosing	To correct a prior protocol error and clarify enrollment of the 10 mg/kg cohort opens after all patients in the 5 mg/kg cohort have enrolled AND at least 5 patients have had 2 doses and the Week 4 evaluation of PK samples and safety assessment have been completed
Section 7.1 Treatments Administered,	Removed reference to maximum volume for injections	Study site feedback indicated that injecting 1 mL subcutaneously in patients weighing 20 kg to ≤40 kg is acceptable and importantly, avoids 2 injections in a

Section # and Name	Description of Change	Brief Rationale
Study Drug Administration		child. Therefore, the maximum volume limitation was removed
Section 7.1.1. Packaging and Labeling	Updated information about study drug supplies Removed pharmacy manual reference	Updated content to state study drug will be provided as CCI [redacted]. The document name was revised internally; the "Pharmacy Manual" does not include study drug administration instructions
Section 9.1.5. Determination of Responder Status/Loss of Response and SoA comments	CCI [redacted]	CCI [redacted]
Section 9.4.3.1 Pregnancy Testing	More clearly define 'women of childbearing potential' and when urine pregnancy testing should be conducted	Feedback from clinical trial sites suggested prior wording was unclear. Providing a list of the possible categories relevant to our study population provides more clarity
Section 10.2. Populations for Analyses, Table AMBU.6. Population Definitions	Updated description of the mITT population	To clarify that the mITT is applicable for both induction and maintenance periods
Appendix 6. Permitted Medications with Dose Stabilization	CCI [redacted]	CCI [redacted]

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1. Synopsis

Title of Study:
A Multicenter, Open-Label PK Study of Mirikizumab in Pediatric Patients with Moderately to Severely Active Ulcerative Colitis.

Rationale:
Current treatments for pediatric patients with ulcerative colitis (UC) have limitations with respect to efficacy, safety, and tolerability; in fact clinical trial data in pediatric populations is scant or lacking completely. In addition, many treatments require close monitoring for adverse effects, which increases undue burden to the child and family. Thus, there is a substantial unmet need for the development, evaluation, and approval of efficacious, safe, and well-tolerated therapies for children and adolescents with UC. Interleukin-23 (IL-23) has been implicated as a pro-inflammatory factor in mucosal inflammation in UC. Study I6T-MC-AMBU (AMBU) is an open-label study to evaluate the safety, pharmacokinetics (PK), pharmacodynamics (PD), and clinical response to mirikizumab to establish induction and maintenance doses to evaluate in Phase 3, in children and adolescents with UC, aged 2 to less than 18 years. Study AMBU will include safety data following mirikizumab treatment for at least 1 year.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the pharmacokinetics (PK) of mirikizumab treatment in pediatric patients	• Clearance and volume of distribution of mirikizumab
Secondary	
• To evaluate the effect of treatment with mirikizumab on achieving **clinical remission** at Week 12 and/or Week 52	• The proportion of patients in modified Mayo score (MMS) clinical remission at Week 12 • The proportion of patients in MMS clinical remission at Week 52 • The proportion of patients in MMS clinical remission at Week 52 among the MMS clinical remitters at Week 12 (durable clinical remission) • The proportion of patients in MMS clinical remission at Week 52 among the MMS clinical responders from Week 12 **MMS clinical remission** is defined as: • Stool frequency (SF) subscore = 0, or SF = 1, and • Rectal bleeding (RB) subscore = 0, and • Endoscopic subscore (ES) = 0 or 1 (excluding friability) **MMS clinical response** is defined below

Objectives	Endpoints
• To evaluate the effect of treatment with mirikizumab on achieving **clinical response** at Week 12 and/or Week 52	• The proportion of patients in clinical response at Week 12 • The proportion of patients in clinical response at Week 52 • The proportion of patients in clinical response at Week 12 who achieve clinical response at Week 52 **Clinical response** is based on the MMS and is defined as: o A decrease in the MMS of ≥2 points and ≥30% decrease from baseline, and o A decrease of ≥1 point in the RB subscore from baseline or a RB score of 0 or 1
• To evaluate the effect of treatment with mirikizumab on achieving **corticosteroid-free remission** without surgery among patients in clinical remission at Week 52 and receiving corticosteroids at baseline	• The proportion of patients who are in MMS clinical remission at Week 52 without the use of corticosteroids CCI [redacted]
• To evaluate the effect of treatment with mirikizumab on **PUCAI clinical remission** at Week 12 and/or Week 52	• The proportion of patients in PUCAI clinical remission at Week 12 • The proportion of patients in PUCAI clinical remission at Week 52 • The proportion of patients in PUCAI clinical remission at Week 12 who achieve clinical remission at Week 52 • The proportion of patients in PUCAI clinical response at Week 12 who achieve clinical remission at Week 52 **PUCAI clinical remission** is defined as a PUCAI score of <10 points **PUCAI clinical response** is defined below
• To evaluate the effect of treatment with mirikizumab on **PUCAI clinical response** at Week 12 and/or Week 52	• The proportion of patients in PUCAI clinical response at Week 12 • The proportion of patients in PUCAI clinical response at Week 52 • The proportion of patients in PUCAI clinical response at Week 12 who achieve PUCAI clinical response at Week 52 **PUCAI clinical response** is defined as a reduction in baseline PUCAI score of ≥20 points

Objectives	Endpoints
• To evaluate the effect of treatment with mirikizumab on achieving **endoscopic remission** at Week 12 and/or Week 52	• The proportion of patients in endoscopic remission at Week 12 • The proportion of patients in endoscopic remission at Week 52 • The proportion of patients in endoscopic remission at Week 12 who maintain endoscopic remission at Week 52 (durable endoscopic remission) **Endoscopic remission** is defined as: o ES = 0 or 1 (excluding friability)
• To evaluate the effect of treatment with mirikizumab on achieving **ES = 0** at Week 12 or Week 52	• The proportion of patients with ES = 0 at Week 12 • The proportion of patients with ES = 0 at Week 52
• To evaluate the effect of treatment with mirikizumab on **symptomatic remission** over time	• Proportion of patients in symptomatic remission at applicable study visits **Symptomatic remission** is defined as: o SF = 0, or SF = 1 with a ≥1-point decrease from baseline and o RB = 0
• To evaluate the effect of treatment with mirikizumab on height velocity at Weeks 12, 24, and 52	• Observed height velocity by gender and age group will be calculated at baseline, Week 12, Week 24, and Week 52
• To evaluate the effect of treatment with mirikizumab on weight throughout the trial	• Change from baseline in weight (kg) at all study visits by gender and age group
• To evaluate the effect of treatment with mirikizumab on pubertal development throughout the trial in appropriate patient groups	• Hormone levels and/or other related clinical measures will be evaluated
• CCI [redacted]	CCI [redacted]
• To evaluate **histologic-endoscopic mucosal remission** following mirikizumab treatment at Week 12 or Week 52	• Proportion of patients with histologic-endoscopic mucosal remission at Week 12 • Proportion of patients with histologic-endoscopic mucosal remission at Week 52 **Histologic-endoscopic mucosal remission** is defined as achieving both histologic remission and endoscopic remission. **Histologic remission** will be defined in the SAP.

Objectives	Endpoints
• To evaluate the development of anti-mirikizumab antibodies and their effect on efficacy, safety, and mirikizumab exposure	• Proportion of patients who have treatment-emergent anti-drug antibodies (TEADA) • Relationship between TEADA and efficacy • Relationship between TEADA and safety • Relationship between TEADA and mirikizumab PK
• CCI [redacted]	• CCI [redacted]

Abbreviations: NRS = numeric rating scale; PUCAI = Pediatric Ulcerative Colitis Activity Index; SAP = statistical analysis plan.

Summary of Study Design:

Study AMBU is a multicenter, Phase 2, open-label study designed to evaluate the safety, PK, PD, and clinical response of mirikizumab in pediatric patients, and to provide data for dose confirmation for Phase 3. The study population includes pediatric patients with moderately to severely active UC, who have an inadequate response to, loss of response to, or are intolerant to non-biologic therapy for UC (biologic-naive), and/or those who have been exposed to at least 1 biologic and/or Janus kinase (JAK) inhibitor therapy for UC (biologic/JAK inhibitor-experienced).

Treatment Arms and Duration:

Patients weighing >40 kg will receive a mirikizumab induction dose of 300 mg via intravenous (IV) infusion and patients weighing ≤40 kg will receive 5 or 10 mg/kg via IV infusion at Weeks 0, 4, and 8. Patients who have met the clinical response criteria at Week 12 will receive subcutaneous (SC) maintenance doses of 200 mg (weight >40 kg), or 100 mg (weight >20 kg to ≤40 kg), or 50 mg (weight ≤20 kg) every 4 weeks (Q4W) from Weeks 12 to 48. Patients who have not achieved clinical response at Week 12 may receive extended induction at the next higher dose, or will be discontinued. In cases where there is no higher dose, patients may receive extended induction dosing at the current dose.

Number of Patients:

Approximately 60 patients with moderately to severely active UC will be screened to enroll approximately 30 patients.

Statistical Analysis:

Analyses of the PK of mirikizumab and relationships between exposure and the efficacy endpoints will be conducted. For both the PK and exposure–response analyses, intrinsic and extrinsic factors will be evaluated to determine their impact. Comparisons of adult and pediatric PK and exposure–response will be performed and may be combined if appropriate.

The PK of mirikizumab (primary objective) will be characterized at interim analysis points using graphical evaluations and mixed-effect (population PK) modelling approaches using the available induction and maintenance mirikizumab concentration data. The modelling will be used to understand the impact of factors, such as body weight and age, to estimate the exposures

expected prior to enrolling the 10 mg/kg dose group in this study using interim analyses of PK data, and to confirm the planned doses for the Phase 3 study. CCI [redacted]

Efficacy analyses for the induction period and the maintenance period will be conducted on the modified intent-to-treat (ITT) population. Safety analyses for the induction period and the maintenance period will be conducted on the induction safety population and the maintenance safety population, respectively.

Descriptive summaries by treatment, by visit, and by weight group for efficacy endpoints (secondary objectives) will be performed using nonresponder imputation (NRI) methodology.

Safety data will be summarized by dose. Safety assessments will include adverse events, laboratory analytes, vital signs, and questionnaires to assess the existence and severity of depression.

2. Schedule of Activities

Table AMBU.1. Schedule of Activities

	Screening	Treatment Period									Notes:
Visit No.	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	CCI
Study Week		CCI									
Study Days	CCI										
Patient assent (if appropriate) and parent/legal guardian informed consent	X										
Inclusion/exclusion criteria	X	X									
Demographic information, medical and surgical history	X										CCI
Pre-existing (current) medical conditions	X										
Review vaccine status	X										
Concomitant medication review (including corticosteroid use)	X	X	X	X	X	X	X	X	X	X	
Review AEs	X	X	X	X	X	X	X	X	X	X	
Tobacco/nicotine use	X	X				X			X		CCI
Alcohol/caffeine use	X										
Investigational Product Administration											
Assignment to treatment weight cohort		X									
CCI											CCI

	Screening	Treatment Period								Notes:
Visit No.	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	CCI
Study Week		CCI								
Study Days	CCI									
CCI										
Physical Evaluation										
Vital signs (temperature, BP using an appropriately sized cuff, and pulse rate)	X	X	X	X	X	X	X	X	X	X	
Occipital head circumference		X				X			X		
Weight	X	X	X	X	X	X	X	X	X	X	
Height	X	X				X			X		
Physical examination	X	X	X	X	X	X			X		
Evaluate for EIMs	X	X	X	X	X	X	X	X	X	X	
12-lead ECG (locally read)	X					X					
Laboratory Investigations											
Urinalysis	X										

	Screening	Treatment Period								Notes:
Visit No.	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	CCI
Study Week		CCI								
Study Days	CCI									
Serum pregnancy test	X[a]									
Urine pregnancy test		X		X	X	X	X	X	X	X
Hormone collection	CCI									
HIV/HBV/HCV testing	X[a]									

	Screening	Treatment Period								Notes:
Visit No.	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	CCI
Study Week		CCI								
Study Days	CCI									
HBV DNA	X[a]					X[a]			X	
Chemistry/Hematology	CCI									
PK assessment										
Pre-dose PK sample				X	X	X[a]	X		X	
Post-dose PK sample		X			X					
PK sample			X							
Immunogenicity (ADA) samples	CCI									

	Screening	Treatment Period								Notes:
Visit No.	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	CCI
Study Week		CCI								
Study Days	CCI									
Hypersensitivity testing (if applicable)		Xa								
Pharmacogenomics blood sample	CCI									
TB testing	Xa									
C-reactive protein	CCI									

	Screening	Treatment Period								Notes:
Visit No.	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	CCI
Study Week		CCI								
Study Days	CCI									
Additional Safety Tests										
Chest radiography for TB screening (optional – see comment)	X									CCI
TB Monitoring	CCI									
C-SSRS	CCI									
CDI 2	CCI									

	Screening	Treatment Period								Notes:
Visit No.	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	CCI
Study Week		CCI								
Study Days	CCI									
Stool Samples										
Stool culture and *Clostridium difficile* toxin	X									CCI
Fecal sample for fecal calprotectin and exploratory biomarker sample	CCI									
Endoscopic Procedure										
Endoscopy with biopsies	X					X				CCI
Tissue samples for exploratory biomarkers	CCI									
Ulcerative Colitis Disease Activity Assessments										
Diary dispensed	X									
CCI diary compliance review		X	X	X	X	X	X	X	X	X CCI
PGA	CCI									
PUCAI	CCI									
Health Outcomes Assessment										

	Screening	Treatment Period									Notes:
Visit No.	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	CCI
Study Week		CCI									
Study Days	CCI										
PGI-C				X	X	X					

	Visits 11 to Post-treatment Follow-up										
	Treatment Period								Post-treatment Follow-up		Notes
Visit No.	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**N/A**	**V997[b]**	**V801**	**V802[c]**	CCI
Study Week	CCI										
Study Days	CCI										
Concomitant medication review (including corticosteroid use)	X	X	X	X	X	X	X	X	X	X	
Review AEs	X	X	X	X	X	X	X	X	X	X	
Tobacco/nicotine use						X	X	X			CCI
Investigational Product Administration											
CCI											

Visits 11 to Post-treatment Follow-up										
	Treatment Period							Post-treatment Follow-up		Notes
Visit No.	V11	V12	V13	V14	V15	V16	CCI	V801	V802[c]	CCI
Study Week	CCI									
Study Days	CCI									
CCI										
Physical Evaluation										
Vital signs (temperature, BP using appropriate size cuffs, and pulse rate)	X	X	X	X	X	X	X	X	X	X
Occipital head circumference		X				X	X			
Weight	X	X	X	X	X	X	X	X	X	X
Height						X	X			
Physical examination		X			X	X	X	X	X	X
Evaluate for EIMs	X	X	X	X	X	X	X	X	X	X

Visits 11 to Post-treatment Follow-up										
	Treatment Period								Post-treatment Follow-up		Notes
Visit No.	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	CCI		**V801**	**V802[c]**	CCI
Study Week	CCI										
Study Days	CCI										
12-lead ECG (locally read)						X	X				
Laboratory Investigations											
Urine pregnancy test	X	X	X	X	X	X	X	X[b]	X	X	CCI
Hormone collection	CCI										

Visits 11 to Post-treatment Follow-up										
	Treatment Period								Post-treatment Follow-up		Notes
Visit No.	V11	V12	V13	V14	V15	V16	CCI		V801	V802[c]	CCI
Study Week	CCI										
Study Days	CCI										
HBV DNA		X				X[a]	X[a]			X[a]	
Chemistry/Hematology	CCI										
PK assessment		X				X[a]	X[a]			X[a]	

Visits 11 to Post-treatment Follow-up											
	Treatment Period								Post-treatment Follow-up		Notes
Visit No.	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	CCI		**V801**	**V802[c]**	CCI
Study Week	CCI										
Study Days	CCI										
Immunogenicity (ADA) samples											
	CCI										
C-reactive protein	CCI										

Visits 11 to Post-treatment Follow-up										
	Treatment Period								Post-treatment Follow-up	Notes
Visit No.	V11	V12	V13	V14	V15	V16	N/A	CCI	V802[c]	CCI
Study Week	CCI									
Study Days	CCI									
Hypersensitivity testing (if applicable)	X[a]									
Pharmacogenomics blood sample	CCI									

Visits 11 to Post-treatment Follow-up										
	Treatment Period							Post-treatment Follow-up		Notes
Visit No.	V11	V12	V13	V14	V15	V16	CCI	V801	V802[c]	CCI
Study Week	CCI									
Study Days	CCI									
Additional Safety Tests										
TB Monitoring	CCI									CCI
CDI 2	CCI									
Stool Samples										
Fecal sample for fecal calprotectin and exploratory biomarker sample	CCI									CCI
Endoscopy Procedure										
Endoscopy with biopsies	CCI									CCI
Tissue samples for exploratory biomarkers	CCI									

Visits 11 to Post-treatment Follow-up										
	Treatment Period							Post-treatment Follow-up		Notes
Visit No.	V11	V12	V13	V14	V15	V16	CCI	V801	V802[c]	CCI
Study Week	CCI									
Study Days	CCI									
Ulcerative Colitis Disease Activity Assessments										
CCI diary compliance review	X	X	X	X	X	X	X			CCI
Diary device collected						X	X			
PGA	CCI									
PUCAI	CCI									
Health Outcomes Assessment										
PGI-C	CCI									CCI

CCI

CCI

[redacted]

3. Introduction

3.1. Study Rationale

Ulcerative colitis (UC) in pediatric patients remains a disease with high morbidity marked by a relapsing and remitting clinical course. The unmet medical need for pediatric UC treatment exists in 3 primary areas:

- To provide new treatments that can induce and maintain remission in patients who have not sufficiently responded to currently available treatment regimens.
- To improve treatment outcomes such that the use of corticosteroids is reduced or eliminated, thus avoiding corticosteroid-induced adverse effects.
- To provide new treatments with improved safety profiles.

Mirikizumab (LY3074828) is a humanized immunoglobulin G4 monoclonal antibody that binds to the p19 subunit of interleukin-23 (IL-23), a cytokine that has been implicated in mucosal inflammation. This study will provide dose evaluation in pediatric patients aged 2 to 17 years, efficacy data in induction and maintenance periods, and safety data following mirikizumab treatment for approximately 1 year.

3.2. Background

3.2.1. Disease State and Treatment Goals

Ulcerative colitis is a chronic relapsing and remitting disease characterized by inflammation, ulceration, and bleeding in the colon. Inflammation in UC is confined to the mucosal surface of the rectum and colon. Ulcerative colitis is thought to be caused by a dysregulated immune response to host intestinal microflora.

The prevalence of pediatric UC over time is increasing as evidenced by a population-based, nationwide cohort study based in Canada (Benchimol et al. 2009 [Canada]). The prevalence of UC in the United States (US) pediatric population as reported in the literature ranges between 25,459 (Betteridge et al. 2013; US Census Bureau [WWW]) and 27,923 people (Kappelman et al. 2013; US Census Bureau [WWW]). In addition, although at least 1 study reported higher male versus female prevalence of UC (Button et al. 2010 [United Kingdom (UK)]), other studies reported the opposite or no significant differences between genders (Kappelman et al. 2013 [US]; Di Domenicantonio et al. 2014 [Italy]).

The management of UC in children and adolescents is multifactorial and is based on treatment goals of:

- induction of remission with endoscopic healing
- maintenance of remission, and
- longer term prevention of cancer of the affected bowel.

Other factors that influence management of pediatric patients with UC include:

- disease severity
- disease distribution (pancolitis, left-sided colitis, or proctitis)
- response to and tolerance of previous treatments, and
- comorbidities.

Age-related considerations (for example, growth, puberty, and bone mineral density accretion) and patient and caregiver preferences also influence treatment plans.

Given this information and the unmet medical need to provide an effective therapy for pediatric patients, this Phase 2 study is being conducted to generate pharmacokinetic (PK) and clinical response data to support clinical development for use of mirikizumab in pediatric patients with moderately to severely active UC.

3.2.2. Currently Available Treatments and Unmet Need

Remission rates in pediatric UC have been evaluated in pediatric clinical trials and retrospective reviews, and these evaluations have indicated that 29% to 50% of children with moderate-to-severe disease achieved steroid-free remission at 1 year (Hyams et al. 2006, 2011, 2012; Zeisler et al. 2013). Current treatments for pediatric patients with UC have significant limitations with respect to efficacy, safety, and tolerability. In addition, many treatments require close monitoring for adverse effects, which increases undue burden on the child and family. Thus, there is a substantial unmet need for the development and approval of efficacious, safe, and well-tolerated therapies for children and adolescents with UC.

To date, the anti-tumor necrosis factor (TNF) antibody, infliximab, is the only biologic therapy approved to treat UC in pediatric patients. Although anti-TNF therapy has improved disease course in UC, lack of efficacy and loss of response continue to be a concern in this patient population (Hyams et al. 2012).

The safety profile of current therapies, including infliximab, may also limit their use in some patients. Treatment with infliximab is associated with an increased risk for serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infection (for example, histoplasmosis), and infections caused by other opportunistic pathogens. Lymphoma and other malignancies, some fatal such as hepatosplenic T-cell lymphoma, have also been reported in children and adolescent patients treated with TNF blockers, particularly when these agents are used in combination with immunomodulators. In addition, the development of anti-TNF antibodies is associated with acute infusion reactions, delayed hypersensitivity reactions, decreased serum drug levels, and loss of response (Miele et al. 2004), leading to potentially significant safety and efficacy concerns.

While treatment with corticosteroids is effective in inducing clinical response or remission in the majority of patients, almost 50% of patients develop corticosteroid dependence and require additional medication to successfully discontinue corticosteroids (Jakobsen et al. 2011b). Corticosteroids are not effective in maintaining remission in patients with UC, and long-term corticosteroid therapy is limited by the potential for significant adverse effects. Although

immunomodulatory therapies, such as azathioprine (AZA), 6-mercaptopurine (6-MP), tacrolimus, and methotrexate (MTX), are used in clinical practice to treat moderate-to-severe UC in pediatric patients, there is limited evidence of efficacy from adequate and well-controlled trials in pediatric patients to recommend the appropriate and safe use of these therapies.

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

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

Interleukin-23 expression is enriched in the intestine of patients with active UC. In addition, genome-wide association scans identified common variants (single nucleotide polymorphisms) in molecules in the IL-23 signaling pathway that modify the risk of UC and/or Crohn's disease (CD) in humans, including IL-23 receptor, STAT3, and Janus kinase (JAK) 2 (Jostins et al. 2012). Taken together, these data provide evidence for IL-23/Th17 pathway as a therapeutic target in UC.

Available clinical data with mirikizumab (Study I6T-MC-AMAC [AMAC]) support such a hypothesis. Published clinical data show efficacy in inflammatory bowel disease (IBD) for ustekinumab, risankizumab, brazikumab, and mirikizumab, and support the role of IL-23 in IBD.

3.2.4. Preclinical and Clinical Studies of Mirikizumab

CCI

Additional preclinical data are summarized in the Investigator's Brochure (IB).

A number of clinical trials of mirikizumab have been completed or are currently ongoing in patients with psoriasis, UC, and CD. Data from these studies are summarized in the IB. Ongoing studies in adult patients with UC include the Phase 2 study AMAC and the Phase 3 LUCENT program comprising of Study I6T-MC-AMAN (AMAN; mirikizumab/placebo induction), Study I6T-MC-AMBG (AMBG; mirikizumab/placebo maintenance), and Study I6T-MC-AMAP (mirikizumab open-label extension).

Study AMAC is a Phase 2, placebo-controlled, double-blind clinical trial of mirikizumab in patients with moderate-to-severe UC, for which induction and maintenance results are available. In the 12-week induction period, mirikizumab demonstrated efficacy for both endoscopic as well as symptomatic indices as assessed by multiple measures (Sandborn et al. 2018). Overall adverse event (AE) frequencies were similar for mirikizumab-treated and placebo-treated patients (Sandborn et al. 2018). In the maintenance period through Week 52, mirikizumab demonstrated durable efficacy for both endoscopic, as well as symptomatic indices: among patients in clinical remission at Week 12, 61.1% (every 4 weeks [Q4W]) and 38.5% (every 12 weeks [Q12W]) remained in clinical remission at Week 52. There were few serious adverse events (SAEs) and few discontinuations due to AEs over 52 weeks (D'Haens et al. 2019).

There were no unexpected adverse findings that would preclude clinical development in pediatric patients aged 2 through 17 years.

3.3. Benefit/Risk Assessment

Ulcerative colitis remains an important public health challenge for which there are currently few therapies available and no cure. Although the pathogenesis and disease course of UC show similarities in patients affected in childhood and adulthood, many pediatric patients with UC have demonstrated more extensive disease and more severe disease course compared with adult patients with UC (Jakobsen et al. 2011a). Given the inevitably long-term medical problems caused by UC along with the adverse effects and limitations of the current therapies, more effective and safer treatment options are needed for pediatric patients.

At the time of this benefit/risk assessment, mirikizumab has demonstrated efficacy in blinded, placebo-controlled, Phase 2 studies in UC (Sandborn et al. 2018; D'Haens et al. 2019) and

psoriasis (Reich et al. 2017). Evaluation of unblinded safety data from the completed and ongoing psoriasis, UC, and CD studies with dose regimens of up to 1000 mg intravenous (IV) Q4W for up to 52 weeks, up to 300 mg SC Q8W for up to 104 weeks, and up to 300 mg SC Q4W for up to 40 weeks, have shown a safety profile generally consistent with the IL-23 antibody class. These data are summarized in the IB. Across the ongoing Phase 2 mirikizumab studies, immediate hypersensitivity reactions, including 2 reports of immediate, infusion-related hypersensitivity events consistent with anaphylaxis, have been reported at the onset or during the IV infusion of mirikizumab. Such reactions are considered by the sponsor to be related to mirikizumab and hence, have been identified as adverse drug reactions (ADRs). The protocol includes specific measures for reducing the incidence and for management of study drug infusion rate and observation during and after infusion. Consult the most current IB for information regarding ADRs and potential risks with mirikizumab.

Given the data from the Phase 2 study in UC, data from other clinical studies completed to date, and the open-label design ensuring active treatment is available to all study participants, potential benefit to patients who receive mirikizumab while participating in Study I6T-MC-AMBU (AMBU) may be reasonably anticipated.

As colonoscopies are required in this study, there are potential risks associated with the procedure, such as a reaction to sedation/anesthesia or the potential of perforation. Personnel knowledgeable and skilled in the administration of sedation/anesthesia to children will be used to minimize this risk.

In summary, the efficacy and safety data from the Phase 2 UC study AMAC support the continued clinical development of mirikizumab in pediatric patients with UC.

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

4. Objectives and Endpoints

Table AMBU.2 shows the objectives and endpoints of the study.

Table AMBU.2. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the pharmacokinetics (PK) of mirikizumab treatment in pediatric patients	• Clearance and volume of distribution of mirikizumab
Secondary	
• To evaluate the effect of treatment with mirikizumab on achieving **clinical remission** at Week 12 and/or Week 52	• The proportion of patients in modified Mayo score (MMS) clinical remission at Week 12 • The proportion of patients in MMS clinical remission at Week 52 • The proportion of patients in MMS clinical remission at Week 52 among the MMS clinical remitters at Week 12 (durable clinical remission) • The proportion of patients in MMS clinical remission at Week 52 among the MMS clinical responders from Week 12 **MMS clinical remission** is defined as: • Stool frequency (SF) subscore = 0, or SF = 1, and • Rectal bleeding (RB) subscore = 0, and • Endoscopic subscore (ES) = 0 or 1 (excluding friability) **MMS clinical response** is defined below
• To evaluate the effect of treatment with mirikizumab on achieving **clinical response** at Week 12 and/or Week 52	• The proportion of patients in clinical response at Week 12 • The proportion of patients in clinical response at Week 52 • The proportion of patients in clinical response at Week 12 who achieve clinical response at Week 52 **Clinical response** is based on the MMS and is defined as: ○ A decrease in the MMS of ≥2 points and ≥30% decrease from baseline, and ○ A decrease of ≥1 point in the RB subscore from baseline or a RB score of 0 or 1

Objectives	Endpoints
• To evaluate the effect of treatment with mirikizumab on achieving **corticosteroid-free remission** without surgery among patients in clinical remission at Week 52 and receiving corticosteroids at baseline	• The proportion of patients who are in MMS clinical remission at Week 52 without the use of corticosteroids CCI [redacted]
• To evaluate the effect of treatment with mirikizumab on **PUCAI clinical remission** at Week 12 and/or Week 52	• The proportion of patients in PUCAI clinical remission at Week 12 • The proportion of patients in PUCAI clinical remission at Week 52 • The proportion of patients in PUCAI clinical remission at Week 12 who achieve clinical remission at Week 52 • The proportion of patients in PUCAI clinical response at Week 12 who achieve clinical remission at Week 52 **PUCAI clinical remission** is defined as a PUCAI score of <10 points **PUCAI clinical response** is defined below
• To evaluate the effect of treatment with mirikizumab on **PUCAI clinical response** at Week 12 and/or Week 52	• The proportion of patients in PUCAI clinical response at Week 12 • The proportion of patients in PUCAI clinical response at Week 52 • The proportion of patients in PUCAI clinical response at Week 12 who achieve PUCAI clinical response at Week 52 **PUCAI clinical response** is defined as a reduction in baseline PUCAI score of ≥20 points
• To evaluate the effect of treatment with mirikizumab on achieving **endoscopic remission** at Week 12 and/or Week 52	• The proportion of patients in endoscopic remission at Week 12 • The proportion of patients in endoscopic remission at Week 52 • The proportion of patients in endoscopic remission at Week 12 who maintain endoscopic remission at Week 52 (durable endoscopic remission) **Endoscopic remission** is defined as: o ES = 0 or 1 (excluding friability)
• To evaluate the effect of treatment with mirikizumab on achieving **ES = 0** at Week 12 or Week 52	• The proportion of patients with ES = 0 at Week 12 • The proportion of patients with ES = 0 at Week 52

Objectives	Endpoints
• To evaluate the effect of treatment with mirikizumab on **symptomatic remission** over time	• Proportion of patients in symptomatic remission at applicable study visits **Symptomatic remission** is defined as: ○ SF = 0, or SF =1 with a ≥ 1-point decrease from baseline and ○ RB = 0
• To evaluate the effect of treatment with mirikizumab on height velocity at Weeks 12, 24, and 52	• Observed height velocity by gender and age group will be calculated at baseline, Week 12, Week 24, and Week 52
• To evaluate the effect of treatment with mirikizumab on weight throughout the trial	• Change from baseline in weight (kg) at all study visits by gender and age group
• To evaluate the effect of treatment with mirikizumab on pubertal development throughout the trial in appropriate patient groups	• Hormone levels and/or other related clinical measures will be evaluated
• CCI [redacted]	CCI [redacted]
• To evaluate **histologic-endoscopic mucosal remission** following mirikizumab treatment at Week 12 or Week 52	• Proportion of patients with histologic-endoscopic mucosal remission at Week 12 • Proportion of patients with histologic-endoscopic mucosal remission at Week 52 **Histologic-endoscopic mucosal remission** is defined as achieving both histologic remission and endoscopic remission. **Histologic remission** will be defined in the SAP.
• To evaluate the development of anti-mirikizumab antibodies and their effect on CCI [redacted]	• Proportion of patients who have treatment-emergent anti-drug antibodies (TEADA) • CCI [redacted]
• CCI [redacted]	• CCI [redacted]
Exploratory	
• To evaluate the effect of treatment with mirikizumab on changes in biomarkers	• Change from baseline in fecal calprotectin • Change from baseline in C-reactive protein

Objectives	Endpoints
• CCI [redacted]	• CCI [redacted]
• To evaluate the time to **symptomatic response**	• Time to **symptomatic response** (defined as at least a CCI [redacted] in the composite clinical endpoint of the sum of SF and RB subscores)
• To evaluate the time to **symptomatic remission**	• Time to **symptomatic remission** (defined as SF = 0, or SF = 1 with a ≥1-point decrease from baseline, and RB = 0)
• To evaluate the numerical value and change from baseline of individual MMS subscores and the composite symptom subscore over time in patients receiving mirikizumab	• The numerical value and change from baseline in each of the following items: ○ SF (Weeks 2, 4, 8, 12, 24, 36, and 52) ○ RB (Weeks 2, 4, 8, 12, 24, 36, and 52) ○ ES (Weeks 12 and 52) ○ The composite clinical endpoint of the sum of the SF and RB subscores (Weeks 2, 4, 8, 12, 24, 36, and 52)
• CCI [redacted]	CCI [redacted]
• CCI [redacted]	CCI [redacted]
• CCI [redacted]	CCI [redacted]
• CCI [redacted]	CCI [redacted]
• CCI [redacted]	CCI [redacted]

Abbreviations: NRS = numeric rating scale; PGI-C = Patient's Global Impression of Change; PGRS = Patient's Global Rating of Severity; PUCAI = Pediatric Ulcerative Colitis Activity Index; SAP = statistical analysis plan; UC = ulcerative colitis.

5. Study Design

5.1. Overall Design

Study AMBU is a multicenter, open-label PK study designed to evaluate the safety, PK, pharmacodynamics (PD), and clinical response of mirikizumab in pediatric patients, and to provide data for dose confirmation for Phase 3.

The study population includes patients with moderately to severely active UC who have an inadequate response to, loss of response to, or are intolerant to non-biologic therapy for UC (biologic-naive), and/or those who have been exposed to at least 1 biologic and/or JAK inhibitor therapy for UC (biologic/JAK inhibitor-experienced).

Patients weighing >40 kg will receive a mirikizumab induction dose of 300 mg via IV infusion and patients weighing ≤40 kg will receive induction doses of 5 or 10 mg/kg via IV infusion at Weeks 0, 4, and 8. Enrollment will begin with the 300 mg and 5 mg/kg dose cohorts. Patients in the 10 mg/kg cohort will be enrolled after 5 patients in the 5 mg/kg dose cohort have received 4 weeks of mirikizumab, an evaluation of the available PK in the 5 mg/kg cohort (as described in Section 10.3.8.1) has been conducted, and enrollment of the 5 mg/kg dose cohort has been filled.

Patients who achieve a Modified Mayo Score (MMS) clinical response (see Table AMBU.5) at Week 12 will proceed to the maintenance period and receive SC doses of 200 mg (weight >40 kg), or 100 mg (weight >20 kg to ≤40 kg), or 50 mg (weight ≤20 kg) mirikizumab Q4W through Week 48.

Patients who do not meet the MMS clinical response definition at Week 12 may receive extended IV induction dosing (either at the same dose or for the 5 mg/kg dose cohort, escalate to the 10 mg/kg dose) for 12 more weeks or discontinue. Following the completion of IV dosing at Week 24, if the investigator determines that the patient has improved, the patient will proceed to the maintenance period and receive Q4W SC doses based on weight class through Week 48. If the investigator determines that sufficient improvement was not made, the patient will discontinue study drug and undergo procedures for early termination of the study drug, including post-treatment follow-up as described in the Schedule of Activities (Section 2).

Upon completion of the maintenance period (Week 52), all patients will have the option to enter the 3-year long-term extension Study I6T-MC-AMAZ (AMAZ) or enter the post-treatment follow-up period (12 weeks following SC administration). With sponsor approval, additional dosing at Week 52 and unscheduled visits (UV) beyond Week 52 may occur as needed for patients eligible to enroll in Study AMAZ where the clinical trial site is not yet open. Patients must have completed all procedures at Visit 16 and additional dosing should occur at 4-week intervals (±7 days) from the prior dose. Patients who discontinue while receiving IV dosing will undergo procedures for early termination of the study drug, including post-treatment follow-up for 16 weeks as described in the Schedule of Activities (Section 2).

Figure AMBU.1 illustrates the study design

Study governance considerations are described in detail in Appendix 3.

Figure AMBU.1. Illustration of study design for clinical protocol I6T-MC-AMBU.

5.1.1. Definition of Baseline

Visit 2 (Week 0) is the baseline visit. The baseline MMS is calculated from valid CCI diary entries obtained prior to endoscopy during the screening period and the endoscopic appearance of the mucosa at this screening endoscopy (Section 9.1.1). For other efficacy, health outcomes, and safety assessments, baseline is defined as the last non-missing assessment recorded on or prior to the date of Visit 2 (Week 0).

5.1.2. Definition of Enrollment

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

5.2. Number of Participants

Approximately 60 patients with moderately to severely active UC will be screened to enroll approximately 30 patients.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

Study AMBU is an open-label, Phase 2 study to evaluate the safety, PK, PD, and clinical response of mirikizumab in pediatric patients with UC, to provide data for dose regimen confirmation in Phase 3.

An open-label study ensures that all patients receive active treatment while allowing the primary evaluation of PK of mirikizumab treatment in pediatric patients.

The 12-week IV dosing induction period was chosen CCI The 40-week maintenance period enables CCI The timing of the induction and maintenance endpoints was chosen based on characterization of the safety and efficacy of mirikizumab through 52 weeks of continuous treatment in Study AMAC, the Phase 2, placebo-controlled, double-blind adult clinical trial of mirikizumab in moderately to severely active UC, as well as consistency with the timing of the induction and maintenance endpoints of the ongoing Phase 3 adult program studies AMAN and AMBG.

Patients are allowed to continue non-biologic background therapy throughout the study (for example, 5-aminosalicylic acids [5-ASAs], corticosteroids, AZAs, and 6-MPs), subject to concomitant medication and dose stabilization criteria. In this context, it is anticipated that mirikizumab will be administered as an add-on therapy in the majority of patients.

The selection of clinical remission at Week 52 using MMS (FDA 2016) and the Pediatric Ulcerative Colitis Activity Index (PUCAI) as secondary endpoints are consistent with regulatory guidance documents (EMA 2016a,b). These endpoints will assess improvement in the clinical signs and symptoms of stool frequency (SF), rectal bleeding (RB), and abdominal pain, and

additionally assess the visual appearance of the mucosa through the endoscopic subscore (ES). CCI [redacted]

5.5. Justification for Dose

Dose regimens and weight categories are based on analyses of PK, exposure–response, and safety data from the Phase 2 adult study AMAC in patients with UC. Study AMAC evaluated mirikizumab IV induction doses of 50, 200, and 600 mg administered Q4W and SC maintenance doses of 200 mg administered Q12W or Q4W. The 50 mg and 200 mg IV induction dose cohorts included exposure-based dose adjustments that resulted in overall average induction doses of 100 and 250 mg, respectively. Evaluation of unblinded safety data from the completed and ongoing clinical studies, which assessed mirikizumab doses up to 1000 mg IV Q4W, demonstrate an acceptable safety profile to date. Based on data from Study AMAC, the doses selected for evaluation in adults in Phase 3 are 300 mg IV Q4W during induction and 200 mg SC Q4W during maintenance.

Previous evaluations of therapeutic antibodies in pediatric subjects indicate that the primary factor that influences PK is body weight rather than age (Dirks and Meibohm 2010). The range of adult body weights in Study AMAC was 40 to 122 kg, with a median of 75 kg. Although there was a trend for decreasing mirikizumab clearance with decreasing body weight in Study AMAC, this relationship was not statistically significant. However, for the purposes of initial dose selection for this study, an allometric relationship between body weight and mirikizumab clearance with an exponent of 0.8 was assumed. This allometric relationship provides a more conservatively high estimate of exposure for a given body weight as compared to assuming no relationship, and also is consistent with historical data for other therapeutic antibodies (Bai et al. 2012).

Based on Study AMAC adult data and the CCI [redacted] Therefore, evaluation of an IV dose of 300 mg is planned for the induction period of the study for patients with a body weight >40 kg. This dose is expected to provide comparable induction exposures as the 300 mg IV Q4W that is being evaluated in Phase 3 adult studies.

Pediatric patients with a body weight of ≤40 kg will receive doses using a weight-based approach (mg/kg) that is expected to provide comparable systemic exposures as doses evaluated in the adult Phase 2 study AMAC and in Phase 3. Intravenous doses of 5 and 10 mg/kg are planned for the induction period for patients with a body weight of ≤40 kg to collect sufficient PK data over a dose range of interest and optimally support the selection of an induction dose in future studies that will produce exposures similar to adults.

Figure AMBU.2 shows a comparison of the exposures projected for the weight-based doses relative to the 300 mg IV planned for adults in Phase 3 and the 600 mg IV dose evaluated in

Study AMAC. The planned weight-based doses are not expected to produce exposures higher than those evaluated in the adult Phase 2 study.

Interim and/or real-time analyses of PK data from pediatric patients that receive the lowest induction doses in this study (300 mg and 5 mg/kg) will be conducted prior to enrolling the 10mg/kg cohort, as shown above in Figure AMBU.1. The 10 mg/kg dose level may be adjusted based on these analyses, but it will be no higher than the 10 mg/kg currently planned.

Figure AMBU.2. Comparison of interquartile range for average induction concentration for the doses planned in pediatric patients ≤40 kg relative to adults.

The dose regimen selected for the maintenance period of the study for patients with a body weight of >40 kg is 200 mg SC Q4W, and this dose is expected to provide comparable maintenance exposures to the 200 mg SC Q4W that is being evaluated in Phase 3 adult studies. The maintenance dose regimens for patients ≤40 kg are divided into 2 fixed SC doses based on body weight. Patients with a body weight between >20 kg and ≤40 kg will receive a 100 mg SC Q4W dose, and patients with a body weight ≤20 kg will receive a 50 mg SC Q4W dose. Figure AMBU.3 shows a comparison of the exposures projected for these dose regimens relative to the 200 mg SC Q4W maintenance regimen planned for adults in Phase 3. The planned SC

maintenance doses are expected to produce exposures similar to the 200 mg SC maintenance dose that was evaluated in the adult Phase 2 study.

CCI

Figure AMBU.3. Comparison of interquartile range for average maintenance concentration for the doses planned in pediatric patients relative to adults.

6. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted. A patient is considered enrolled into the study once the patient is assigned to treatment.

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria within the screening period, which is CCI [redacted], unless otherwise specified below:

Informed Consent

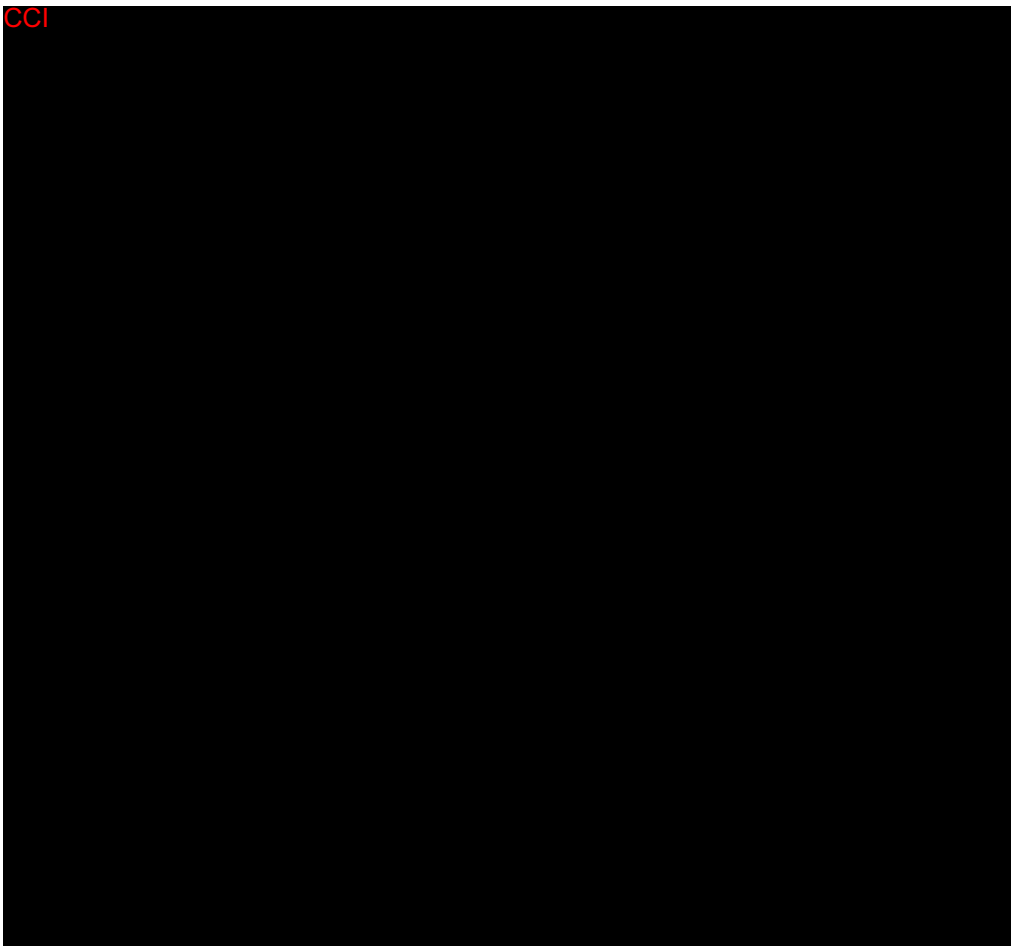
[1] Have given assent (if appropriate) with parent/legal guardian signed informed consent approved by the ethical review board (ERB) governing the site.

Patient Characteristics

[2] Male or female patients weighing >10 kg AND ≥2 and <18 years of age at the time of informed consent.

[2a] CCI [redacted]

[2b] CCI [redacted]



[3] Both the parent or legal representative and child (if capable) must agree to comply with the requirements of the protocol.

[4] CCI

Type of Patient and Disease Characteristics

[5] Have an established diagnosis of UC of ≥3 months in duration before baseline, CCI

[6] Have moderately to severely active UC as defined by a CCI within CCI before first dose of study treatment (baseline).

[7] Have evidence of UC extending proximal to the rectum CCI

Prior Medication Failure Criteria

[8] Patients must have an inadequate response to, loss of response to, or intolerance to at least 1 of the medications described in Criteria [8a] OR [8b]. **Documentation of dose, frequency, route of administration, and duration of the prior failed treatment is required.**

[8a] **Biologic-naive patients:** Patients who have an inadequate response to, loss of response to, or are intolerant to at least 1 of the following medications:

- Corticosteroids
  - Corticosteroid-refractory colitis, defined as signs and/or symptoms of active UC despite a CCI [redacted]
- Immunomodulators:
  - Signs and/or symptoms of persistently active disease despite at least 3 months' treatment with 1 of the following:
    - Oral AZA CCI [redacted] or 6-MP CCI [redacted], or
  - History of intolerance to at least 1 immunomodulator CCI [redacted]

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

[8b] **Biologic/JAK inhibitor-experienced patients:** Patients who have an inadequate response to, CCI [redacted] to biologic therapy for UC (such as anti-TNF antibodies or anti-CCI [redacted] antibodies) and/or to JAK inhibitors (such as tofacitinib), as described below. **Investigators must document an adequate trial of the medication**. Patients should fulfill at least 1 of the following criteria:

- Inadequate response: Signs and symptoms of persistently active disease despite prescribed induction treatment, or
- CCI [redacted]
- Intolerance: History of intolerance to infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or other biologics or JAK inhibitors (including but not limited to infusion-related event, demyelination, congestive heart failure, or any other drug-related AE that led to a reduction in dose or discontinuation of the medication), or

CCI [redacted]

Dose Stabilization Inclusion Criteria

[9] Are on stable doses of the following permitted drugs (see Appendix 6):

[9a] Oral 5-ASA compounds: if the prescribed dose has been stable for CCI [redacted] before screening endoscopy.

[9b] Oral corticosteroid therapy CCI [redacted]: if the prescribed dose has been CCI [redacted] before the screening endoscopy.

[9c] CCI [redacted] have been prescribed at a stable dose for at least CCI [redacted] before the screening endoscopy.

Study Procedure Inclusion Criteria

[10] Are willing and able to complete the scheduled study assessments, including endoscopy, and CCI [redacted] diary entry.

[11] Have clinically acceptable central laboratory results or local laboratory results reviewed and approved by sponsor medical monitor or designee during screening, as assessed by the investigator, including:

[11a] Hematology:

CCI [redacted]

[11b] Chemistry:

CCI [redacted]

- CCI [redacted] may be allowed to enroll but cases must be discussed and judged not clinically significant by the sponsor medical monitor prior to enrollment.

- Patients with CCI [redacted]

Retesting within the screening period is allowed for hematology and chemistry; see Section 6.4.

[12] Are CCI [redacted] guidelines as noted by country specific pediatric authorities (for example, the American Academy of Pediatrics). CCI [redacted]

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria within the screening period, which is CCI [redacted] to the start of study drug, unless otherwise specified below:

For rescreening activities within the screening period, see Section 6.4.

Gastrointestinal Exclusion Criteria

[13] Have a current diagnosis of CD, IBD-Unclassified (formerly known as indeterminate colitis), ulcerative proctitis (distal disease limited to the rectum), or primary sclerosing cholangitis.

[14] Have a documented history of CCI [redacted]

[15] Previous bowel resection or intestinal or intra-abdominal surgery:

CCI [redacted]

- Have had any small bowel or colonic surgery within CCI [redacted] prior to baseline.
- Have had any non-intestinal intra-abdominal surgery within CCI [redacted] of baseline.

[16] Have evidence of toxic megacolon, CCI [redacted] the small bowel or colon.

[17] Have any history or current evidence of cancer of the gastrointestinal tract.

CCI [redacted]

Criteria for Discontinuing Prohibited Medications

[19] Have received any of the following for treatment of UC within the timeframes specified below:

[19a] Corticosteroid enemas, corticosteroid suppositories, or IV corticosteroids CCI [redacted] prior to screening endoscopy.

[19b] 5-ASA enemas or 5-ASA suppositories CCI [redacted] prior to screening endoscopy.

[19c] CCI [redacted]

CCI [redacted]

[19d] Anti-TNF antibodies (for example, infliximab, adalimumab, or golimumab) within CCI [redacted] prior to screening endoscopy.

[19e] CCI [redacted]

[19f]

[19g] Any investigational therapy (biologic or non-biologic) within CCI [redacted] prior to the screening endoscopy or within 5 half-lives prior to the screening endoscopy, whichever is longer.

[19h] CCI [redacted]

[19i] CCI [redacted]

[20] Have failed anti-IL12p40 antibodies (for example, ustekinumab [STELARA®]) or have ever received anti-IL-23p19 antibodies (for example, risankizumab [BI-655066/ABBV-006], brazikumab [MEDI-2070], guselkumab [CNTO1959], or tildrakizumab [MK-3222]) for any indication, including investigational use.

Infectious Disease Exclusion Criteria

[21] Patients who:

[21a] Have evidence of active TB, or

[21b] Have a past history of active TB, regardless of treatment, or

[21c] Have a past history of latent tuberculosis infection (LTBI) and have not completed an appropriate TB treatment regimen (Section 9.4.5.2) or

[21d] Are diagnosed with LTBI at screening.

CCI [redacted]

[22] CCI [redacted]

[23] Have human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), test positive for HIV antibodies at screening (see Section 6.2.1).

[24] Have acute or chronic hepatitis B infection or test positive for hepatitis B virus (HBV) at screening, defined as:

[24a] Positive for hepatitis B surface antigen (HBsAg+).

OR

[24b] Positive for anti-hepatitis B core antibody (anti-HBc+) and positive confirmatory PCR for HBV deoxyribonucleic acid (DNA) (see Section 9.4.5.4).

OR

[24c] Detectable HBV DNA (see Section 9.4.5.4).

[25] Have current hepatitis C infection, or test positive for hepatitis C virus (HCV) at screening, defined as:

- Positive for hepatitis C antibody and detectable HCV ribonucleic acid (RNA) (see Section 9.4.5.5).

CCI [redacted]

[26] Had *Clostridium difficile* or other intestinal infection within CCI of screening endoscopy, or test positive at screening for *C. difficile* or for other intestinal pathogens. CCI [redacted]

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

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

[28a] Infections requiring IV antibiotics.

[28b] Infections requiring hospitalization.

[28c] Infections that are considered "opportunistic" (examples are listed in Appendix 9).

[28d] Chronic, recurrent infections (for example, osteomyelitis and recurring cellulitis).

Patients with an opportunistic infection or chronic, recurrent infection CCI [redacted] should be discussed on a case-by-case basis with the medical monitor.

[29] Have evidence of active/infectious herpes zoster infection or primary varicella zoster infection CCI [redacted] prior to screening. Infections are considered active until all vesicles are crusted over.

General Exclusion Criteria

[30] Have had lymphoma, leukemia, or any malignancy within CCI [redacted] of screening.

Exceptions: The following conditions are not exclusionary:

a) Basal cell or squamous epithelial carcinoma of the skin that has been adequately treated with no evidence of metastatic disease for at least CCI [redacted]

b) Cervical carcinoma in situ that has been adequately treated with no evidence of recurrence within CCI [redacted] of baseline.

[31] 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.

[32] Are Eli Lilly and Company (Lilly) employees or employees of third-party organizations involved with the study.

[33] 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.

[34] Have previously completed or withdrawn from this study or any other study investigating mirikizumab after receiving study drug. This criterion does not apply to patients undergoing rescreening procedures.

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

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

OR

For patients CCI [redacted] during the screening period prior to dosing at Visit 2;

OR

CCI [redacted]

AND

CCI [redacted]

[37] Have an unstable or uncontrolled illness, including but not limited to a cardiovascular, respiratory, gastrointestinal (excluding UC), neurological or neuropsychiatric disorders, that would potentially affect patient safety within the study or confound efficacy assessment.

[38] Have a known hypersensitivity to any component of mirikizumab or monoclonal antibodies.

[39] Have a solid organ transplant or hematopoietic stem cell transplantation.

[40] Are unwilling or unable to comply with the use of a data collection device to directly record data from the subject.

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

[42] Are pregnant, lactating, or planning pregnancy (both males and females) while enrolled in the study or within CCI [redacted] after receiving the last dose of study drug.

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

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

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

[46] Had a blood transfusion in the last CCI [redacted] prior to hematology blood sample collection.

6.2.1. Rationale for Exclusion of Certain Study Candidates

Children younger than 2 years of age are excluded from this study due to the difficulty in obtaining a definitive diagnosis of UC in children/infants younger than 2 years of age and the potential for lack of efficacy in this age group. CCI

CCI

6.3. Lifestyle Restrictions

If applicable, study participants should be instructed not to donate blood or blood products during the study or for CCI following their last dose. In order to participate in the study, patients must agree to the contraception, reproduction, and breastfeeding criteria detailed in study entry criteria (Section 6.1 and Section 6.2).

6.4. Screen Failures

Allowed rescreening of patients after initial screen failure

Patients who have failed screening because of the following Inclusion/Exclusion Criteria may be rescreened when the reason for screen failure has resolved:

- [5]
- [6]
- [7]
- [8]
- [9]
- [11]
- [12]
- [15]
- [18c] (once polyps have been removed)
- [19]
- [22]
- [27] to [30]
- [35]
- [42]
- [45], and
- [46].

Individuals may be rescreened up to 2 times, for a maximum total of 3 screens unless additional rescreening is approved via sponsor's medical monitor or designee.

Participants who have failed screening because of Exclusion Criterion [21c] CCI may be rescreened 1 time (see Section 9.4.5.2).

Participants who have failed screening because of Exclusion Criterion [26] may be rescreened 1 time for *C. difficile* stool toxin. Additionally, a participant may be rescreened 1 time for stool culture or ova parasite. In either situation, participant rescreening should only occur after the reason for screen failure has resolved. It is recommended that the investigator confirms the participant has a negative *C. difficile* stool toxin/stool culture/stool ova parasite (as applicable) before performing additional rescreening investigations (see also Section 9.4.5.7). The interval between rescreening visits should be at CCI unless a shorter interval has been agreed with the study's medical monitor. Each time rescreening is performed the participant, parent/guardian must sign a new informed consent form (ICF) and will be assigned a new identification number.

Participants who screen fail because they are unable to complete their endoscopy prior to Visit 2 will not be required to undergo repeat TB testing, chest X-ray (CXR) or computed tomography (CT), HIV, HBV, and HCV testing stool cultures, and *C. difficile* testing if these were normal or negative during screening after discussion with sponsor medical monitor or designee. These tests should be repeated if based on the investigator's judgment the patient has risk factors and/or signs and symptoms of illness. Participants may undergo repeat rescreening sooner than CCI between screen failure and rescreening.

Disallowed rescreening of patients after initial screen failure

Patients who have failed screening because of the following Exclusion Criteria may **not** be rescreened:

- [10]
- [13]
- [14]
- [16]
- [18a] and [18b]
- [20]
- [21a] and [21b] (if current or past history of active TB)
- [23] to [25]
- [31] to [34]
- [36] to [41]
- [43], and
- [44].

6.4.1. Allowed Retesting of Screening Investigations

The screening investigations specified below may be retested once without the need for rescreening at the discretion of the investigator.

- **Screening hematology and chemistry blood tests:** where 1 or more results are outside the acceptable range for inclusion in the study but may be within the acceptable range for inclusion on retesting, due to test-retest variability.
- **Stool testing**: if there is a technical difficulty in performing or reporting the *C. difficile* or stool culture assays.
- **Retesting or confirmatory testing with an interferon-γ release assay (IGRA)**: for example, QuantiFERON®-TB Gold or T-SPOT® assay) in selected patients as part of screening for LTBI (see Section 9.4.5.2 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 investigations should be discussed with the medical monitor prior to retesting.

7. Treatments

7.1. Treatments Administered

In this study, mirikizumab is administered by IV or SC routes to pediatric patients in a staggered approach based on dose level as per Table AMBU.3. Assignment to weight classes will be based on body weight at enrollment for induction period dosing and Week 12 for dosing at Week 12 and beyond; patients will continue in the assigned weight group throughout the duration of the study.

Patients in the high weight cohort will receive flat dosing, while patients in the low weight cohort will receive weight-tiered dosing in order to obtain similar exposures as flat dose regimens in the higher weight cohort.

Patients who achieve clinical response at Week 12 will follow the treatment regimens described in Table AMBU.3. Patients who do not achieve clinical response at Week 12 will follow the treatment regimens described in Table AMBU.4.

If any patient experiences loss of response and meets the criteria for loss of response in Section 9.1.5 at or after Week 16 and up to Week 40, they may receive rescue or discontinue the study based on their physician's discretion. Rescue treatment is IV mirikizumab Q4W for 3 doses based on their weight cohort. Once IV loss of response dosing is complete, patients who, in the opinion of the investigator, are receiving clinical benefit from mirikizumab therapy may continue with further SC dosing. Patients who are not considered by the investigator to be receiving clinical benefit from mirikizumab IV rescue therapy, will be discontinued and proceed to post-treatment follow-up.

Table AMBU.3. Treatment Regimens: Week 12 Clinical Responders

Weight Cohort	Dose Weeks 0, 4, and 8	Dose Weeks 12 through 48	Enrollment Initiation
>40 kg	300 mg mirikizumab IV	200 mg mirikizumab Q4W SC	CCI [redacted]
≤40 kg	5 mg/kg mirikizumab IV	≤20 kg: 50 mg mirikizumab Q4W SC >20 to ≤40 kg: 100 mg mirikizumab Q4W SC	CCI [redacted]
≤40 kg	10 mg/kg mirikizumab IV	≤20 kg: 50 mg mirikizumab Q4W SC >20 to ≤40 kg: 100 mg mirikizumab Q4W SC	CCI [redacted]

Abbreviations: IV = intravenous; PK = pharmacokinetics; Q4W = every 4 weeks; SC = subcutaneous.

Table AMBU.4. Treatment Regimens: Week 12 Clinical Nonresponders

Weight Cohort	Dose Weeks 0, 4, and 8	Dose Weeks 12 through 48
>40 kg	300 mg mirikizumab IV	CCI
≤40 kg	5 mg/kg mirikizumab IV	
≤40 kg	10 mg/kg mirikizumab IV	

Abbreviations: IV = intravenous; Q4W = every 4 weeks; SC = subcutaneous.

Study Drug Administration

Intravenous infusion of mirikizumab will occur over at CCI [redacted] All patients should be monitored for CCI or longer following IV administration, according to investigator practice or local standard of care. Sites must have resuscitation equipment, emergency medications, and appropriately trained staff available during the infusion and monitoring period. Detailed instructions for investigational product administration will be provided separately by the sponsor.

Subcutaneous administration of mirikizumab will be given CCI [redacted]. Patients should be monitored according to investigator practice or local standard of care. Acceptable locations for SC administration include the abdomen, front upper thighs, upper arms, and buttocks.

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

- Explaining the correct use of the investigational agent to the site personnel
- Verifying that instructions are followed properly
- Maintaining accurate records of investigational product dispensing and collection
- At the end of the study returning all unused medication to Lilly, or its designee, unless the sponsor and sites have agreed that all unused medication is to be destroyed by the site, as allowed by local law

7.1.1. Packaging and Labelling

Mirikizumab will be supplied to the investigator by Lilly or its designee. Clinical trial materials will be labeled according to the country's regulatory requirements. All investigational products will be stored, inventoried, reconciled, and destroyed according to applicable regulations.

Clinical trial materials are manufactured in accordance with current Good Manufacturing Practices (GMP).

Study drug will be supplied as:

- Single use solution pre-filled syringe containing mirikizumab. The CCI syringe of mirikizumab is manufactured to deliver CCI
- Single use solution vial containing mirikizumab. The CCI vial of mirikizumab is manufactured to deliver CCI

Study drug will be provided with study-specific labels. Syringes and vials will be supplied in cartons, with the appropriate quantity specific to the planned dispensing schedule of the investigational product.

7.2. Method of Treatment Assignment

Study AMBU is open-label and patients will be assigned to mirikizumab dose groups based on weight at Visit 2.

An interactive web-response system (IWRS) will be used to assign investigational product to each patient. Site personnel will confirm that they have located the correct investigational product package by entering a confirmation number found on the package into the IWRS.

At Week 12, patients who meet the clinical response criteria (see Table AMBU.5) may proceed to the maintenance period and will continue with open-label mirikizumab SC dosing based on current body weight.

Nonresponding patients (see Section 9.1.5) may enter into extended induction dosing via IV administration for the next 12 weeks or discontinue the study.

7.2.1. Selection and Timing of Doses

Patients who meet all criteria will be assigned to treatment and will receive their assigned study drug as outlined in Sections 7.1 and 7.2. The actual time of all dose administrations will be recorded in the patient's electronic case report form (eCRF).

7.3. Blinding

This is an open-label study.

7.4. Dosage Modification

Dose adjustments, other than CCI , are not permitted in this study.

7.5. Preparation/Handling/Storage/Accountability

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

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

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

Mirikizumab should be stored in refrigerated conditions CCI [redacted].

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

7.6. Treatment Compliance

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

Every attempt will be made to select patients and caregivers who have the ability to understand and comply with study instructions. The investigator is responsible for discussing methods to ensure high treatment compliance with the patient and caregiver before study enrollment.

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

- the review of caregiver remission SF value as a critical data point
- how to evaluate their UC symptoms and to record them on the CCI [redacted] diary, and
- the importance of being compliant with the CCI [redacted] diary recording.

If a patient is noncompliant with study procedures and/or investigational product administration, the investigator should assess the patient to determine the reason for noncompliance and educate and/or manage the patient as appropriate to improve compliance. Overall compliance with therapy is defined in the statistical analysis plan (SAP). If, in consultation with Lilly or its designee, the noncompliance is deemed to be significant or if further noncompliance occurs, the patient may be discontinued from the study.

7.7. Concomitant Therapy

The list of prohibited medications and the list of permitted medications with dose stabilization guidance are provided in Appendix 5 and Appendix 6, respectively.

All concomitant medications (including medications for bowel preparations) taken during the study must be recorded in the Concomitant Medication eCRF. This includes concomitant medications for UC as well as for underlying conditions or diseases, and for AEs. All patients are encouraged to maintain their usual medication regimens for concomitant conditions or diseases throughout the study, unless those medications are specifically excluded (Appendix 5).

Stable doses of permitted UC concomitant medications (other than oral corticosteroids) are encouraged, unless dose modification is required due to AEs, or dose modification is otherwise specified in Appendix 6. Patients taking oral corticosteroids are to follow the corticosteroid taper instructions described in Section 7.7.1.

Administration of prohibited UC medications for the management of symptoms 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 patient safety. Patients who require a prohibited medication to treat their UC (see Appendix 5) need to be discontinued from study drug and complete an early termination visit (ETV) and post-treatment follow-up visits.

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

Patients are allowed to continue or initiate any concomitant medication for non-UC conditions, diseases, or AEs, insofar that the medication is not specifically prohibited (Appendix 5) and use of the medication complies with the dosing requirements as described in Appendix 6.

7.7.1. Corticosteroid Taper

The investigator should use clinical judgement of the benefit/risk of steroid tapering for each individual subject as corticosteroids should be tapered as soon as possible following the recommended tapering regimen per local practice. Patients who enter Study AMBU on corticosteroid therapy for treatment of UC CCI [redacted] may initiate corticosteroid tapering based on the investigator's discretion. CCI [redacted] who have not already begun tapering corticosteroid therapy should initiate corticosteroid tapering no later than CCI [redacted] CCI [redacted] with mirikizumab will begin CCI [redacted] is achieved at any time after starting CCI [redacted]

Symptomatic response is defined as at least a CCI [redacted] from baseline in the composite clinical endpoint of the sum of SF and RB subscores.

The recommended tapering schedule for oral corticosteroids (other than budesonide) is as follows:

CCI

CCI

CCI In situations where the steroid tapering is paused, the tapering regimen (as described above) should be reinitiated within CCI of interruption of taper if possible, with a goal to complete tapering CCI

7.7.2. Vaccine Administration During the Study

Every effort should be made to vaccinate patients with standard of care vaccines prior to entry in the trial.

CCI

7.8. Treatment after the End of the Study

7.8.1. Study Extensions

Patients who complete this study through Week 52 and achieve clinical benefit may be eligible to participate in Study AMAZ. Patients who do not meet enrollment criteria for Study AMAZ or do not opt to continue into Study AMAZ, will be asked to complete the post-treatment follow-up period, as described in the Schedule of Activities (Section 2), which will complete their study participation.

7.8.2. Treatment after Study Completion

Mirikizumab will not be made available to patients after conclusion of the study, except through enrollment in the long-term extension trial, Study AMAZ.

7.8.3. Special Treatment Considerations

7.8.3.1. Premedication for Infusions

CCI Any premedication for infusions or injections should be discussed with the medical monitor. Any premedication given should be documented as a concomitant therapy.

CCI

Other Infusion-Related Events

If a patient experiences a reaction consisting of CCI during or up to 6 after an infusion of study drug, the following guidance should be followed:

CCI

CCI

[redacted]

Injection Site Reactions or Infusion Site Reactions

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

CCI

[redacted]

8. Discontinuation Criteria

8.1. Discontinuation from Study Drug

8.1.1. Permanent Discontinuation from Study Drug

Study drug may be permanently discontinued during the study. Patients who discontinue study drug early will undergo early termination procedures, which include an ETV and post-treatment follow-up visits.

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

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

- Patients who discontinue investigational product during CCI [redacted] will return for post-treatment follow-up visits (Visits 801 and 802) CCI [redacted] after the end-of-treatment visit.
- Patients who discontinue study drug CCI [redacted] will return for post-treatment follow-up visits (Visits 801 and 802) CCI [redacted] after the end-of-treatment visit.

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

Patient Decision

- The patient or the patient's designee, for example, parents or legal guardian, requests to discontinue investigational product.

CCI [redacted]

CCI [redacted]

Disease Worsening

- The patient requires rescue therapy for exacerbation of UC at doses higher than those specified in the "dose stabilization" inclusion criterion (for example, prednisone CCI Inclusion Criterion [9]), or with medications specified in the "prohibited medications" exclusion criterion (for example, IV corticosteroids, infliximab, or IV cyclosporine; Exclusion Criterion [19]) (see also Appendix 5).

Safety Criteria for Study Drug Discontinuation

- The patient has a diagnosis of any of the following during the study:
    - Cancer other than squamous cell or basal cell carcinoma of the skin
    - Polypoid or non-polypoid dysplasia that is endoscopically visible or invisible
    - Active TB (see Section 9.4.5.2)
    - HIV/AIDS
    - Hepatitis B or development of detectable HBV DNA (see Section 9.4.5.4)
    - Hepatitis C or development of detectable HCV RNA (see Section 9.4.5.5).
- The patient requires a colectomy during the study.
- The patient has a systemic hypersensitivity event or anaphylaxis to mirikizumab (Section 7.8.3.2). Study drug should be discontinued after a systemic hypersensitivity event or anaphylaxis.
- The patient becomes pregnant. Pregnant patients **will not** undergo an endoscopy/flexible sigmoidoscopy at the ETV.
- The patient has absolute lymphocyte count CCI after retesting (see Section 8.1.2).
- The patient is non-compliant with LTBI treatment (see Section 9.4.5.2).
- The patient experiences an AE or SAE that, in the opinion of the investigator or sponsor, would preclude him/her from continuing to receive study drug or if they experience disease worsening that requires rescue therapy with protocol excluded medications.

Other Reasons for Study Drug Discontinuation

- The investigator determines that the patient is repeatedly noncompliant with study procedures and/or study drug (see Section 7.6).
- Inadvertent enrollment (see Section 8.1.3).

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

8.1.2. Temporary Interruption (Withholding) of Study Drug

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

- Patient develops *C. difficile*, or other clinically important intestinal or extraintestinal infection during the study (including LTBI), see Section 6.2.
- Patient requires major surgery (administration of the investigational product may be restarted only after adequate wound healing).
- Patient develops a confirmed absolute neutrophil count [redacted]
- Patient develops absolute lymphocyte count [redacted] must be discontinued, if applicable, for a confirmed absolute lymphocyte count [redacted] (2 assessments below this threshold). The hematology must be repeated in [redacted]. If the absolute lymphocyte count remains [redacted], the hematology will be repeated again in [redacted] (that is, prior to the next dose of study drug). If the absolute lymphocyte count remains [redacted], the next dose of study drug will not be administered. The hematology will be repeated again in [redacted] If the absolute lymphocyte count remains [redacted], study drug will be permanently discontinued. White blood cell and lymphocyte counts will be followed for these patients until they return to an acceptable level.
- The patient has other laboratory abnormalities that may lead investigator to hold the study drug until resolution of the abnormalities.

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

8.1.3. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from study drug, unless there are extenuating circumstances that make it medically appropriate for the patient to continue on study drug. If the investigator and the sponsor agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor to allow the inadvertently-enrolled patient to continue in the study with or without treatment with the investigational product. Patients who are discontinued from study drug should have safety follow-up as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety), including ETV and post-treatment follow-up visits (Visit 801 and Visit 802).

8.2. Discontinuation from the Study

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

- Enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practices
- Investigator decision
    - The investigator decides that the patient should be discontinued from the study
    - If the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study will occur prior to introduction of the new agent
    - For patients who develop a condition, require a live vaccine, or begin a therapy that would have excluded entry into the study, the investigator must consult with Lilly-designated medical monitor to decide whether the patient can continue taking study drug and remain in the study.
- Patient decision
    - The patient or the patient's designee, for example, parents or legal guardian requests to be withdrawn from the study

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

8.3. Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or are otherwise unable to be followed up by the site.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, with the study procedures and their timing (including tolerance limits for timing). Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

Appendix 2 lists the laboratory tests that will be performed for this study.

A summary of the maximum number and volume of invasive samples for all sampling during the study will be provided separately.

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within CCI of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

Efficacy endpoints are found in Table AMBU.2. Secondary efficacy endpoint definitions are found in Table AMBU.5. Additional details are provided below.

Table AMBU.5. Secondary Efficacy Endpoint Definitions in Study AMBU

Endpoint	Definition
Modified Mayo Score (MMS) clinical remission	• Stool frequency (SF) subscore = 0, or SF = 1, and • Rectal bleeding (RB) subscore = 0; and • Endoscopic subscore (ES) = 0 or 1 (excluding friability)
MMS clinical response	• A decrease in the MMS of ≥2 points and ≥30% decrease from baseline, and • A decrease of ≥1 point in the RB subscore from baseline or a RB score of 0 or 1
Corticosteroid-free remission without surgery	CCI [redacted]
Pediatric Ulcerative Colitis Activity Index (PUCAI) clinical remission	• A PUCAI score of <10 points
PUCAI clinical response	• A reduction in baseline PUCAI score of ≥20 points
Endoscopic remission	• ES = 0 or 1 (excluding friability)
Symptomatic remission	• SF = 0, or SF = 1 with ≥1-point decrease from baseline, and • RB = 0
Histologic-endoscopic mucosal remission	• Defined as achieving both histologic remission and endoscopic remission. **Histologic remission** will be specified in the statistical analysis plan (SAP).
Loss of clinical response	• **Week 12 responders:** An increase from the Week 12 Partial Mayo score of CCI [redacted] (with confirmation of negative *C. difficile* testing) **or** • **Week 12 nonresponders who had extended induction:** An increase from the Week 24 Partial Mayo score of CCI [redacted] (with confirmation of negative *C. difficile* testing)
Symptomatic response	• CCI [redacted] from baseline in the composite clinical endpoint of the sum of SF and RB subscores

9.1.1. Mayo Score

This study utilizes components and permutations of the Mayo score (Schroeder et al. 1987) to assess UC disease activity for the primary and secondary endpoints (see Appendix 7). **Complete and accurate recording of the Mayo SF and RB subscores by patients or their parent/caregiver in their daily electronic diary is necessary for the success of the study**. Adequate bowel preparation and an endoscopy with adequate visualization of the mucosa will enable calculation of the Mayo ES.

Note: The investigator is responsible for ensuring that study participants receive adequate training on and appropriate understanding of:

- the importance of complete bowel preparation prior to endoscopies/flexible sigmoidoscopies
- how to record "remission/ normal" SF at the beginning of the study
- how to evaluate their UC symptoms and to record them on the CCI diary, and
- the importance of being compliant with the CCI diary recording.

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

Stool Frequency (SF): The SF subscore is a patient-reported measure. This item reports the number of stools in a CCI, relative to the normal number of stools for that patient in the same period, on a 4-point scale (see Appendix 7). CCI The total number of stools passed CCI will be recorded by the patient or caregiver in a daily electronic diary. The reference "normal" SF for that patient will be recorded electronically at the screening visit. Normal SF for that patient is based on reported SF when the patient was in remission or reported SF before initial onset of signs and symptoms of UC. Study software will use the patient-reported daily SF and the reference normal SF to automatically calculate the Mayo SF subscore. Further details on the analysis of CCI diary items are contained in the SAP.

Rectal Bleeding (RB): The RB subscore is a patient-reported measure. This item reports the most severe amount of blood passed with stool for a given day, on a 4-point scale (see Appendix 7). The patient or caregiver will record this in a CCI electronic diary.

Endoscopic Subscore (ES): The ES is a physician-reported measure that reports the worst appearance of the mucosa on flexible sigmoidoscopy or colonoscopy, on a 4-point scale (see Appendix 7). Determination of the ES is further detailed in Section 9.1.2. Consistent with current clinical practice and regulatory advice, this study subscore excludes friability from the definition of an ES of 1. Also consistent with best clinical trial practice, endoscopy scores will be determined from blinded central readers. The CCI endoscopy score is collected on paper and CCI) in the eCRF. The entry of the local endoscopy is critical to initiate the blinded central reading process.

Physician's Global Assessment (PGA): The Physician's Global Assessment (PGA) is a physician-reported measure that summarizes the investigator's assessment of the patient's UC disease activity on a 4-point scale (see Appendix 7). The investigator will record the PGA electronically as source data in the tablet device at appropriate study visits. Consistent with regulatory guidance, the PGA will not be used solely for efficacy assessment in this study.

Each subscore is scored on a 4-point scale, ranging from 0 to 3, to give a maximum Mayo score of 12. The study will use the following permutation of the Mayo score:

- Modified Mayo score (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

Additional permutations of the Mayo score have been described and may be used in analyzing data from this study.

Observer-reported outcomes will be used in place of patient-reported outcomes for children less than 8 years of age. To maintain consistency in reporting of SF and RB data, the patient's age at baseline will determine whether an observer-reported method (ages 2 through 7 years) or a patient-reported method (ages 8 through 17 years) will be used, irrespective of patient's age at later study visits. Efficacy assessments will be conducted in study population age range for which the scale/instrument was validated.

9.1.2. Endoscopy

Endoscopy will be used to determine the Mayo ES at CCI [redacted] Site and blinded central reading of endoscopies will be used to determine ES.

A flexible sigmoidoscopy or colonoscopy will be performed on all patients during screening, within CCI [redacted] to Visit 2. The endoscopy report and histopathology report (if biopsies are sent to the local histopathology laboratory) must be available in the source documents. Prior to performing the screening endoscopy, investigators should ensure that patients have SF and RB scores that suggest they will meet entry criteria (see Inclusion Criterion [6]) and clinically acceptable laboratory test results, including stool tests that are "negative" for *C. difficile* and other intestinal pathogens (see Inclusion Criterion [11] and Exclusion Criteria [21] and [23] to [26]).

Flexible sigmoidoscopy is generally recommended. However, full colonoscopy may be appropriate in some patients (for example, those with mild-to-moderate pan-colitis). The choice of flexible sigmoidoscopy or full colonoscopy is at the investigator's discretion. Other situations that may warrant a full colonoscopy at screening include:

CCI [redacted]

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

- Patients requiring screening for colorectal cancer, who do not have a current screening colonoscopy according to local guidelines. This may include:
  - Personal history indicating increased colorectal cancer risk, for example, previous adenomatous polyps.
  - Patients with other known risk factors.
- Where, in the opinion of the investigator, a colonoscopy is indicated at screening, for example, to confirm that a recent removal of an adenomatous polyp is complete prior to study enrollment.
- Patients who do not have the report of a completed, full colonoscopy available in source documents.

Patients who undergo colonoscopy at screening do not require a separate flexible sigmoidoscopy.

Patients will undergo a CCI [redacted] The endoscopy report and histopathology report (if biopsies are sent to the local histopathology laboratory) must be available in the source documents. Patients who discontinue the study drug because of pregnancy will not undergo a flexible sigmoidoscopy or full colonoscopy at their ETV.

The endoscopist will be a CCI [redacted] Investigators may delegate endoscopy to other members of the study team. However, all study staff performing endoscopy must CCI [redacted] at each endoscopy and it will be recorded in the eCRF.

All endoscopic procedures will be video recorded using a storage medium provided by the sponsor or designee. The video images will be sent for independent central reading. 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, and the qualifications required of the central reader.

The central readers will determine the centrally-read Mayo ES at each CCI [redacted] in a blinded manner, as detailed in the image review charter.

The procedure to address disagreement between the site readers and central readers is detailed in the image review charter. The final Mayo ES will be provided to the site prior to being enrolled at Visit 2 to enable determination of the MMS for eligibility.

9.1.3. Endoscopic Biopsies

A histopathology report supporting the diagnosis of UC must be available in the source documents prior to study enrollment, in order to satisfy Inclusion Criterion [5]. If a histopathology report is not available, the investigator can obtain additional biopsies for this purpose at the screening endoscopy (sent to the local histopathology laboratory).

Biopsies will be obtained at each endoscopy to support assessment of the histopathology endpoints in this study and, where permitted, CCI [redacted]. In rare circumstances, the investigator may consider it unsafe to collect all required biopsies; in this situation, fewer biopsies may be collected so as not to jeopardize patient safety. Biopsies will be sent to the central study laboratory for processing. A detailed biopsy reference guide from the central reading laboratory will provide the number of biopsies to be collected, and outline the procedures to be used for secure specimen transfer, processing, slide preparation, and digitization of slides for histopathologic scoring. These results will not be made available to study sites.

9.1.4. Pediatric Ulcerative Colitis Activity Index

The PUCAI (Turner et al. 2007) is a clinician-administered, 6-item questionnaire that measures: abdominal pain; RB; stool consistency; number of stools; nocturnal stools; and activity level (see Appendix 7). All items are answered as an average over the 'past 2 days'. A total disease activity score is calculated from 0 to 85, with severe: 65-85, moderate: 35-60, mild: 10-30, and none: <10. The clinician will record the patient or caregiver/legal guardian responses for the PUCAI electronically as source data in the tablet device at appropriate visits.

9.1.5. Determination of Responder Status/Loss of Response

At Week 12, patients who achieve an MMS clinical response as defined in Table AMBU.5 may move into the maintenance period.

Week 12 Nonresponders are defined as those that **do not meet** the following criteria:

- A decrease in the MMS of CCI [redacted] from baseline, and
- A decrease of CCI [redacted] in the RB subscore from baseline or a RB score CCI [redacted].

Nonresponding patients may receive extended induction dosing via IV infusion Q4W for 12 weeks as noted in Table AMBU.4.

CCI [redacted]

CCI

[redacted]

9.1.6. Growth and Pubertal Assessments

9.1.6.1. Occipital Head Circumference

Occipital head circumference measurements will be performed on patients less than 3 years of age at baseline. Measurements will be taken at baseline and then approximately Q12W thereafter, until the patient reaches the age of 3 years.

9.1.6.2. Height Velocity

Height will be collected 3 times per visit at the visits indicated in Section 2 using a stadiometer or other instrument of equivalent measuring capacity. Observed height velocity by gender and age group will be calculated at CCI [redacted], based on height measurements from the 3 to 12 months (preferably 4 to 6 months) preceding the study (from screening) or those obtained at baseline according to the following formula:

- (Present Height [cm] - Previous Height [cm])/Interval (months) Between Measurements × 12

Age-specific z-scores for height velocity by gender and age group will be calculated for each patient with reference to standard height velocity tables according to the following formula:

- (Observed Height Velocity [cm/y] - Mean Height Velocity for Age and Sex [cm/y])/(Standard Deviation of the Mean)

Full details on height velocity analyses can be found in the SAP.

9.1.6.3. Assessment of Puberty

CCI [redacted] The date of onset of menstruation will also be collected.

9.1.7. Health Outcomes Instruments

Observer-reported outcomes will be used in place of patient-reported outcomes for children less than CCI [redacted] for the following scales. The patient's age at entry into the study will determine which scale/instrument is used and this will not change as the patient ages during the study.

Abdominal Pain Numeric Rating Scale: The abdominal pain numeric rating scale (NRS) is a single item that measures the "worst abdominal pain in the past 24 hours" using a Pain NRS ranging from 0 to 5 (8-11 years old) and 0 to 10 (12-17 years old). For children less than 8 years old, caregivers will complete an observer-reported outcome ranging from 0 to 10. Patients or caregivers will be provided with an electronic diary tool during screening to record information daily pertaining to the patient's worst abdominal pain experience.

Urgency Numeric Rating Scale: CCI [redacted]

9.1.8. Histopathology Scoring Instrument

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

9.1.9. Exploratory Assessments

Exploratory endpoints are found in Table AMBU.2. Additional details are provided below.

9.1.9.1. Inflammatory Biomarkers

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

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

9.1.9.2. Patient-Reported Outcome/Observer-Reported Outcome Instruments for Exploratory Assessments

Observer-reported outcomes will be used in place of patient-reported outcomes for children less than CCI of age.

CCI

9.1.9.3. Extraintestinal Manifestations

Review of extraintestinal manifestations (EIMs) will be performed at the time points described in the Schedule of Activities (Section 2). Extraintestinal manifestations that occur prior to baseline or existing EIMs that change in severity or resolve during the study will be documented on the appropriate eCRF. Extraintestinal manifestations include, but are not limited to: CCI

[redacted]

9.1.9.4. Physician-Reported Instrument

CCI

[redacted]

9.1.10. Appropriateness of Assessments

All of the clinical and safety assessments in this study are standard, widely used, and generally recognized as reliable, accurate, and relevant. The disease activity measurements are used in clinical practice and UC clinical trials, and the health outcomes measures will allow assessment of symptoms and quality of life that are important to patients and their caregivers. Immunogenicity monitoring will provide information for future development of mirikizumab.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

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

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the patient to discontinue the investigational product before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator. The investigator will record all relevant AE/SAE information in the eCRF.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed, study site personnel will record via eCRF the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the

disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure or investigational product, via eCRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study drug, study device, or a study procedure, taking into account the disease, concomitant treatment, or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, study device and/or study procedure and the AE. The investigator answers yes/no when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a patient's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

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

Cardiovascular and venous thromboembolic AEs and other events leading to death are collected as described in Section 9.2.1 and its subsections; also see Section 9.2.2.4.

9.2.1. Serious Adverse Events

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

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

All AEs occurring after signing the ICF are recorded in the eCRF, assessed for serious criteria, and all serious criteria that are met are recorded in the eCRF. The required timeframe for SAE reporting to the sponsor begins after the patient has signed the ICF and has received

investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines (see Section 9.2) if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator's awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Patients with a CCI should have additional data collected using the hepatic eCRF.

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy that begins at any point after the start of study drug and until at least CCI after the participant's last dose of study drug should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (that is, the patient disposition case report form has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study drug or study participation, the investigator must promptly notify Lilly.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording, and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.1.2. Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the sponsor of an SAE as stated in Section 9.2.1 is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators.

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

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

9.2.2. Adverse Events of Special Interest

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

CCI

Additional samples and data will be collected for hypersensitivity events (Section 2). For some AESIs, sites should provide additional information regarding the event, as instructed on the eCRF. For all AESIs, including hypersensitivity events, the protocol and IB provide monitoring and management guidance to the investigator.

CCI

CCI

[redacted]

9.2.3. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

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

9.3. Treatment of Overdose

In case of suspected overdose, participants should be monitored for any signs or symptoms of adverse reactions or effects, and hematology, chemistry, vital signs, and oxygen saturation should be monitored; supportive care should be provided as necessary. The medical monitor and sponsor must be informed as soon as possible when an overdose has been identified, and all AEs

associated with the overdose will be recorded in the eCRF. CCI [redacted]

9.4. Safety

When multiple safety assessments are scheduled for the same visit, the preferred order of completion is as follows:

CCI [redacted]

9.4.1. Vital Signs

Measurements of vital signs (body temperature, blood pressure, and pulse rate) will be conducted at the study visits specified in the Schedule of Activities (Section 2).

Sitting blood pressure and pulse rate should be measured after the patient has been sitting for at least 5 minutes.

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

9.4.2. Electrocardiograms

Electrocardiograms (CCI [redacted]) should be collected according to the Schedule of Activities (Section 2).

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

Evaluation of ECGs should be performed by appropriately trained personnel with experience in reading pediatric ECGs. Electrocardiograms will be read locally by a health care professional trained in the reading of pediatric ECGs.

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

9.4.3. Laboratory Tests

Laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Section 2).

Retesting is allowed during the screening period (see Section 6.4.1).

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

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

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

Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, where appropriate.

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

9.4.3.1. Pregnancy Testing

Female subjects of childbearing potential will undergo a urine pregnancy test at the clinic CCI during scheduled visits through Week 52.

Childbearing potential is defined as females meeting one or more of the following criteria:

CCI

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

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

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

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

9.4.3.2. Hormone Testing

CCI will be collected to assess the onset of puberty in patients aged CCI and older who have not attained full maturation by Visit 1 and at other visits specified in the Schedule of Activities (Section 2).

9.4.4. Immunogenicity Assessments

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine antibody production against mirikizumab.

- Pre-dose samples will be obtained per the Schedule of Activities.
- The actual date and time (24-hour clock time) of each sample collection will be recorded.

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

In the event of a systemic allergic/hypersensitivity reaction (Section 9.2.2.2), additional blood samples will be obtained as specified in the Schedule of Activities (Section 2).

Sample collection, handling, and use

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

Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of mirikizumab at a laboratory approved by the sponsor. Antibodies will be further evaluated for their ability to neutralize the activity of mirikizumab.

Sample retention

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

9.4.5. Other Tests

9.4.5.1. Physical Examination

Physical examinations are mandated and will be performed as specified in the Schedule of Activities (Section 2). Physical examinations can also be performed at the discretion of the investigator at any additional timepoints, for example, to assist in the evaluation of a new symptom during the study.

At screening, 1 complete physical examination (excluding pelvic, rectal, and breast examinations) will be performed and will include an assessment of peripheral lymph nodes.

After screening, physical examinations should include a symptom-directed evaluation, as well as examination of eyes, heart, lungs, abdomen, and skin. For all participants, a thorough exam to evaluate for TB will be performed (Section 9.4.5.2).

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

9.4.5.2. Tuberculosis Testing

Initial Screening

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

- Thorough medical and social history to determine risk factors for TB infection over lifetime, symptoms or signs of active TB, and physical examination, including body temperature measurement and assessment of peripheral lymph nodes, as described in Section 9.4.5.1.
- Two tests to assess immune response to mycobacterial antigens (unless patient has a history of a positive IGRA):
  - IGRA (for example, QuantiFERON-TB Gold or T-SPOT.TB), and
  - Tuberculin skin test (TST, also called a purified protein derivative [PPD] or Mantoux test).
- CXR, as described in Section 9.4.5.3.

This testing paradigm follows the recommendation from NASPGHAN for pediatric patients with IBD starting on anti-TNF therapy (Ardura et al. 2016).

Tests for Immune Response to Mycobacterial Antigens

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

Interpretation of Screening Tests for LTBI

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

The TST should be read 48 to 72 hours after test application. Skin induration CCI in diameter is interpreted as positive in patients without a BCG vaccination history. In patients with a prior BCG vaccination history, a positive result shall be defined using local criteria recommendation/guidelines. Any questions should be referred to the medical monitor.

Patients with a diagnosis of LTBI based on a positive IGRA test result or a positive TST response, and no evidence of active TB on medical history, physical examination, and CXR, may be evaluated as described in Retesting and Confirmatory testing or rescreened once, as indicated in Section 6.4.

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

- No history of risk of re-exposure since their treatments were completed
- Have received at least CCI of appropriate ongoing prophylactic therapy for LTBI, based on national or international guidelines, for example, United States Centers for

Disease Control and Prevention (CDC 2016); or the World Health Organization (WHO 2018), with documentation of having completed the appropriate TB prophylaxis regimen,
- No evidence of reactivation of LTBI, and
- Have no evidence of hepatotoxicity (ALT and AST levels must remain ≤2xAAULN) upon retesting of serum ALT and AST levels before treatment assignment).

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

Retesting and Confirmatory Testing

One retest is allowed for patients with an "indeterminate" QuantiFERON-TB Gold assay or "borderline" T-SPOT assay. Patients with 2 indeterminate QuantiFERON-TB Gold assays or 2 borderline T-SPOT assays will be required to have a CXR (see Section 9.4.5.3). If both the CXR and TST are negative and there are no other risk factors for TB exposure present, the patient is eligible to be enrolled in the study.

Confirmatory testing with an IGRA is allowed for selected patients who have a positive TST, positive QuantiFERON-TB Gold assay or positive T-SPOT assay who meet all of the following criteria, and are assessed by the investigator as likely having a false-positive test result:

- No risk factors for LTBI
- No risk factors for increased likelihood of progressing from LTBI to active TB, and
- Have never resided in a high-burden country, as detailed in Appendix 8.

If the confirmatory test is positive, the patient will be excluded from the study unless they complete at least CCI of appropriate therapy for LTBI based on national or international guidelines (as defined above), and have no evidence of hepatotoxicity CCI upon retesting of serum CCI of LTBI treatment. Such patients must continue and complete appropriate full course of LTBI therapy during the course of the study to remain eligible to participate in the study. If the confirmatory test is negative, these results will be discussed with the medical monitor in order to determine eligibility for the study.

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

Monitoring for TB During the Study

For all patients, monitoring for TB is to be continuous throughout the study. At a minimum, each participant is to have the following documented at least every CCI

CCI

If the patient has a risk factor (Appendix 8), the investigator should collect CCI, as described in Section 9.4.5.3

Diagnosis of LTBI During Study

Patients diagnosed with LTBI during the study CCI If treatment for LTBI is considered to be appropriate, the patient must complete CCI of appropriate therapy for LTBI, based on national or international guidelines (as defined above), and have no evidence of hepatotoxicity CCI upon retesting of serum ALT and AST levels after at least CCI of LTBI treatment. Such patients may then resume study drug and must continue with and complete a full course of treatment for LTBI in order to continue on study drug. Non-compliance with LTBI treatment during the study is a reason for permanent discontinuation from study drug (Section 8.1.1).

Household Contact

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

Prior Treatment for LTBI

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

Active TB

Patients with a past history of active TB, without documented treatment by WHO and/or CDC criteria are excluded from the study (Section 6.2).

Patients diagnosed with active TB at screening will be excluded (Section 6.2) and should be referred by the investigator for appropriate TB treatment and follow-up.

If a patient is diagnosed with active TB during the study, the study drug will be permanently discontinued (Section 8.1.1), and the patient will undergo an ETV and then enter the post-treatment follow-up period. The patient should also be referred by the investigator for appropriate TB treatment and follow-up.

9.4.5.3. Chest Radiography

A posterior-anterior chest x-ray (CXR), interpreted and reported by a radiologist or pulmonologist, may be obtained at screening, as specified in the Schedule of Activities (Section 2) if both the TST and QuantiFERON-TB Gold assay or T-Spot assay are indeterminate or borderline. A CXR may be taken at any time in the study at the discretion of the investigator when clinically indicated, for example, as part of an evaluation for active TB and LTBI. A lateral CXR can also be obtained, if in the opinion of the investigator, a lateral view is indicated. The CXR will be performed and interpreted locally.

A CT scan can be performed as an alternative to the CXR based on regional standard of practice. The CT scan will be performed and interpreted locally.

If the CXR or CT is performed for TB evaluation, it should be interpreted and reported by a radiologist or physician who specializes in the treatment of TB.

Certain findings from CXR may be consistent with a condition that excludes a participant from the study; see Section 6.2.

9.4.5.4. Hepatitis B Testing

HBV Screening and Interpretation

CCI

Exclusion Based on HBV Serology and HBV DNA Testing

CCI

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

CCI

Management of Patients with the Following HBV Serology at Baseline: HBsAg-, anti-HBc+, HBV DNA Not Detected

CCI

Management of Patients with a Newly Positive anti-HBc Test During the Study

CCI

Management of Patients with Detectable HBV DNA During the Study

CCI

[redacted]

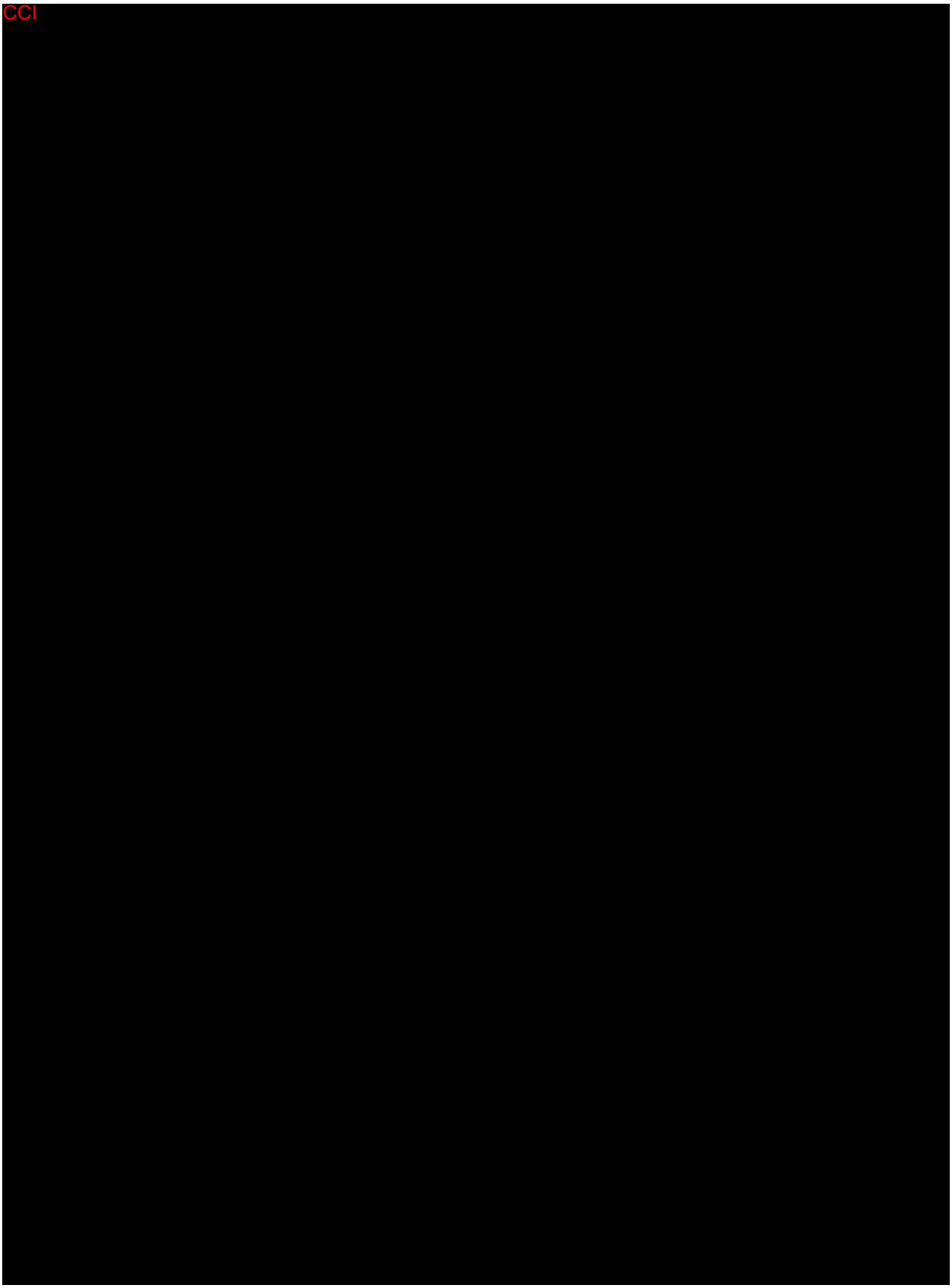
9.4.5.5. Hepatitis C Testing

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

CCI

[redacted]

CCI



9.4.5.7. Stool Testing

Stool Culture

A stool sample for culture will be obtained at screening.

Patients must have a "negative" stool culture from which no enteric pathogens are isolated in order to be enrolled.

Retesting is allowed within the same screening period if there is a technical difficulty in performing or reporting the stool culture assay, as stated in Section 6.4.1.

Patients who have a "positive" stool culture result can be re-screened once, as stated in Section 6.4, provided that the following conditions have been met:

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

The stool culture should be retested prior to rescreening.

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

Participants with a positive stool culture result are excluded from the study (see Section 6.2).

C. difficile

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

This assay may be tested locally (if available for antigen, toxin, and PCR reflex evaluation) or centrally for the presence of *C. difficile* antigen (GDH) and toxin (toxin A and toxin B), followed by a possible reflex to PCR confirmatory test for *C. difficile* gene expression in the stool sample. See flow chart below.

Retesting is allowed within the screening period if there is a technical difficulty in performing or reporting the *C. difficile* result, as stated in Section 6.4.1.

Patients who test positive at screening for *C. difficile* can be rescreened once, as stated in Section 6.4, provided that the following conditions have been met:

- The patient has been adequately treated, and
- The patient has been off antibiotics for .

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

A *C. difficile* stool toxin assay should be repeated prior to rescreening.

Patients with a positive test for *C. difficile* toxin are excluded from the study (Section 6.2).

9.4.6. Safety Monitoring

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

9.4.6.1. Hepatic Safety Monitoring

If a study patient experiences elevated , or , liver testing (described in Appendix 4) should be repeated within 3 to 5 days, including to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study medical monitor. Monitoring of should continue until levels normalize or return to approximate baseline levels.

If a study patient experiences an CCI and CCI or international normalized ratio CCI, the study medical monitor should be consulted as soon as possible for further guidance on evaluation of the laboratory abnormalities.

Hepatic Safety Data Collection

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

- Elevation of serum ALT to CCI on 2 or more consecutive blood tests
- Elevated serum TBL to CCI (except for cases of known Gilbert's syndrome)
- Elevation of serum ALP to CCI on 2 or more consecutive blood tests
- Patient discontinued from treatment due to a hepatic event or abnormality of liver tests
- Hepatic event considered to be a SAE
- Patient with a history of HCV infection develops elevated ALT CCI. Patient will be tested for HCV RNA.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine the serum concentrations of mirikizumab. Pre-dose samples can be collected at any time prior to dosing during the visit, and post-dose samples should be collected within CCI after dosing.

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.

Additional samples

A maximum of 3 additional samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. In the case of systemic allergic/hypersensitivity reactions (Section 9.2.2.2), additional blood samples will be obtained, as described in the Schedule of Activities (Section 2).

Sample retention

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

9.6. Pharmacodynamics

See Section 9.8.

9.7. Pharmacogenomics

CCI

may be tested. These are genetic markers that are related to the biology of inflammatory and autoimmune disease.

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

Sample retention

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

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

9.8. Biomarkers

CCI

Sample use

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

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

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

Sample retention

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

9.9. Medical Resource Utilization and Health Economics

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

10. Statistical Considerations

10.1. Sample Size Determination

Lilly plans to enroll approximately 30 patients into Study AMBU, to achieve at least 25 evaluable patients with respect to evaluating mirikizumab PK. The enrollment target includes approximately [CCI] patients in the >40 kg category and approximately [CCI] patients in the ≤40 kg category.

This sample size is considered adequate to evaluate the PK of mirikizumab treatment in pediatric patients.

10.2. Populations for Analyses

For purposes of analysis, the populations are defined in Table AMBU.6.

Table AMBU.6. Population Definitions

Population	Description
Modified Intent-to-Treat (mITT) Population	All enrolled patients that took at least 1 dose of treatment, even if the patient does not receive the correct treatment, or otherwise does not follow the protocol. Patients will be analyzed according to the treatment to which they were assigned. Unless otherwise noted, efficacy and health outcomes analyses will be conducted on this population.
Induction Safety	All Induction ITT patients who received at least 1 dose of the study drug. Patients will be analyzed according to the treatment to which they were assigned. Safety analyses for the induction period will be conducted on this population.
Maintenance Safety	All Maintenance ITT patients who have received at least 1 maintenance dose. Safety analyses for the maintenance period will be conducted on this population.
PK evaluable	All patients who received at least 1 dose of investigational product and have sufficient blood sampling to allow for PK evaluation.

Abbreviations: ITT = intent-to-treat; PK = pharmacokinetic.

Additional populations will be defined in the SAP.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

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

Efficacy analyses for the induction period and the maintenance period will be conducted on the modified ITT population. Safety analyses for the induction period and the maintenance period will be conducted on the induction safety population and the maintenance safety population, respectively.

Summary statistics for continuous variables will include mean, standard deviation, median, and minimum and maximum values; categorical variables will be presented as counts and percentages.

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

10.3.1.1. Missing Data Imputation

While every effort will be made to reduce missing data, the missing data imputation method of NRI will be used when patients are permanently discontinued from study drug or otherwise have missing data.

For analysis of categorical efficacy and health outcomes variables, missing data will be imputed using an NRI method. Patients will be considered a nonresponder for the NRI analysis if they do not meet the categorical response criteria or have missing clinical response data at a time point of interest.

Imputation details based on NRI will be provided in the SAP. Additional missing data imputation methodologies may be considered and will also be fully detailed in the SAP.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

The number of enrolled patients will be summarized. Frequency counts and percentages of all patients who are enrolled and completing the study or discontinue the study drug/study early will be presented. Reasons for discontinuing the study drug/study will be summarized.

10.3.2.2. Patient Characteristics

Full date of birth (unless prohibited by local law), sex, weight, height, smoking habits, previous biologic therapy, corticosteroid use, and other demographic characteristics will be recorded. Age and body mass index will be calculated. Demographic and baseline characteristics will be summarized for each treatment group. Certain characteristics, such as weight, that are collected after baseline, will be reported as a listing.

10.3.2.3. Concomitant Therapy

Concomitant therapy will be collected at each visit, and the reported term will be classified by the World Health Organization drug dictionary. Previous concomitant therapy (reported before study enrollment) and current concomitant therapy (reported after study enrollment) will be presented separately in frequency tables by drug name for all enrolled patients.

10.3.2.4. Treatment Compliance

Patients who are noncompliant will be listed by treatment. A contingency table of numbers of noncompliant patients by treatment will be provided.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary objective of this study is to evaluate the PK of mirikizumab treatment in pediatric patients. See Section 10.3.5 for a description of PK analyses.

10.3.3.2. Secondary Analyses

The secondary efficacy endpoint of clinical remission will be assessed using the MMS, a 9-point instrument that includes the SF, RB, and ES subscores of the Mayo Score.

The SF and RB subscores of the Mayo Score will be calculated from daily electronic diary data by averaging the most recent CCI (possibly non-consecutive) prior to the Week 52 visit or CCI prior to the Week 52 bowel preparation/endoscopy. If data from fewer than CCI are available from the CCI to Week 52 visit, the subscores will be considered as missing. The CCI of patient diary data must exclude data from days when bowel preparation or endoscopic exam (flexible proctosigmoidoscopy/colonoscopy) occur and exclude data from the day after the endoscopic exam.

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

To calculate the RB subscore, the CCI RB scores will be averaged and the RB subscore will be rounded to the nearest integer. Rates of clinical remission at Week 12, as defined in Section 9.1.1, will be analyzed. Patients who do not achieve clinical remission or who do not reach the Week 12 assessment will be considered to be nonremitters.

Descriptive summaries by treatment, by visit, and by weight group for this endpoint, as well as for the rest of the secondary efficacy endpoints described in Table AMBU.2 will be performed using NRI methodology.

Additional analyses of the secondary endpoint may be considered and details will be provided in the SAP.

10.3.3.3. Tertiary/Exploratory Analyses

The exploratory endpoints of the trial are presented in Table AMBU.2. Details of the analyses of exploratory endpoints, as well as additional exploratory endpoints will be described in the SAP.

10.3.4. Safety Analyses

Safety data will be summarized by dose. Safety and tolerability including but not limited to AEs, infections, injection site reactions, clinical chemistry, hematology, immunogenicity, tolerability and acceptability of SC injection volumes of CCI, and questionnaires to assess the existence and severity of depression will be assessed.

For AEs, the number of treatment-emergent adverse events (TEAEs), as well as the number and percentage of patients who reported at least 1 TEAE will be summarized using Medical Dictionary for Regulatory Activities (MedDRA) for each system organ class and preferred term.

Serious adverse events (including deaths), treatment-emergent AESIs, and AEs that lead to treatment discontinuation will also be summarized using MedDRA for each system organ class and preferred term.

For laboratory analytes and vital signs, treatment-emergent abnormal shifts to low/high will be presented.

Summary tables or listings for CCI will be produced as needed.

Immunization history will be recorded at baseline, and any unexpected outcomes or effects related to standard of care vaccination during the study will be summarized.

Further analyses may be performed as deemed appropriate and will be detailed in the SAP.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Analyses of the PK of mirikizumab and relationships between exposure and the efficacy endpoints will be conducted. For both the PK and exposure-response analyses, intrinsic and extrinsic factors will be evaluated to determine their impact. Comparisons of adult and pediatric PK and exposure-response will be performed and may be combined if appropriate.

The PK of mirikizumab will be characterized CCI

Analyses of exposure-response relationships may be conducted using both exploratory graphical approaches and model based approaches. Exploratory graphical analysis approaches may consist of graphs showing the change in CCI versus exposure of mirikizumab. Model based analyses may utilize population exposure-response models, where maximum effect (Emax) or other model structures may be used to relate mirikizumab exposure to the probability of achieving clinical response, clinical remission, endoscopic healing, or change in the MMS score. These models may be used to evaluate patient factors that may impact the exposure-response relationships. Similar graphical and model based analyses relating mirikizumab exposure to CCI may also be conducted.

Additional analyses may be conducted if they are deemed appropriate. Data from this study may be combined with other study data, if appropriate. Comparison of data in this study with data from adult studies will be addressed in a separate analysis plan. Further details on PK and exposure-response analyses will be provided in the PK/PD analysis plan.

10.3.6. Evaluation of Immunogenicity

The frequency and percentage of patients with preexisting (baseline) ADA, ADA at any time post baseline, and with treatment-emergent anti-drug antibody (TEADA) to mirikizumab will be tabulated. If no ADAs are detected at baseline, TEADAs are defined as those with a CCI

CCI greater than the minimum required dilution (MRD) of the assay. For samples with ADA detected at baseline, TEADAs are defined as those with a CCI increase in titer compared to baseline. For patients who have TEADA, the distribution of maximum titers will be described. The frequency of neutralizing antibodies will also be tabulated.

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

10.3.7. Other Analyses

10.3.7.1. Subgroup Analyses

Subgroup analyses may be conducted for select secondary endpoints. Subgroups to be evaluated may include sex, age CCI, weight (≥40 kg versus <40 kg), race, geographic region, baseline disease severity, duration of disease, previous use of biologic therapy, and no previous use of biologic therapy. Details of the subgroups and associated analyses (including any additional subgroups) will be defined in the SAP.

10.3.8. Data Snapshot and Interim Analyses

The planned data snapshot and interim analyses are described as follows.

10.3.8.1. Data Snapshots

There will be 2 data snapshots taken of PK and safety data:

- The first snapshot will be taken when at least CCI patients reach Week 4. This will provide an early assessment of PK and safety data. This analysis is planned to enable dose confirmation for the Phase 3 study for patients >40 kg.
- The second snapshot will be taken when approximately CCI patients in the ≤40 kg group (5 mg/kg IV Q4W) reach Week 4. This analysis is planned to enable the enrollment of the 10 mg/kg treatment group.

10.3.8.2. Interim Analyses

- An interim analysis is planned when approximately CCI patients in the ≤40 kg group reach Week 12. This analysis will allow confirmation of dose for patients ≤40 kg to begin the Phase 3 study.

No multiplicity adjustment will be made due to multiple comparisons or due to interim analyses.

Additional data snapshots and/or interim analyses may be performed as deemed necessary, based on emerging data from the study.

Study sites will receive information about interim results ONLY if it is required for the safety of their patients.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
AAULN	age-adjusted upper limit of normal
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse events of special interest
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
anti-HBc	hepatitis B core antibody
AST	aspartate aminotransferase
AZA	azathioprine
CCI [redacted]	
CCI [redacted]	
CD	Crohn's disease
CCI [redacted]	
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.
CRF	case report form
CSR	clinical study report
CCI [redacted]	

CT	computed tomography
CXR	chest x-ray
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
eCRF	electronic case report form
EDC	electronic data capture
EIM	extraintestinal manifestation
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ePPND	enhanced pre- and postnatal development
ERB	ethical review board
ES	endoscopic subscore
ETV	early termination visit
CCI	
GDH	*C. difficile* antigen
GMP	Good Manufacturing Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
hs-CRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Council for Harmonisation

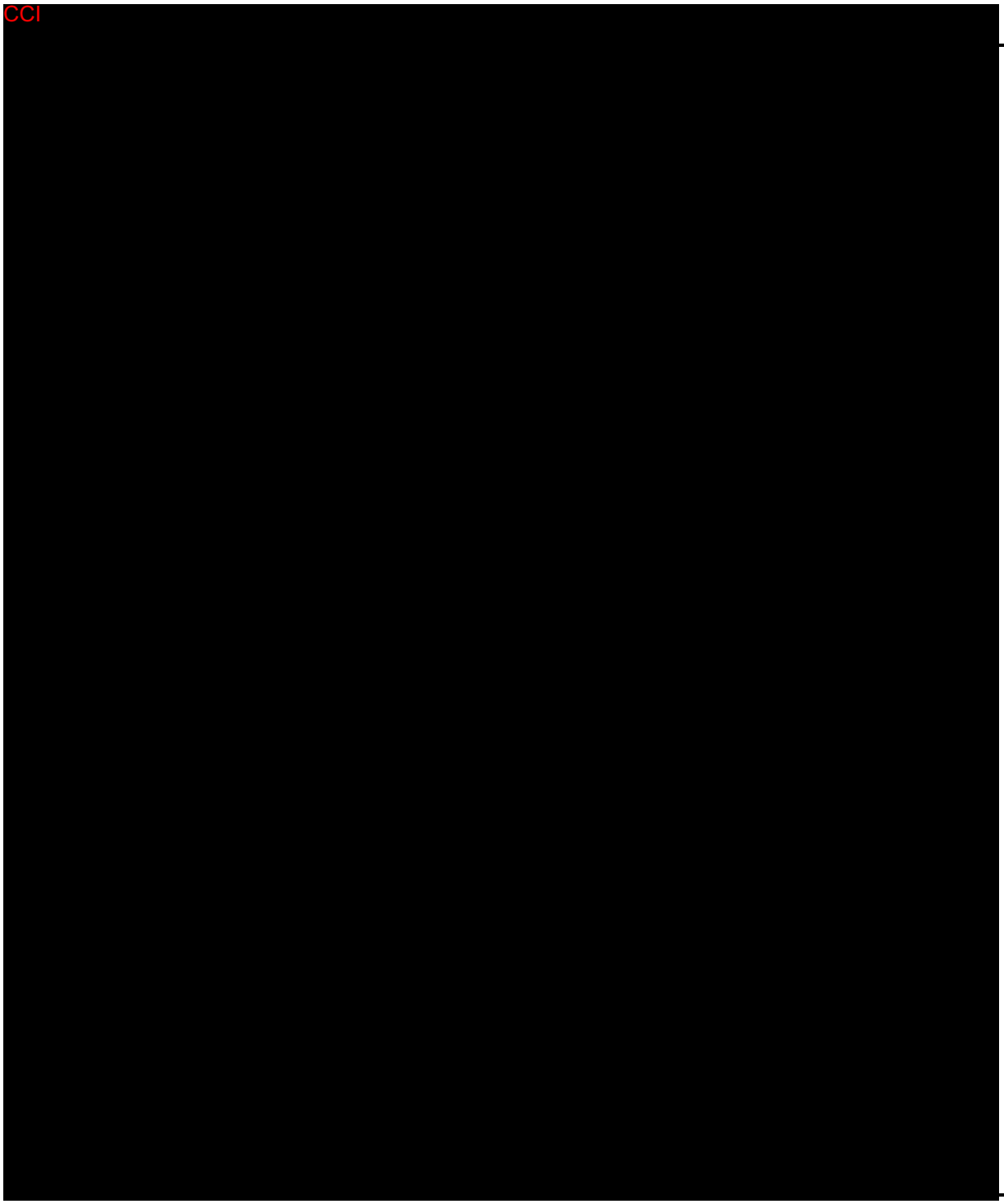
IEC	Independent Ethics Committee
IGRA	interferon-γ release assay
IL	interleukin
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IP	investigational product
IRB	Institutional Review Board
ITT	intent-to-treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IV	intravenous
IWRS	interactive web-response system
JAK	Janus kinase
CCI [redacted]	
LTBI	latent tuberculosis infection
MedDRA	Medical Dictionary for Regulatory Activities
MMS	Modified Mayo Score
MTX	methotrexate
NIMH	National Institute of Mental Health
NOS	not otherwise specified
NRI	nonresponder imputation
NRS	numeric rating scale

PCR	Polymerase Chain Reaction
PD	pharmacodynamics
PGA	Physician's Global Assessment
PGI-C	Patient's Global Impression of Change
PGRS	Patient's Global Rating of Severity
PK	pharmacokinetics
PPD	purified protein derivative
PRN	as needed
PUCAI	Paediatric Ulcerative Colitis Activity Index
Q4W	every 4 weeks
Q12W	every 12 weeks
RB	rectal bleeding
RNA	ribonucleic acid
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.
SF	stool frequency
SUSARs	suspected unexpected serious adverse reactions
TASA	Treatment of Adolescent Suicide Attempters
TB	tuberculosis
TBL	total bilirubin level
TEADA	treatment-emergent anti-drug antibody
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TNF	tumor necrosis factor

TST	tuberculin skin test
UC	ulcerative colitis
CCI	[redacted]

Appendix 2. Clinical Laboratory Tests

CCI



CCI

[redacted]

Selected tests may be obtained in the event of systemic allergic/hypersensitivity events.

Hypersensitivity Tests[a]	
Immunogenicity testing (ADA)	Tryptase
Serum mirikizumab concentration (PK)	Complement
	Cytokine Panel

Abbreviations: ADA = anti-drug antibody; PK = pharmacokinetics.

[a] Assayed by Lilly-designated laboratory and for immediate hypersensitivity events only.

Laboratory Test Prioritization

Care should be taken to safeguard study participants with regard to the amount of blood drawn for study procedures. All efforts have been made to minimize required sampling in this protocol; however, in the case of younger and lower body weight patients, the following guidance is provided. Importantly, sites should follow local institutional review board guidelines, where applicable. Patients CCI [redacted] old with body weight lower than CCI [redacted] will require reduced blood volume collection, and some tests will need to be excluded. In the situation where blood volume is limited and all tubes cannot be collected, the following sample tubes should be removed in this order:

CCI

[redacted]

Please refer to the lab manual for collection tube volumes for each of the above mentioned tests.

Appendix 3. Study Governance Considerations

Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 3.1.1. Informed Consent

The investigator is responsible for:

- Ensuring that the patient/patient's legal representative understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- Ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product.
- Ensuring that informed consent is given by pediatric participants for continued participation once the patient reaches the age of legal consent.
- Answering any questions the patient/patient's legal representative may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's/patient's legal representative's willingness to continue his or her participation in the study.
- Ensuring that a copy of the ICF is provided to the participant or the participant's legal representative and is kept on file.
- Ensuring that the medical record includes a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

A legal representative must give informed consent for a child to participate in this study. In addition to the informed consent given by the legal representative, the child may be required to give documented assent, if capable.

Appendix 3.1.2. Recruitment

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

Appendix 3.1.3. Ethical Review

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

Documentation of ERB approval of the protocol and the ICF and Assent Form must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on Good Clinical Practice (GCP).

The study site's ERB(s) should be provided with the following:

- The protocol and related amendments and addenda, current Investigator's Brochure and updates during the course of the study
- Informed consent form and Assent Form
- Other relevant documents (for example, curricula vitae and advertisements)

Appendix 3.1.4. Regulatory Considerations

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

- Consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

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

Appendix 3.1.5. Investigator Information

Physicians with a specialty in pediatric gastroenterology and/or at least CCI of experience with pediatric patients may participate as investigators in this clinical trial.

Appendix 3.1.6. Protocol Signatures

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

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

Appendix 3.1.7. Final Report Signature

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

An investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

The sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Appendix 3.2. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate

- Provide sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the case report forms (CRFs), and study procedures.
- Make periodic visits to the study site
- Be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- Review and verify data reported to detect potential errors

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Appendix 3.2.1. Data Capture System

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

An electronic data capture (EDC) system 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 (questionnaires, scales, self-reported diary data, etc.) will be collected by the investigator site personnel, via a paper source document and will be transcribed by the investigator site personnel into the EDC system.

Additionally, electronic clinical outcome assessment (eCOA) data (questionnaires, scales, self-reported diary data, etc.) will be directly recorded by the subject/caregiver/investigator site personnel into an instrument (for example, hand held smart phone or tablet, or by means of an interactive voice/web system). The eCOA data will serve as the source documentation and the investigator will 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 a third party. 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 an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and electronic transfers will be provided to the investigator

for review and retention. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

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

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3.3.2. Discontinuation of the Study

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

Appendix 3.4. Publication Policy

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

CCI [redacted]

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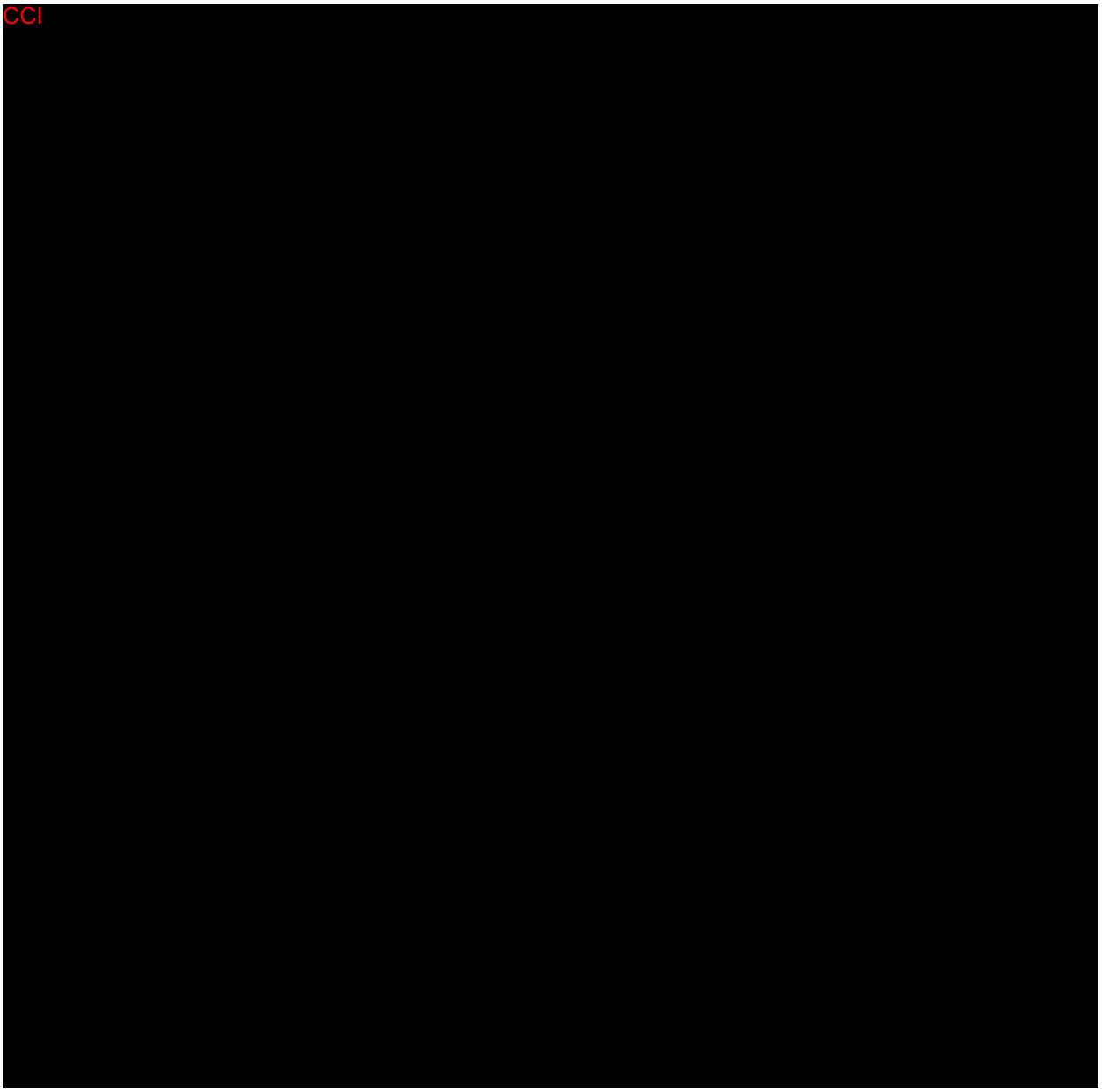

Appendix 5. Prohibited Medications

This section outlines medications that are prohibited during the treatment phase of the study and during washout periods prior to the screening endoscopy, if applicable. Use of the medications listed in this appendix is allowed at the discretion of the investigator after a participant discontinues study drug and completes the ETV.

Drug Class	Comments
Anti-TNF antibodies (for example, infliximab, adalimumab or golimumab)	Discontinue at least CCI prior to screening endoscopy and prohibited throughout duration of study
Anti-integrin antibodies (for example, vedolizumab)	Discontinue at least CCI prior to screening endoscopy and prohibited throughout duration of study
Agents depleting B or T cells (for example, rituximab, alemtuzumab, or visilizumab)	Discontinue at least CCI prior to baseline; patients remain excluded if evidence of persistent targeted lymphocyte depletion at the time of screening endoscopy
Immunomodulatory medications, including oral cyclosporine, IV cyclosporine, tacrolimus, mycophenolate mofetil, thalidomide, or Janus kinase (JAK) inhibitors (for example, tofacitinib)	Discontinue at least CCI prior to screening endoscopy and prohibited throughout duration of study
Intravenous corticosteroids	Discontinue at least CCI prior to screening endoscopy and prohibited throughout duration of study
Systemic corticosteroids for non-UC indications (oral or IV)	Patients requiring systemic corticosteroids for CCI for non-UC conditions are excluded. Exceptions include CCI
Topical corticosteroids and 5-ASA therapies (enemas or suppositories)	Discontinue at least CCI prior to screening endoscopy and prohibited throughout duration of study
Any investigational therapy (biologic or non-biologic)	Discontinue at least CCI, or 5 half-lives whichever is longer, prior to screening endoscopy and prohibited throughout duration of study
CCI	CCI
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Anti-IL12p40 antibodies (for example, ustekinumab [Stelara®]) or anti-IL-23p19 antibodies (for example, risankizumab [BI-655066/ABBV-066], brazikumab [MEDI-2070], guselkumab [CNTO1959], tildrakizumab [MK-3222]) for any indication, including investigational use	Patients with any previous exposure of p19 antibodies are not eligible to be enrolled

Drug Class	Comments
CCI [redacted]	CCI [redacted]
Medicinal and recreational marijuana (includes cannabidiol [CBD] oil)	Must be stopped prior to enrollment. Marijuana use is prohibited for the duration of the study. If use is identified during the trial, it may result in discontinuation; consult the medical monitor.

Abbreviations: 5-ASA = 5-aminosalicyclic acid; IV = intravenous; TNF = tumor necrosis factor; UC = ulcerative colitis.

Appendix 6. Permitted Medications with Dose Stabilization

Drug Class	Comments
Oral 5-ASAs (for example, mesalamine, balsalazide, olsalazide)	May continue during study with stable doses encouraged
Oral corticosteroids [redacted]	Responder patients who are receiving oral corticosteroids at the start of Study AMBU will start corticosteroid taper at [redacted] will begin corticosteroid tapering if symptomatic response or symptomatic improvement based on investigator discretion is achieved at any time after starting extended induction (see *Corticosteroid Taper* in Section 7.7.1.
Corticosteroids for non-UC indications: corticosteroids to treat adrenal insufficiency, as premedication for investigational product infusion, or locally administered corticosteroids (e.g., inhaled, intranasal, intra-articular, topical)	May continue corticosteroids to treat adrenal insufficiency or locally administered corticosteroids during study with stable dose encouraged. [redacted] corticosteroids as premedication to investigational product administration are allowed in patients with prior investigational product or other previous biologic injection reactions. A short course [redacted] is allowed to treat non-UC conditions.
Immunomodulators (for example, AZA, 6-MP, or MTX)	Prescribed dose will remain [redacted] unless medication is discontinued due to a toxicity related to the medication. [redacted] at the discretion of the investigator unless medication is discontinued due to a toxicity related to the medication
Antidiarrheals (for example, loperamide, diphenoxylate with atropine)	May continue during study with stable doses encouraged
Non-live (killed, inactivated or subunit) vaccines	Allowed during the study. The efficacy of non-live vaccinations with concomitant mirikizumab treatment is unknown. If a non-live vaccine is needed, it is recommended that study drug not be administered on the same day as a vaccination.
Homeopathic and alternative treatments	Vitamins and probiotics are allowed. Other non-prescription drug therapies may be permitted following discussion with the sponsor. The dose of medication should remain constant for the 52-week duration of the study

Abbreviations: 5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; AZA = azathioprine; IV = intravenous; MMX = multi matrix colonic delivery technology; MTX = methotrexate; UC = ulcerative colitis.

Appendix 7. Ulcerative Colitis Disease Activity Measures

Mayo Scoring System for the Assessment of Ulcerative Colitis Disease Activity

CCI

PUCAI: Pediatric Ulcerative Colitis Activity Index

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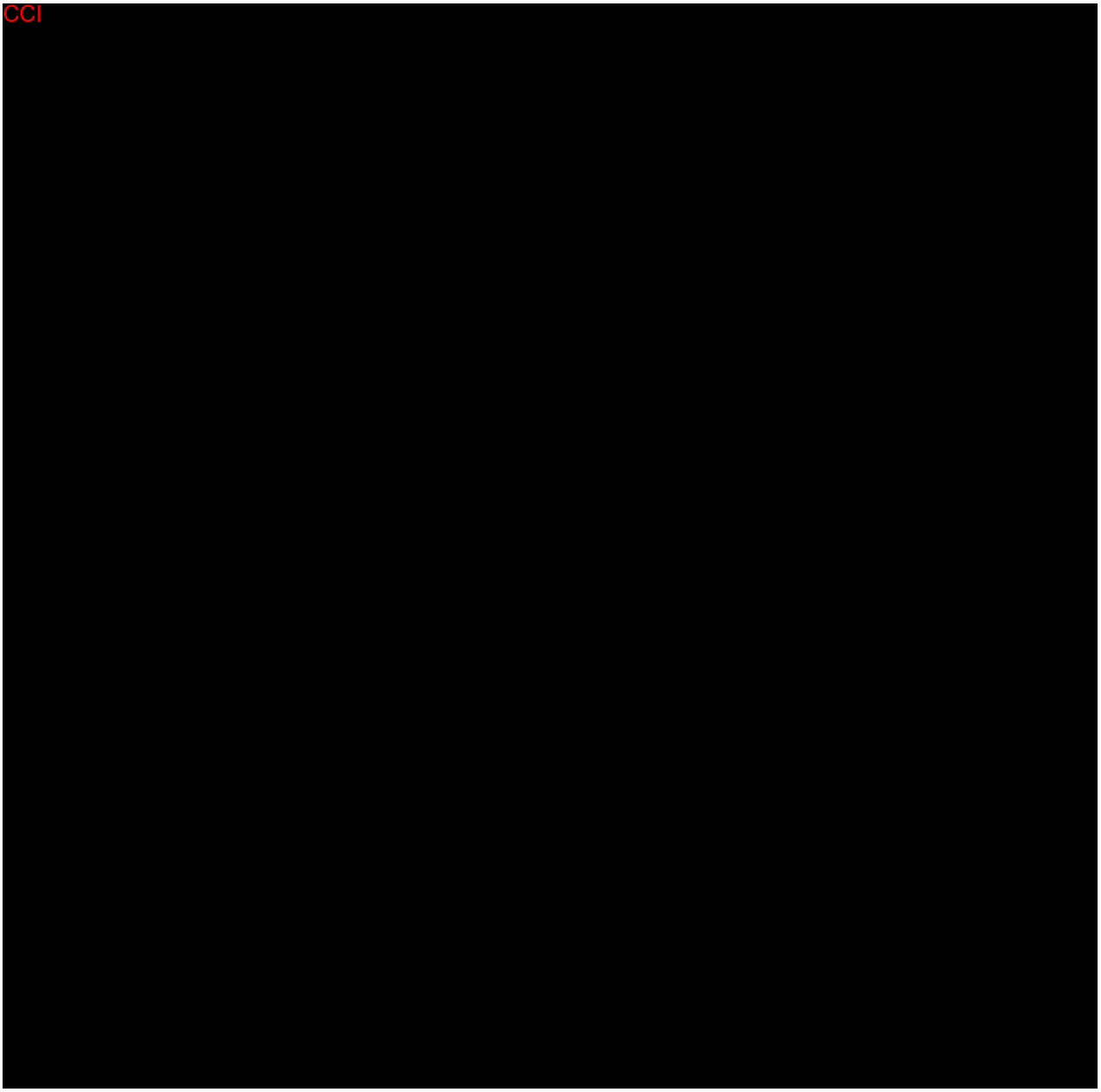

Appendix 8. Risk Factors for Latent Tuberculosis Infection

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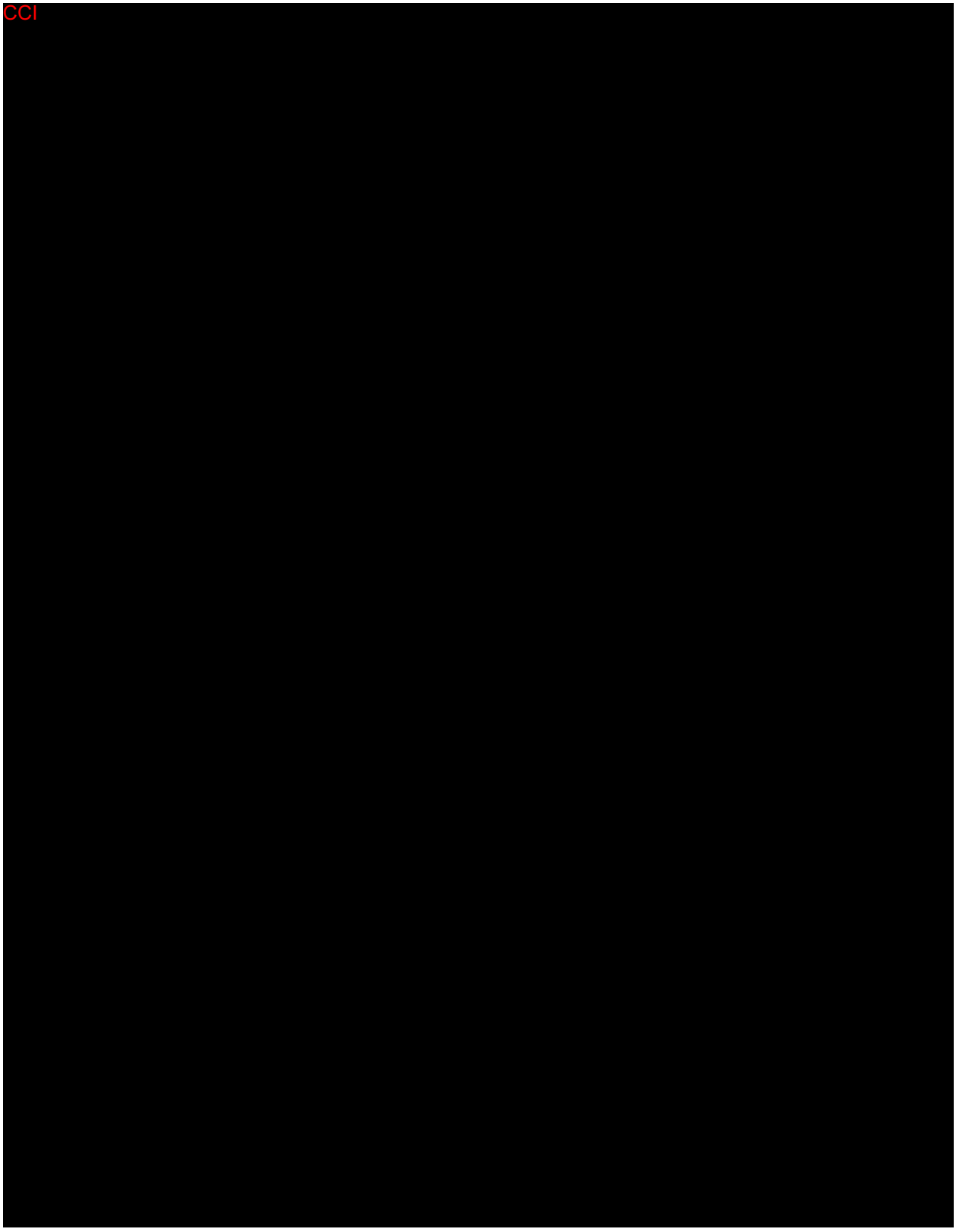

Appendix 9. Examples of Infections that May Be Considered Opportunistic in the Setting of Biologic Therapy

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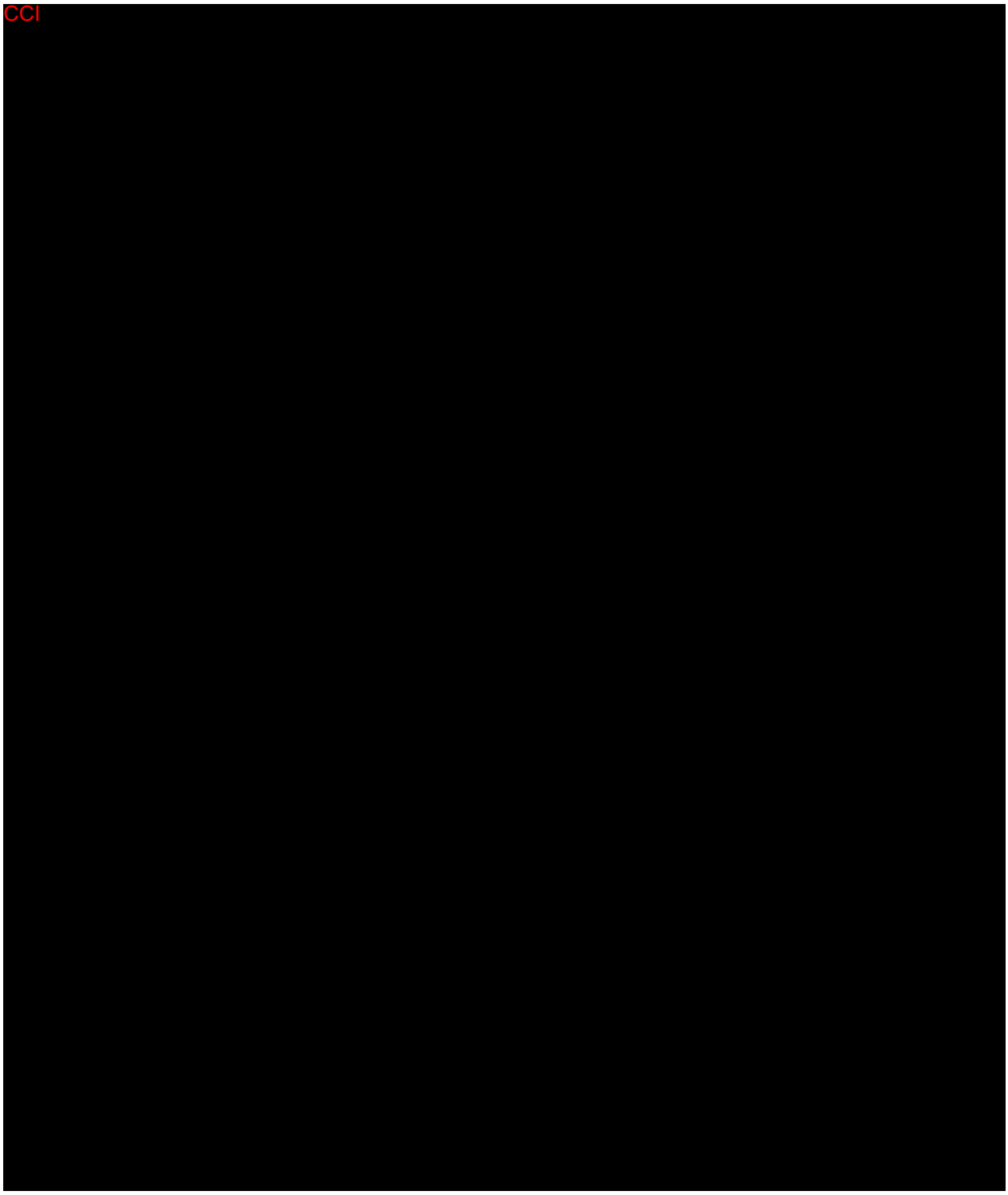

Appendix 10. Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

Exceptional circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Implementing changes under exceptional circumstances

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

After approval by local Ethical Review Boards, regulatory bodies, and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required (for example, upon implementation and suspension of changes). All approvals and notifications must be retained in the study records.

If the sponsor grants written approval for changes in study conduct, the sponsor will also provide additional written guidance, if needed.

Considerations for making a change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with Good Clinical Practice, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed consent

CCI

Changes in study conduct during exceptional circumstances

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations.

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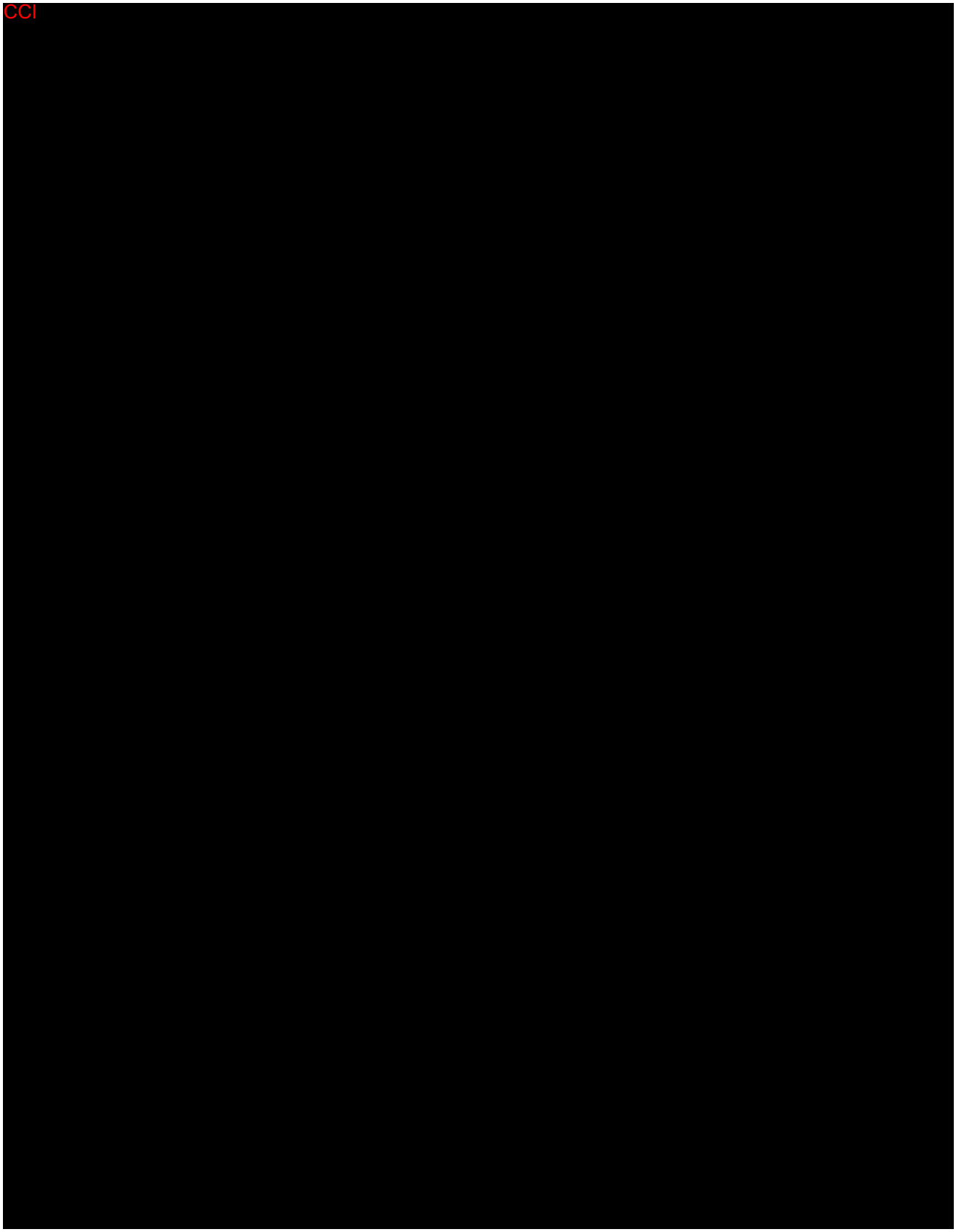

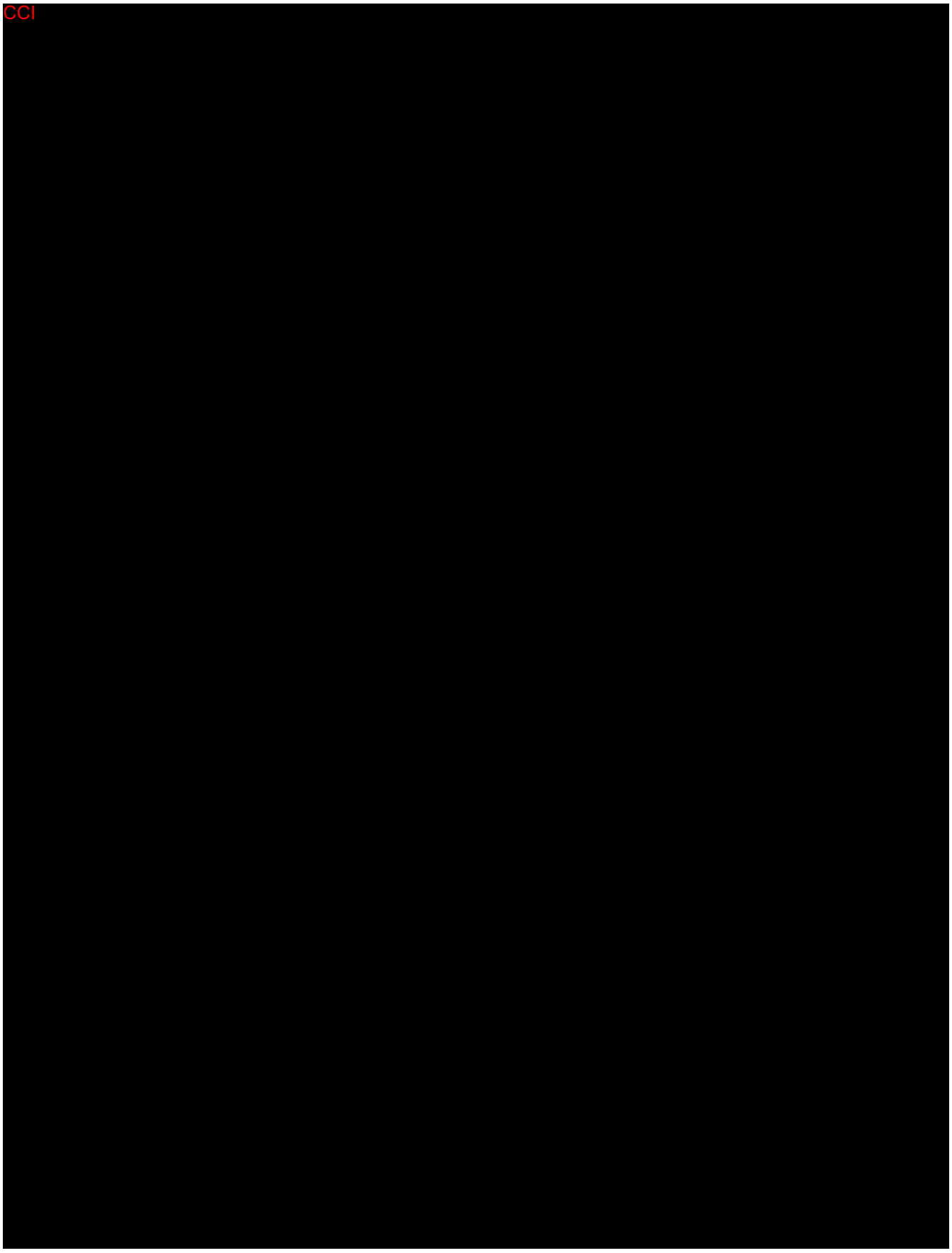
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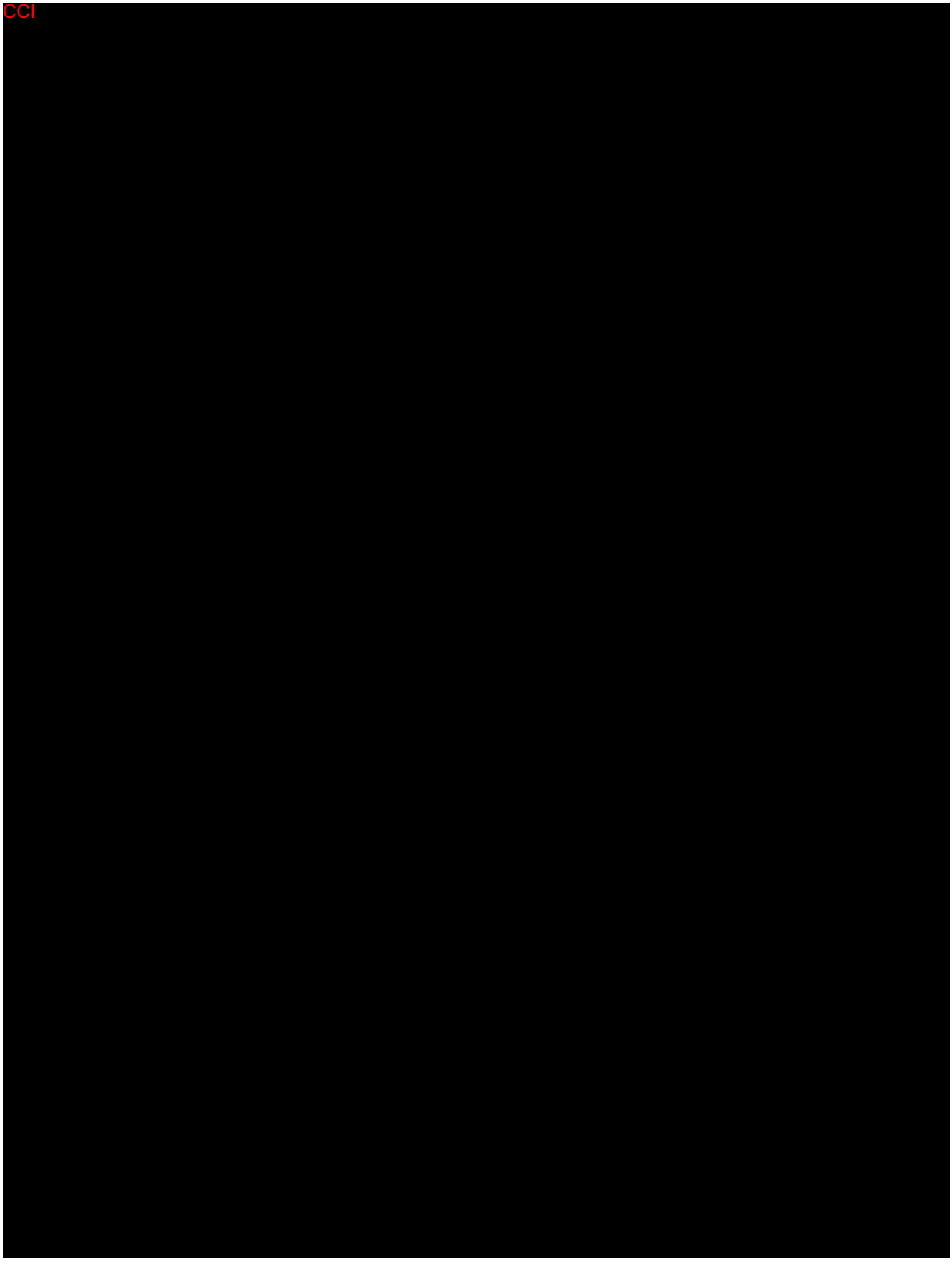

Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at the screening visit are valid for a maximum of CCI. The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to exceptional circumstances:

- If screening is paused for less than CCI from screening/lead-in visits to randomization visit: the participant will proceed to the study visit per the usual Schedule of Activities, provided that randomization visit must be conducted within CCI from first screening procedure.
  - The site should conduct the randomization visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay.
  - Due to the pause in screening, sites should also reconfirm the impacted participant's legal guardian consent, participants assent if not of legal age and document this confirmation in the source documentation.

- If screening is paused for more than CCI from screening/lead-in visits to randomization visit and without an endoscopy procedure completed: the participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. The participant can reconsent and be rescreened as a new participant. [This rescreen is in addition to the one allowed by the main protocol.] The screening procedures per the usual Schedule of Activities should be followed, starting at screening visit to ensure participant eligibility prior to randomization visit.

Adjustments to Visit Windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual Schedule of Activities. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study.

This table describes the allowed adjustments to visit windows.

Table 1: Extended Visit Windows

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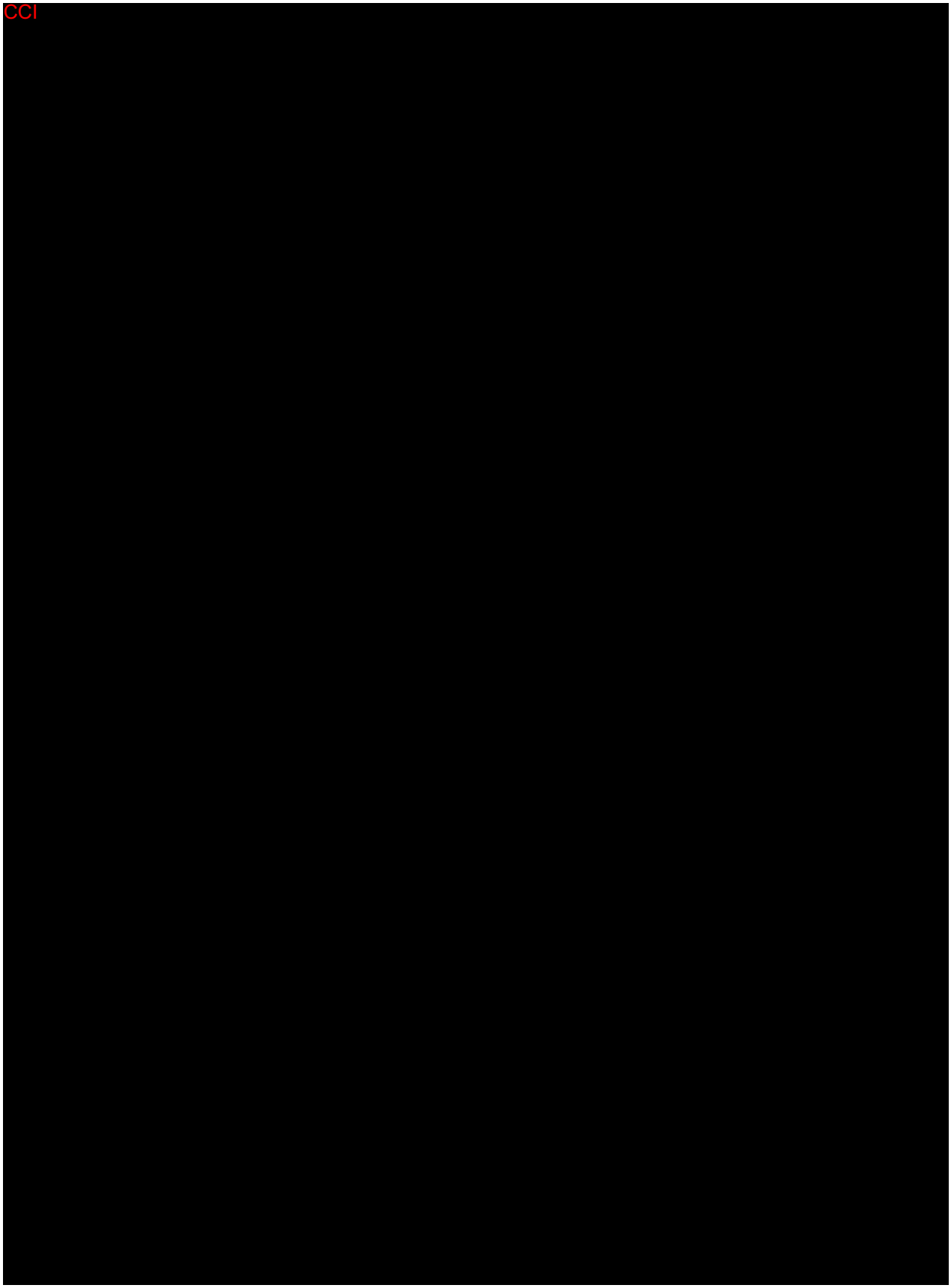

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For participants whose visits have extended windows, additional study intervention may need to be provided to avoid interruption and maintain overall integrity of the study.

Documentation

Changes to study conduct will be documented

- Sites will identify and document the details of how participants, visits types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.

Source documents at alternate locations

- Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

Appendix 11. Protocol Amendment I6T-MC-AMBU(b) Summary
A Multicenter, Open-Label PK Study of Mirikizumab in Pediatric Patients with Moderately to Severely Active Ulcerative Colitis

Overview

Protocol I6T-MC-AMBU(a) A Multicenter, Open-Label PK Study of Mirikizumab in Pediatric Patients with Moderately to Severely Active Ulcerative Colitis has been amended. The new protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

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

Amendment Summary for Protocol I6T-MC-AMBU Amendment (b)

Section # and Name	Description of Change	Brief Rationale
Section 1. Synopsis Section 4. Objectives and Endpoints Section 9.1 Efficacy Assessments, Table AMBU 5	Revised secondary objective wording for MMS clinical remission definition	Endpoint has been updated based on revised regulatory expectations.
	Updated secondary objective mucosal healing endpoint	Endpoint has been updated for clarity from mucosal healing to histologic-endoscopic mucosal remission to align with other mirikizumab protocols.
Section 2. Schedule of Activities	CCI [redacted]	
	TB monitoring language was clarified	Clarification of TB monitoring process to align with sponsor safety guidance for TB assessments and other mirikizumab protocols.
	CCI [redacted]	
	Addition of language for Stool culture and *Clostridium difficile* toxin	In some cases, local laboratory testing results may be available sooner than the central lab results. Given the need to shorten the screening period for these sick children, the protocol will now allow specific *C. difficile* local laboratory tests for screening into the study.

Section 2. Schedule of Activities Section 5.1. Overall Design	Additional footnote and language added for unscheduled visits	Footnote b was added to the SoA to allow, with prior Sponsor approval, additional dosing at Week 52 and beyond, after completing Visit 16 procedures if participant is waiting for regulatory and/or ethics approval to enroll into Study AMAZ. This provision was also added to the overall study design for clarity.
Section 2. Schedule of Activities Section 9.1.6.3. Assessment of Puberty Section 9.4.3.2. Hormone Testing	CCI [redacted]	CCI [redacted]
Section 5.1. Overall Design	Addition of wording to clarify intended use of data snapshot and how it pertains to the opening of CCI [redacted] group for enrollment	Addition of wording to clarify intended use of data snapshot and provide alignment with updates in Section 10.3.8.1. Data Snapshots
Section 6.1. Inclusion Criteria	Addition of wording in inclusion criterion [2b] for female contraception	Clarification that 2 effective methods of contraception must continue CCI [redacted]
	Revision of language in hemoglobin inclusion criterion [11a]	Update of language to reference additional exclusion criterion [46] clarifying a hematology blood sample cannot be drawn within CCI [redacted] of a blood transfusion.
Section 6.2. Exclusion Criteria	Revised language in exclusion criteria [19d], [19e], and [19i]	Clarification that therapies must be discontinued within designated time window prior to screening endoscopy.
	Removal of wording in exclusion criterion [23]	Removal of redundant wording on primary immune deficiencies as this is previously noted in exclusion criterion [14].
	Additional language in exclusion criterion [26]	Further clarification for *C difficile,* other intestinal pathogens, and CCI [redacted]
	Revised language in exclusion criterion [42]	Clarification of timing for enrollment for participants to require CCI [redacted] after receiving last dose of study drug

	Clarification with addition of exclusion criterion [45]	Clarification to separate marijuana from illicit drugs exclusion criterion [43] to avoid potential confusion.
	Clarification with addition of exclusion criterion [46]	By requiring that hematology blood samples cannot be collected within CCI [redacted]
Section 6.4. Screen Failures	Clarification of inclusion/exclusion criteria numbers and language related to rescreening	Clarification of Inclusion/Exclusion criteria numbers that weren't previously documented as allowed or disallowed for rescreening in the event of a screen failure.
Section 6.4.1. Allowed Retesting of Screening Investigations	Removal of first paragraph and additional language added	Paragraph was removed to avoid redundancy and language was added for clarity.
Section 7.1. Treatments Administered	Correction of typo for timing IV administration of mirikizumab and sentence removal	Correction of typo for IV administration time for mirikizumab to be CCI [redacted] to align with investigational product administration instructions provided to the sites and removal of sentence for clarity.
Section 7.6. Treatment Compliance Section 9.1.1. Mayo Score	Clarification language added and paragraphs moved from Section 7.6 to Section 9.1.1	Clarification of investigator responsibility for training of participant and paragraphs moved to align with section in protocol discussing bowel preparation and UC symptom diary recording.
Section 7.7.1. Corticosteroid Taper	Clarification language was added	Clarification that steroids can be tapered before CCI [redacted] following investigator judgement.
Section 7.7.2. Vaccine Administration During the Study	CCI [redacted]	CCI [redacted] .
Section 8.1.1. Permanent Discontinuation from Study Drug	CCI [redacted]	CCI [redacted]

Section 9.1.2. Endoscopy	Clarification of timing from baseline for those requiring full colonoscopy and additional wording for central readers	Timing for participants who require surveillance colonoscopy for UC associated dysplasia and malignancy noted to be within CCI of baseline to align with surveillance guidance. Also, clarification of procedures for central readers
Section 9.1.9.3. Extraintestinal Manifestations	Clarification of diagnoses	Updates for content regarding extraintestinal manifestation diagnoses.
Section 9.4.5.1. Physical Examination	Clarification of language for TB screening physical examination	Clarification of physical examination for TB at screening for all participants.
Section 9.4.5.2. Tuberculosis Testing	Clarification of language for monitoring for TB during the study	Clarification for interpretation of screening test for LBTI for patients with BCG vaccination history. Updated guidance for TB monitoring to be documented at least every CCI for each participant: (1) to determine any risk factors for TB infection and progression; (2) and thorough physical examination for signs of active TB. Additions were made to align with updated Lilly safety guidance.
Section 9.4.5.3. Chest Radiography	Clarification of language for CXR and allowance of a CT Scan in place of CXR	Clarified guidelines for CXR and additional language to allow CT Scan based on regional standard of practice. Additional guidance for the CXR or CT Scan for TB evaluation to be interpreted and reported by a radiologist or physician specialized in the treatment of TB.
Section 9.4.5.4. Hepatitis B Testing	Clarification of language for patient management	Clarification for Management of Patients with a Newly Positive anti-HBc Test During the Study to give guidance for management of this potential patient population during the study.
Section 9.4.5.6. Depression and Suicidality Section 11 References	CCI	CCI

Section 9.4.5.7. Stool Testing	Additional language and flow chart for *C. difficile* testing	Clarification on *C. difficile* screening using local and central testing. A flow chart was added to clarify process for determining results for *C. difficile* infection.
Section 10.3.8.1. Data Snapshots	Updated language	Clarification of data snapshots for patients >40 kg.
Section 10.3.8.2. Interim Analyses	Updated language	Clarification of interim analysis timing based on number of patients in the ≤40 kg group necessary to make a dosing decision to enable Phase 3 trial.
Appendix 2 Clinical Laboratory Tests	Addition of language for hypersensitivity tests	Clarification of Lilly-designated laboratory to be used for immediate hypersensitivity events only.
Appendix 5. Prohibited Medications	Revised language in comments section for anti-TNF antibodies, anti-CCI antibodies, and CCI	Clarification that therapies must be discontinued within specified time window prior to screening endoscopy to align with exclusion criteria.
	Clarification of BCG and live attenuated vaccine and marijuana use including CBD oil	Clarification of prohibited medications to align with other mirikizumab protocols.
Appendix 6. Permitted Medications and Dose Stabilization	Clarification regarding rectally administered medications	Clarification of guidance for rectally administered 5-ASAs and rectally administered corticosteroids to align with other mirikizumab protocols.
	Addition of language for non-live vaccines	Addition of recommendation noting study drug should not be administered on the same day as a vaccination.
Appendix 10. Provision for Changes in Study Conduct During Exceptional Circumstances	Addition of appendix	Provisions were added in the event of exceptional circumstances that may cause study disruptions and sites needing additional flexibility.
Throughout	Minor typographical corrections, clarifications, or semantic changes	Changes do not affect content.

Signature Page for VV-CLIN-008288 v1.0

Approval	PPD 22-Oct-2021 20:48:56 GMT+0000

Approval	PPD 23-Oct-2021 00:58:37 GMT+0000

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