Protocol: I6T-MC-AMAM(15.2)

An Open Label Addendum to the AMAM adult study to Assess Efficacy and Safety of Mirikizumab in the Induction and Maintenance of Remission in Adolescents (15 to <18 years of age) with Moderately to Severely Active Crohn's Disease (CD)

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Title Page

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Protocol Addendum Number: I6T-MC-AMAM Adolescent Addendum (15.2)

Compound Number: LY3074828

Study Phase: 3

Short Title: VIVID-1 Adolescent Addendum

Sponsor Name: Eli Lilly and Company

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Approval Date: Revised Protocol Addendum (15.2) Electronically Signed and Approved by Lilly on date provided below.

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Protocol Addendum Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Revision 15.1	*15-Jan-2021*
Original Protocol Addendum	*08-Jun-2020*

Revision 15.2

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

Overall Rationale for the Revision:

The rationale for this revision to the adolescent addendum (AA) are provided below:

- Lilly is in the process of opening a mirikizumab intervention-specific appendix (I6T-MC-AMAY [AMAY]) under the MACARONI-23 IL-23 pediatric platform master protocol that will enroll pediatric participants 2 to ≤18 years of age with moderately to severely active CD. Study AMAY provides a better option for adolescents with moderately to severely active CD as it allows fo CCI [redacted] Therefore, Lilly has stopped new patient enrollment into the AMAM AA. Patients already enrolled will continue in the AMAM AA until completion.
- Due to the planned significant reduction in adolescent sample size the data for both induction and maintenance phases, the efficacy of mirikizumab-treated adolescent patients will be summarized instead of comparison with the adult placebo group and the adult mirikizumab group. For the adolescents that were enrolled in the study prior to stopping enrollment, their safety and efficacy information will be summarized.
- Primary and secondary objectives and endpoints are revised in response to regulatory feedback and alignment with study AMAY.

Overall changes, including the above, specific to certain protocol sections and a brief rationale are provided in the below table.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Removed the specific number of adolescent patients planned for enrollment in the study	See rationale provided in the text preceding this table.
1.3 Schedule of Activities	CCI [redacted] CCI [redacted]	CCI [redacted] CCI [redacted]

Section # and Name	Description of Change	Brief Rationale
	CCI [redacted] Added footnote "ad" to allow Visit 2 assessments to be performed over 2 days after consultation with the medical monitor	Alignment with revised objective and endpoint on height Provides a contingency until Study AMAZ is ready to enroll at the patient's clinical trial site. Alignment with Study AMAY Alignment with Study AMAM
2.2.5 Preclinical and Clinical Studies of Mirikizumab	Updated the status of studies in Ulcerative Colitis that are part of the LUCENT Phase 3 clinical development program for mirikizumab Updated the status for clinical studies in Crohn's Disease	Reflect most recent data
3 Objectives and Endpoints	CCI [redacted]	See rationale provided in the text preceding this table.
3 Objectives and Endpoints	Overall revision of secondary objectives and endpoints	Alignment with rationale provided in the text preceding this table and with Study AMAM

Section # and Name	Description of Change	Brief Rationale
3 Objectives and Endpoints	CCI [redacted]	Details of the analyses will be described in the addendum SAP
3 Objectives and Endpoints	Removed tertiary/exploratory objectives and endpoints	Details of the tertiary/exploratory objectives and endpoints will be described in the addendum SAP
4.1 Overall Design	CCI [redacted]	CCI [redacted]
4.2 Scientific Rationale for Study Design	Removed definition for active CD; specified that definition is provided in the inclusion criteria.	Adapted to more concise language.
4.2 Scientific Rationale for Study Design	Revised based on changes made to objectives and endpoints	See rationale provided in the text preceding this table.
5.1 Exclusion Criteria	Updated Criterion #40 to replace monoclonal antibodies with CCI [redacted]	Clarification to state adult comparator and mirikizumab
5.4 Screen Failures	CCI [redacted]	CCI [redacted]
6.5.3 Corticosteroid Taper	Added, “Investigators must contact the Study Medical Monitor to discuss any participant who does not CCI [redacted]	CCI [redacted]
6.7.3.2 Management of Hypersensitivity, Infusion-Related Events, Infusion Site Reactions, and Injection Site Reactions	Modified instructions for nonsystemic hypersensitivity reactions.	For consistency across the mirikizumab protocols and with the current Lilly standardized safety language.

Section # and Name	Description of Change	Brief Rationale
7.1.2 Criteria for Temporary Interruption (Withholding) of Study Drug	Added wording to clarify that an CCI [redacted].	Clarification.
8.1 Efficacy Assessments	Added endpoint definitions for clinical response by CCI [redacted] clinical remission CCI [redacted] Updated definition for clinical remission CCI [redacted] endoscopic remission endpoint of SES-CD ≤4	Alignment with revised objectives and endpoints and with Study AMAY
8.1.1 Primary Efficacy Assessment	Added clinical response CCI [redacted] clinical remission CCI [redacted] CCI [redacted] from secondary efficacy assessment to primary efficacy assessment. CCI [redacted] Removed the description for clinical remission CCI [redacted] assessment and moved it to secondary efficacy assessments	Alignment with revised objectives and endpoints
8.1.2 Secondary Efficacy Assessments	CCI [redacted] from secondary efficacy assessment and moved to primary efficacy assessment	Alignment with revised objectives and endpoints
8.2.1 Growth Monitoring	CCI [redacted]	Emerging information from internal updates CCI [redacted]

Section # and Name	Description of Change	Brief Rationale
8.2.12 Depression, and Suicidal Ideation and Behavior	CCI [redacted]	Alignment with the Schedule of Activities.
9.1 Statistical Hypotheses	Revised coprimary endpoints	Alignment with revised objectives and endpoints
9.2 Sample Size Determination	Revised the original sample size	See rationale provided in the text preceding this table.
9.4.1 General Statistical Considerations	For both induction and maintenance phases, the efficacy of mirikizumab-treated adolescent patients will be summarized instead of comparison with the adult placebo group and the adult mirikizumab group	For the adolescents that were enrolled in the study prior to stopping enrollment, their safety and efficacy information will be summarized
9.4.1.2 Estimand	For both induction and maintenance phases, the efficacy of mirikizumab-treated adolescent patients will be summarized instead of comparison with the adult placebo group and the adult mirikizumab group CCI [redacted]	For the adolescents that were enrolled in the study prior to stopping enrollment, their safety and efficacy information will be summarized
9.4.1.3. Missing Data Imputation	Removed NRI method that may be used when the estimand of interest uses the hypothetical strategy for handling the intercurrent event of switching adult participants who do not achieve some type of response from placebo to mirikizumab	Alignment with revised objectives and endpoints
9.4.1.4 Multiple Comparisons/Multiplicity	Removed “as hypothesis testing is only occurring for the primary objective”.	CCI [redacted]
9.4.3.1 Primary Analyses	Added clinical response by CCI [redacted] clinical remission CCI [redacted] to the coprimary endpoint	Alignment with revised objectives and endpoints

Section # and Name	Description of Change	Brief Rationale
9.4.3.2 Secondary Analyses	CCI [redacted] secondary endpoints description from primary analyses and moved it to secondary analyses Added endoscopic remission SES-CD ≤4	Alignment with revised objectives and endpoints
	Additional secondary analysis details have been removed	These analyses of the secondary endpoints will be fully detailed in the SAP
9.4.3.3 Tertiary Exploratory Analyses	Removed reference to exploratory endpoints from Section 3	Details of exploratory endpoints will be described in the addendum SAP
9.4.4 Safety Analyses	CCI [redacted]	CCI [redacted]
9.4.5 Pharmacokinetic /Pharmacodynamic Analyses	Revised PK analyses of mirikizumab and relationships between exposure and the efficacy endpoints	With reduction in sample size, the analysis methods needed to be updated.
9.4.7.2 Subgroup Analyses	Removed "Subgroup analyses for selected endpoints in Section 3 will be conducted"	Updated to accommodate the reduced sample size.
9.5 Interim Analyses	Removed primary database lock for the addendum Updated with adolescent pharmacokinetic (PK) and safety data from Study AMAM Updated external data monitoring committee information	See rationale provided in the text preceding this table.
10.2 Appendix 2: Clinical Laboratory Tests	CCI [redacted]	Clarification
11 References	Updated Citations	Editorial change
Throughout	Minor editorial changes.	Correction

Table of Contents

1. Protocol Addendum Summary

1.1. Synopsis

Protocol Addendum Title: An Open Label Addendum to the AMAM adult study to Assess Efficacy and Safety of Mirikizumab in the Induction and Maintenance of Remission in Adolescents (15 to <18 years of age) with Moderately to Severely Active Crohn's Disease (CD)

Acronym: VIVID-1 Adolescent Addendum
Rationale:

Mirikizumab (LY3074828) is a humanized immunoglobulin G4 (IgG4) monoclonal antibody that binds to the p19 subunit of interleukin-23 (IL-23), a cytokine that has been implicated in mucosal inflammation. This addendum to Study I6T-MC-AMAM (AMAM) is a Phase 3 open label study to assess efficacy and safety of mirikizumab in the induction and maintenance of remission in adolescents (15 to <18 years of age) with moderately to severely active Crohn's Disease (CD) in achieving endoscopic and clinical outcomes through Week 52 in adolescent patients. Patients who have an inadequate response to, loss of response to, or are intolerant to corticosteroid or immunomodulator therapy for CD (termed "conventional-failed"), and those who have an inadequate response to, loss of response to, or are intolerant to biologic therapy for CD (termed "biologic-failed") will be included in the study.

Few medications have been approved for the treatment of adolescent patients with CD and the treatments that do exist require close monitoring for the potential of serious adverse effects. 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 CD.

Overall Design:

This study is a 52-week open-label addendum to the AMAM adult study to assess efficacy and safety of mirikizumab in the induction and maintenance of remission in adolescents (15 to <18 years of age) with moderately to severely active Crohn's disease.

Number of Participants:

Adolescents aged 15 to <18 years evaluable for primary analysis.

Intervention Groups and Duration:

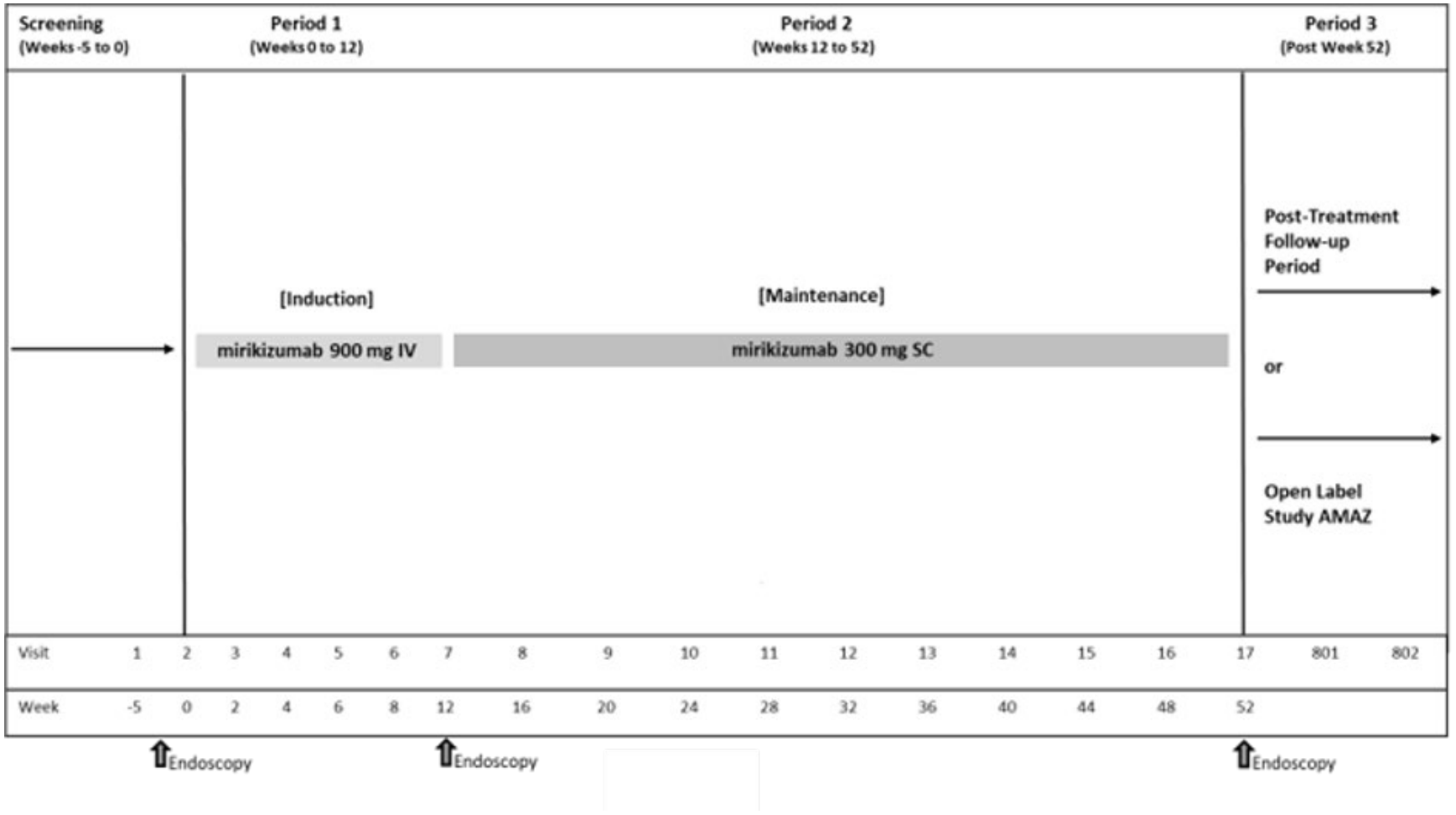
Sites and adolescent participants will know that participants are receiving mirikizumab treatment for the full duration of the study, though the study material assigned and dispensed will be labeled in a blinded fashion (See Section 6.3). During the induction period, participants will receive mirikizumab 900 mg by intravenous (IV) infusion at Weeks 0, 4, and 8. In the maintenance period, participants will receive mirikizumab 300 mg by subcutaneous (SC) injection every 4 weeks until Week 48.

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

Screening Period: up to 5 weeks
Intervention Periods 1 and 2:
Induction: 12 weeks
Maintenance: 40 weeks (Week 12 to Week 52)
CCI , patients may enter 3-year extension study AMAZ or enter Post-Treatment Follow-up Period:CCI

Data Monitoring Committee: Yes

1.2. Schema



Abbreviations: IV = intravenous; mg = milligram; SC = subcutaneous.

1.3. Schedule of Activities (SoA)

	Screening	Period 1: Induction						Period 2: Maintenance												UA/SV[z]	Post-Treatment Follow-up	
Visit Number	V1[a,b]	V2[b]	V3[c]	V4	V5[c]	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	ETV[w]	V997[x]		V801	V802
Week Relative to Study Drug Start	CCI																					
Days Relative to Study Drug Start and Visit Interval Tolerance (Days)[ad]																						
Informed consent/assent																						
Preexisting conditions / Medical and vaccine history / Relevant surgical history																						
Inflammatory bowel disease diagnosis forms																						
Inclusion/Exclusion Criteria																						
Concomitant medications																						
Alcohol use																						
Tobacco / Nicotine use																						
Adverse events																						
CCI																						
VS (T, PR, BP)[d]																						
Height[r]																						
Weight																						
Physical exam[e]																						
EIMs																						
Fistula evaluation																						
CCI																						
CCI																						

	Screening	Period 1: Induction						Period 2: Maintenance												UA/SV[z]	Post-Treatment Follow-up	
Visit Number	V1[a,b]	V2[b]	V3[c]	V4	V5[c]	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	ETV[w]	V997[x]		V801	V802
Week Relative to Study Drug Start	[redacted]																					
Days Relative to Study Drug Start and Visit Interval Tolerance (Days)[ad]																						
CXR[g]																						
CCI																						
TB Monitoring[y]																						
CCI																						
CCI																						
Urine pregnancy[i]																						
Serum pregnancy[j]																						
CCI																						
CCI																						
Interferon-γ release assay (or tuberculin skin test)[k]																						
HIV testing																						
HBV testing																						
HBV DNA[l]																						
HCV testing[m]																						
CCI																						
CCI																						
PK sample[n, o]																						
Immunogenicity (ADA) samples[o]																						
CCI																						

	Screening	Period 1: Induction						Period 2: Maintenance												UA/SV[z]	Post-Treatment Follow-up	
Visit Number	V1[a,b]	V2[b]	V3[c]	V4	V5[c]	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	ETV[w]	V997[x]		V801	V802
Week Relative to Study Drug Start																						
Days Relative to Study Drug Start and Visit Interval Tolerance (Days)[ad]																						
CCI																						
CCI																						
CCI																						
CCI																						
CCI																						
Stool culture[s]																						
C. difficile testing[s]																						
CCI																						
Supply stool collection kit[t]																						
CCI																						
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	Screening	Period 1: Induction						Period 2: Maintenance												UA/SV[z]	Post-Treatment Follow-up	
Visit Number	V1[a,b]	V2[b]	V3[c]	V4	V5[c]	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	ETV[w]	V997[x]		V801	V802
Week Relative to Study Drug Start	CCI																					
Days Relative to Study Drug Start and Visit Interval Tolerance (Days)[ad]																						
CCI																						
CCI																						
CCI																						
CCI																						
CCI																						
Assign to Treatment																						
Dosing[aa]																						

Abbreviations: ADA = anti-drug antibodies (immunogenicity); anti-HBc+ = positive for anti-hepatitis B core antibody; AP = abdominal pain; BMC = bowel movement count; BP = blood pressure; CCI CDAI = Crohn's Disease Activity Index; CDAI-SF= Crohn's Disease Activity Index – Stool Frequency; CCI ; CXR = chest X-ray; CCI ; CCI ; EIM = extraintestinal manifestation; ETV = early termination visit; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; [redacted]; IP = investigational product; LV = last visit; N/A = not applicable; CCI [redacted] SES-CD = Simple Endoscopic Score for Crohn's Disease; T = temperature; TB = tuberculosis; UA/SV = Unscheduled Assessments during a Scheduled Visit; V997 = unscheduled visit; V = visit; VS = vital signs; CCI [redacted]

[a] Visit 1 procedures may be conducted over more than 1 day as long as all tasks are completed within the allowable visit tolerance, it is required that sites have received and reviewed all screening laboratory test results, as well as screening endoscopy results, prior to randomization and dosing at V2. CCI [redacted]

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

[c] Telephone visit.

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

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

[f] CCI

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

[h] CCI

[i] Urine pregnancy test to be performed on all female patients. Done locally and **prior** to dosing.

[j] Serum pregnancy test to be performed on all female patients.

[k] Tuberculin skin tests (TST) are to be read by a qualified professional 48 to 72 hours after placement with results noted in source documentation.

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

[m] CCI

[n] CCI

[o] In the event of an systemic allergic/hypersensitivity event, blood samples will be collected f CCI

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

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

[r] During the study, collect height 3 times per visit at the indicated visits using a calibrated stadiometer.

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

[t] Instruct patients that the stool samples must be collected up to 3 days before endoscopy and prior to beginning bowel prep CCI .

[u] CCI

[v] CCI

[w] ETVs may occur on any day without regard to visit interval. CCI

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

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

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

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

[ab] With sponsor approval, CCI

[ac] CCI .

[ad] Visit 2 may be done over CCI .

2. Introduction

2.1. Study Rationale

Mirikizumab (LY3074828) is a humanized immunoglobulin G4 (IgG4) monoclonal antibody that binds to the p19 subunit of interleukin-23 (IL-23), a cytokine that has been implicated in mucosal inflammation. Study I6T-MC-AMAM (AMAM) is a Phase 3 clinical trial designed to evaluate the safety and efficacy of mirikizumab in achieving endoscopic and clinical outcomes up to Week 52 in patients with moderately to severely active Crohn's disease (CD). Patients who have an inadequate response to, loss of response to, or are intolerant to corticosteroid or immunomodulator therapy for CD (termed "conventional-failed") and those who have an inadequate response to, loss of response to, or are intolerant to biologic therapy for CD (termed "biologic-failed") will be included in the study.

2.2. Background

2.2.1. Disease State and Treatment Goals

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

Crohn's disease is similar in adult and pediatric/adolescent patients in terms of overall disease pathology and progression and potential treatment targets (Jakobson et al. 2011). In addition, pediatric patients with CD are at increased risk of growth failure, retarded puberty, and reduced peak bone mass due to factors such as undernourishment, corticosteroid dependency, and pro-inflammatory cytokines (Gasparetto et al. 2014). According to both the Food and Drug Administration (FDA) (FDA Guidelines 2019) and European Medicines Agency (EMA) (EMA Guidelines 2019), these marginal differences in disease pathology between pediatric and adult CD should not prohibit the inclusion of adolescents with CD into trials with adults.

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

2.2.2. Currently Available Treatments and Unmet Need

Medications used for the treatment of CD in both adolescents and adults may include aminosalicylic acid (5-ASA) containing medications (sulfasalazine, mesalazine, balsalazide, olsalazine), corticosteroids or budesonide, immunomodulators (example: azathioprine [AZA], 6-mercaptopurine [6-MP], and methotrexate), antimicrobial therapy specific for CD, diet, and anti-TNF agents (infliximab, adalimumab, certolizumab pegol) for treatment of CD resistant to treatment with corticosteroids or refractory to methotrexate or thiopurine therapy. Agents targeting leukocyte trafficking such as vedolizumab (an anti-integrin) are currently used in patients who have failed other therapies. Adult approved treatments like ustekinumab, an interleukin-12 (IL-12)/23 (anti-p40) antibody, are recommended in patients who have failed prior treatments with corticosteroids, immunomodulators, or anti-TNF agents. Infliximab is the only biologic agent recommended for treatment of perianal fistulas, albeit in adult patients. For adolescent patients, off-label use of adult treatments is common.

A sizable proportion of the overall adolescent and adult population with moderately to severely active CD is unresponsive to, fails to tolerate, or loses response to conventional therapies or approved biologic therapies. Studies have shown that up to 40% of patients show no clinical benefit in response to treatment with the first anti-TNF agent (Ding et al. 2015). Further, for those that do respond initially, a recent meta-analysis showed, with a median follow-up of 1-year, the incidence of secondary loss of response is 33%, with an annual risk for loss of response as 21% per patient-year (Qiu et al. 2017). Compounding the primary and secondary loss of response data, there are currently only 2 biologics (infliximab, adalimumab) approved in any 1 country for use in pediatric CD (Shi and NG 2018).

Thus, there remains considerable unmet medical need for new treatment options, especially therapies with novel mechanisms of action that have the potential to have improved efficacy and maximize the proportion of patients who achieve clinical remission while maintaining a reassuring safety profile.

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

The contribution of IL-12 and IL-23 in driving the pathophysiology of CD have been explored in genetic and animal model studies. These studies would suggest that IL-23 plays a predominant role in inflammatory bowel disease (IBD) and, indeed, blocking IL-23 alone may be a more effective strategy than blocking both IL-12 and IL-23 (Parrello et al. 2000).

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

The relative contribution of IL-12 and IL-23 to disease pathology in IBD has been explored in several studies. The results of these studies would indicate that IL-23, but not IL-12, promotes intestinal inflammation (Hue et al. 2006; Kullberg et al. 2006; Uhlig et al. 2006; Yen et al. 2006). Data from murine models of psoriasis demonstrating a protective role in dermatologic

inflammation (Kulig et al. 2016), as well as clinical trials (Blauvelt et al. 2017; Reich et al. 2017a), would imply that IL-12 blockade may actually be counterproductive to the control of intestinal inflammation. These data suggest that the efficacy obtained with IL-12/23p40 blockade may be through the inhibition of IL-23 and provide a strong rationale for inhibiting IL-23 in CD.

2.2.4. IL-23p19 Blockade in Crohn's Disease

The efficacy of IL-23p19 blockade in CD has been demonstrated in recent Phase 2 studies evaluating the short-term efficacy and safety of 2 different IL-23p19 mAbs, risankizumab and MEDI2070 (Feagan et al. 2017, 2018; Sands et al. 2017). These Phase 2 studies explored a range of doses from 200 mg to 700 mg intravenous (IV) given up to every 4 weeks (Q4W) through up to Week 12 and provide information regarding the short-term dose-response profile of IL-23p19 blockade in patients with moderately to severely CD. The data from these studies showed evidence of improvements in clinical signs and symptoms, reduction in inflammatory disease burden as evaluated by biomarkers, and evidence of endoscopic healing after a typical short-term induction period. It should be noted that although these studies were small, no safety signals were identified relative to placebo through 12 weeks of treatment, and no additional safety signals were seen in open-label extensions of up to 52 weeks of treatment.

2.2.5. Preclinical and Clinical Studies of Mirikizumab

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

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

Clinical Studies in Ulcerative Colitis

Study 16T-MC-AMAC (AMAC) was a Phase 2, placebo-controlled, double-blind clinical trial of mirikizumab in 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% (Q4W) and 38.5% (every 12 weeks [Q12W]) remained in clinical remission at Week 52. There were few serious adverse events (SAEs) and few discontinuations due to AEs over 52 weeks (D'Haens et al. 2019).

The LUCENT Phase 3 clinical development program for mirikizumab includes studies LUCENT-1 (16T-MC-AMAN), LUCENT-2 (16T-MC-AMBG) and LUCENT-3 (16T-MC-AMAP).

- Study 16T-MC-AMAN (AMAN) was a 12-week double-blind, placebo-controlled, Phase 3 induction study of mirikizumab in participants with moderate-to-severe UC who had failed conventional and/or biologic treatments

  Efficacy results

  A significantly greater proportion of participants treated with mirikizumab achieved clinical remission at Week 12 (Miri: 24.2%; PBO: 13.3% [99.875%CI: 3.2, 19.1]; p=0.00006). Mirikizumab-treated participants achieved all key secondary endpoints including reduced bowel urgency , clinical response, endoscopic remission, symptomatic remission and improvement in endoscopic histologic inflammation. Mirikizumab also reduced symptoms among participants who had previously not responded to or stopped responding to biologic and/or JAK inhibitor therapies.

  Safety results

  The incidence of treatment-emergent AEs and SAEs among participants treated with mirikizumab was consistent with that of the previous Phase 2 mirikizumab study in UC and other studies with the anti-IL-23p19 antibody class. The frequencies of treatment-emergent AEs in mirikizumab-treated participants were similar to placebo. There were numerically fewer SAEs (Miri: 27 [2.8%], PBO: 17 [5.3%]) and discontinuations due to adverse events (Miri: 15 [1.6%], PBO: 23 [7.2%]) in mirikizumab-treated participants compared to placebo (D'Haens et al. 2022).

- Study 16T-MC-AMBG (AMBG) was a multicenter, randomized, double-blind, parallel-arm placebo-controlled, Phase 3 maintenance study in participants who completed AMAN.

  Efficacy results

  A statistically higher proportion of participants met the primary endpoint of clinical remission at one year compared to participants who were re-randomized to placebo ($p<0.001$). All key secondary endpoints were also met ($p<0.001$), including significantly higher proportions of participants treated with mirikizumab achieving endoscopic remission, corticosteroid-free remission, resolution or near-resolution of bowel urgency, improvement in endoscopic histologic intestinal inflammation and maintenance of remission, and greater reduction from baseline in bowel urgency symptoms at one year compared to placebo.

  Safety results

  The frequency of SAEs among participants treated with mirikizumab was numerically lower compared to placebo, and the overall safety profile was consistent with that of the previous mirikizumab studies in UC and studies with the anti-IL-23p19 antibody class. The most common TEAEs reported among participants treated with mirikizumab were nasopharyngitis, arthralgia and exacerbation of ulcerative colitis (Lilly 2021).

- 16T-MC-AMAP (AMAP) is a multicenter, open-label extension study to evaluate the long term efficacy and safety of mirikizumab in participants with moderately to severely active UC. This study is ongoing at the time of this writing.

Pediatric Ulcerative Colitis Study

Study I6T-MC-AMBU (AMBU) is an ongoing Phase 2, 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.

Clinical Studies in Crohn's Disease

Study 16T-MC-AMAG (AMAG) was a Phase 2, placebo-controlled, double-blind clinical trial of mirikizumab in adult patients with active CD. The primary efficacy objective was to test the hypothesis that treatment with mirikizumab is superior to placebo in the proportion of adult patients with endoscopic response at Week 12, defined as a 50% reduction from baseline in Simple Endoscopic Score for Crohn's Disease (SES-CD) score.

At Week 12, endoscopic response was significantly higher by the predefined 2-sided significance level of 0.1 for all mirikizumab groups compared with placebo (200 mg: 25.8%, 8/31, 95% confidence interval [CI], 10.4–41.2, $P = .079$; 600 mg: 37.5%, 12/32, 95% CI, 20.7–54.3, $P = .003$; 1000 mg: 43.8%, 28/64, 95% CI, 31.6–55.9, $P < .001$; PBO: 10.9 %, 7/64, 95% CI, 3.3–18.6). Endoscopic response at Week 52 was 58.5% (24/41) and 58.7% (27/46) in the IV-C and SC groups, respectively. Thus, mirikizumab effectively induced endoscopic response after 12 weeks in participants with moderate-to-severe CD and demonstrated durable efficacy to Week 52.

Frequencies of TEAE in the mirikizumab groups were similar to PBO. Treatment with mirikizumab has shown clinically relevant and consistent treatment effect in reducing or resolving endoscopic inflammation and patient-reported symptoms in participants with moderately to severely active CD. Through Week 52, frequencies of treatment-emergent AEs were similar across all groups. Frequencies of serious AE and discontinuations due to AE were higher in the nonrandomized maintenance cohort. There were no deaths in any study period, and no malignancies or instances of veno-occlusive disease (including pulmonary embolism) reported in the induction or maintenance period of the study (Sands et al. 2021).

Pediatric CD Study

- Study PLATFORMPBCRD3001-16T-MC-AMAY is a Phase 3, multicenter, randomized, platform study of p19 inhibition of the IL-23 pathway to establish efficacy in pediatric CD
    - Study I6T-MC-AMAY (AMAY) is an intervention-specific appendix to the Master protocol PLATFORMPBCRD3001-I6T-MC-AMAY and contains unique study elements specific for mirikizumab.

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

2.3. Benefit/Risk Assessment

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

Patients ≥15 and <18 years of age and body weight >40 kg were selected for the adolescent addendum due to the similarity to the adult population. Specifically, by 15 years of age patients will often have reached sexual maturity and a weight above 40 kg (the weight required for study enrollment) based on available growth chart data (Emmanuel and Bokor 2020; CDC [WWW] 2019) and their immune systems are fully functional (Georgountzou and Papadopoulos 2017). The lower age of 15 years old required for study enrollment represents the onset for the peak age-specific incidence for CD (15 to 30 years of age for peak incidence), and thus is representative of the general adolescent CD population (Ananthakrishnan 2015).

Given both the efficacy and safety data from the Phase 2 adult study in CD and data from other mirikizumab clinical studies completed to date, potential benefit to both adult and adolescent patients receiving mirikizumab in Study AMAM is reasonably anticipated.

Adverse events of special interest (AESIs)—which are not necessarily ADRs but are of special interest based on standard drug registration topics, safety findings from previous studies in development programs, potential risks associated with biologic immunomodulators as noted in product labels and published literature, and comorbidities and risk factors prevalent in the studied populations—are noted in Section 8.3.7 of this protocol. For all AESIs, including hypersensitivity events, the protocol and IB provide monitoring and management guidance to the investigator. In addition, an independent, external data monitoring committee (DMC) will review clinical trial data at prespecified, regular intervals during the study (Appendix 10.1.4). This independent assessment of clinical trial data will contribute to the overall ongoing evaluation and management of potential risks associated with mirikizumab administration.

In summary, the efficacy and safety data from the Phase 2 CD study AMAG support the continued clinical development of mirikizumab as a treatment in both adult and adolescent patients with CD.

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

3. Objectives and Endpoints

Participants in the AMAM Adolescent Addendum will be assigned mirikizumab with clinical trial material provided to sites as blinded treatment. This allows the use of the same test article in both the adult study and the adolescent addendum. The primary and secondary efficacy objectives will summarize the data for open-label mirikizumab-treated adolescents and placebo-treated adults from Study AMAM for endpoints collected in both adolescents and adults.

Objectives	Endpoints
Co-Primary	
To evaluate the efficacy of mirikizumab as assessed by • Clinical response at Week 12 and endoscopic response at Week 52 and • Clinical response at Week 12 and clinical remission at Week 52	The proportion of patients achieving: • clinical response CCI at Week 12 and endoscopic response by SES-CD at Week 52 and • clinical response CCI at Week 12 and clinical remission CCI at Week 52
Secondary	
To evaluate the efficacy of mirikizumab as assessed by • clinical response CCI and endoscopic response at Week 52 • clinical response CCI and clinical remission by CDAI at Week 52	The proportion of patients achieving: • clinical response CCI and endoscopic response at Week 52 • clinical response CCI and clinical remission by CDAI at Week 52
• To evaluate the efficacy of treatment with mirikizumab in endoscopic response at Week 12	• Proportion of patients achieving endoscopic response at Week 12
• To evaluate the efficacy of treatment with mirikizumab in endoscopic remission at Week 52	• Proportion of patients achieving endoscopic remission SES-CD ≤4[a] at Week 52
• CCI	• CCI
• To evaluate the efficacy of treatment with mirikizumab in endoscopic remission at Week 12	• Proportion of patients achieving endoscopic remission SES-CD ≤4[a] at Week 12
• To evaluate the efficacy of treatment with mirikizumab in clinical remission	• Proportion of patients achieving clinical remission by CDAI at Week 12

Objectives	Endpoints
by CDAI	• Proportion of patients achieving clinical remission by CDAI at Week 52
• To summarize the efficacy of treatment with mirikizumab in clinical remission CCI	• Proportion of patients achieving clinical remission CCI • Proportion of patients achieving clinical remission CCI
• To summarize the efficacy of treatment with mirikizumab CCI	Mean change from baseline at Week 12 and at Week 52: • CCI • CCI
• To summarize the efficacy of treatment with mirikizumab CCI	Change from baseline in the following CCI • CCI • CCI
• To summarize the proportion CCI	• Proportion of patients who had CCI • Proportion of patients who had CCI • Proportion of patients who had CCI
• To evaluate the pharmacokinetic and pharmacokinetic/pharmacodynamic relationships of mirikizumab	• CCI • CCI
• To summarize the change CCI	• Change from baseline CCI • Change from baseline CCI
• To summarize the change CCI	• Change from baseline CCI • Change from baseline CCI
• To summarize the efficacy of treatment with mirikizumab in endoscopic	• Proportion of patients achieving endoscopic remission CCI

Objectives	Endpoints
CCI [redacted]	CCI [redacted] • Proportion of patients achieving endoscopic remission CCI [redacted]

[redacted]

4. Study Design

4.1. Overall Design

Design Summary

This open-label addendum to the AMAM adult study will assess efficacy and safety of mirikizumab in the induction and maintenance of remission in adolescents (15 to <18 years of age) with moderately to severely active Crohn's Disease. See Schema in Section 1.2.

Addendum participants with moderate-to-severe CD will be unblinded to treatment for the full duration of the study, though the study material assigned and dispensed has blinded labeling (Section 6.3). During the induction period, participants will receive 900 mg mirikizumab by IV infusion doses at Weeks 0, 4, and 8. In the maintenance period, participants will receive 300 mg mirikizumab by SC injection every 4 weeks until Week 48.

Adult double-blind and double dummy placebo-treated participants will be used as the comparator for adolescent mirikizumab treated patients, noting:

- When Period 1 induction dosing concludes (Week 12), placebo responders continue receiving placebo, and placebo nonresponders (NRs) at Week 12 will receive mirikizumab as described in the adult protocol.

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

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

Participant Visit Scheme

Study participants will undergo screening assessments, be assigned to treatment with investigational product, and participate[redacted] if they do not proceed to the long-term extension Study AMAZ.

Screening may be done on more than 1 day, as long as all activities are completed within [redacted] It is required that sites have received and reviewed all the screening laboratory test results, as well as screening endoscopy results, prior to treatment assignment and dosing at V2. Please note that laboratory results could take[redacted]

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

Participants who complete Study AMAM adolescent addendum through [redacted] will be given the option to enroll in Study AMAZ if they are eligible (Section 6.7.1). With sponsor approval, additional dosing at [redacted] may occur as needed for participants eligible to enroll in Study AMAZ where the clinical trial site is not yet open. Participants must have completed all procedures at [redacted]

CCI from the prior dose. Urine pregnancy test must be negative prior to study drug administration. Refer to study AMAZ main protocol inclusion criteria for participants moving into study AMAZ.

Participants who do not meet enrollment criteria for Study AMAZ or who do not choose to participate in Study AMAZ will continue for CCI follow-up visits in Study AMAM. CCI

Participants who permanently discontinue study drug early will undergo early termination procedures, including an ETV and the post-treatment follow-up visits (Section 7.1).

Assessments and Procedures

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

Adolescent Responders/Nonresponders within the AMAM Addendum

All adolescent participants consented in the addendum, irrespective of response status or age during their enrollment in the trial, will proceed from the induction period at CCI .

Adult Placebo Nonresponders within the AMAM Adult Trial

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

Adult Placebo Responders within the AMAM Adult Trial

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

4.2. Scientific Rationale for Study Design

The AMAM adolescent addendum (AA) is designed to evaluate the safety and efficacy of mirikizumab in the induction and maintenance of remission in adolescent patients (15 to <18 years of age) with moderately to severely active CD.

Endpoints

To evaluate the effect of mirikizumab on decreasing intestinal mucosa inflammation and symptoms of CD, the following endpoints will be used for the primary objective of Study AMAM AA: SES-CD CCI

The SES-CD will be determined at baseline, Week 12, and Week 52 (or end of study for patients with early discontinuation) with evaluation of endoscopic response (defined as ≥50% reduction from baseline in SES-CD total score) as a coprimary endpoint. At the GREAT 3 Workshop,

endoscopic response as a coprimary endpoint was considered clinically meaningful and relevant and would provide sufficient evidence of efficacy for CD trials at various time points (FDA Workshop). The 50% reduction from baseline in SES-CD as a definition of endoscopic response in CD was ranked first by 11 of 12 participants (Vuitton et al. 2016) in a modified Delphi process by members of the International Organization of Inflammatory Bowel Disease. Based on this consensus of gastroenterology experts, endoscopic response is considered a meaningful and relevant endpoint for assessment of therapies in CD. Additionally, the 50% cutoff point was shown to correlate with steroid-free remission at a later time point based on a post hoc analysis of the SONIC trial (Ferrante et al. 2013). Thus, 50% improvement in the SES-CD correlates with long-term clinical improvement and provides a robust and meaningful assessment of endoscopic improvement.

CCI [redacted]

Use of Adult Placebo Comparator

The control arm in this addendum is placebo-treated adult patients from study AMAM (main study).

The extrapolation approach from adults to pediatric patients with CD is scientifically justified and is based on:

- similar disease progression based on shared pathobiology and similar response to intervention between adults and children (Turner et al. 2016), and
- CCI [redacted]

A Week 12 timepoint for the addendum was chosen to match that of the adult protocol. This timepoint falls within the study duration (from 6 week to 12 weeks) recommended for demonstration of short-term efficacy. Week 52 assessments will document the efficacy of mirikizumab in long-term treatment.

4.3. Justification for Dose

The mirikizumab 900 mg IV Q4W induction and 300 mg SC Q4W maintenance dose regimens selected for this study were based primarily on analyses of CCI [redacted]

Pharmacokinetic Considerations

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 adult Phase 2 Study AMAG enrolled subjects who had baseline body weights ranging from 35.5 to 125 kg, with a median of 71.6 kg. Population PK analyses of the AMAG data were used to understand the relationship between body weight and clearance and body weight and volume of distribution.

These analyses indicate that compared to the median adult body weight, subjects with a body weight of CCI would typically be expected to have a clearance CCI and a volume

of distribution CCI . CCI [redacted] The magnitude of these impacts is small relative to the overall random interpatient variability in clearance and volume of distribution. CCI [redacted] These results indicate that, for body weights included in this trial, weight does not have a clinically relevant impact on the PK of mirikizumab.

Based on the above observations in adults and PK data analyses, IV doses of up to 1000 mg that produced exposures higher than those produced with CCI [redacted] relationship could be expected across adult and pediatric CD populations.

Therefore, the available efficacy and nonclinical and clinical safety data support th CCI [redacted]

It is expected that the CCI [redacted] predicted exposures similar to that of adults.

Safety Considerations

The safety data collected for mirikizumab in completed and ongoing clinical studies and in nonclinical toxicology studies support the proposed dose regimen. Details of the clinical studies are outlined in Section 2.2.5.

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

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

with psoriasis (Study AMAF) and of the unblinded safety data available to date in the ongoing Phase 2 study of mirikizumab in patients with UC (Study AMAC) has not revealed a safety concern that differs from the safety findings noted above for Study AMAG.

The nonclinical safety profile of mirikizumab supports the proposed dose regimens in this study on the basis of the NOAELs established in studies in monkeys. CCI [redacted]

CCI [redacted]

Considerations of Efficacy and Exposure–Response Relationships

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

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

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

CCI [redacted]

4.4. End of Study Definition

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

5. Study Population

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

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

5.1. Inclusion Criteria

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

Informed Consent

[1] the investigator, or a person designated by the investigator, will obtain written informed consent approved by the Ethical Review Board (ERB) from each study participant or the participant's parent/legal guardian and the subject's assent, when applicable, before any study-specific activity is performed. The investigator will retain the original copy of each participant's signed consent/assent document.

Patient Characteristics

[2] are male or female patients 15 to <18 years of age weighing >40 kgs with moderate to severely active CD as defined in points 5 and 6 below at the time of initial screening/consent.

[2a] male patients:

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

[2b] female patients:

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

AND

B. must agree to either remain abstinent, if complete abstinence is their preferred and usual lifestyle, or remain in same-sex relationships, if part of their preferred and usual lifestyle, without sexual relationships with males. Periodic abstinence (for example, calendar, ovulation, symptothermal, or postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

OR

must use 2 effective methods of contraception for the entirety of the study. Abstinence or contraception must continue following completion of study drug administration for CCI .

i. Two effective methods of contraception (such as male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges) will be used. The participant may choose to use a double barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide. It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable because of the high failure rate when these methods are combined.

ii. Of note, 1 of the 2 methods of contraception may be a highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine devices).

women not of childbearing potential may participate and include those who are:

infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as Mullerian agenesis.

[3] have venous access sufficient to allow blood sampling and IV administration as per the protocol.

Disease-Specific Inclusion Criteria

[4] have had a diagnosis of CD or fistulizing CD established at least 3 months prior to enrollment confirmed by clinical, endoscopic, or surgical, and histological criteria.

Note: A histopathology report supporting the diagnosis of CD must be available in the source documents prior to randomization, in order to satisfy this inclusion criterion. If a histopathology report supporting the diagnosis of CD is not available in the source documents prior to randomization, the investigator can obtain additional biopsies for this purpose at the screening endoscopy (sent to the local histopathology laboratory).

[5] have moderately to severely active CD as defined by symptoms of inflammation attributable to CD evaluated CCI

[6] have signs of inflammation attributable to CD defined as a centrally read SES-CD score CCI

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

Prior Medication Failure Criteria

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

[8a] **Conventional-failed 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 disease, defined as signs and/or symptoms of active CD despite a minimum of CCI :
    - oral prednisone (or equivalent) at doses of at least CCI , or
    - CCI .
  - corticosteroid-dependent disease, defined as:
    an inability to reduce corticosteroids below the equivalent of prednisone CCI CCI of completing a course of corticosteroids.
  - history of intolerance of corticosteroids (which includes evidence of a side-effect sufficiently serious as to precluding continued treatment with corticosteroids including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, or neuropsychiatric side-effects, including insomnia, associated with corticosteroid treatment).
- immunomodulators:
  - signs and/or symptoms of persistently active disease despite at CCI
    - oral AZA CCI
    - oral AZA or 6-MP within a therapeutic range as judged by thioguanine metabolite testing, or
    - a combination of a thiopurine and allopurinol within a therapeutic range as judged by thioguanine metabolite testing.
  - history of intolerance to at least 1 immunomodulator (including but not limited to nausea/vomiting, AP, pancreatitis, liver function test abnormalities, and lymphopenia).

AND

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

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

[8b] **Biologic-failed patients:** Participants who have an inadequate response to, loss of response to, or are intolerant to a biologic therapy for CD (such as anti-TNF antibodies or anti-integrin antibodies). **Investigators must be able to document an adequate history of induction and/or maintenance dose use.** Participants should fulfill 1 of the following criteria:

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

  OR

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

  OR

- Intolerance: History of intolerance to infliximab, adalimumab, certolizumab pegol, vedolizumab, natalizumab, or other biologics (including but not limited to infusion-related event, demyelination, congestive heart failure, or any other drug-related AE that led to a reduction in dose or discontinuation of the medication).

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

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

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

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

CD Medication Dose Stabilization Criteria

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

[9a] oral 5-ASA therapy: CCI [redacted].

[9b] oral corticosteroid therapy (prednisone ≤30 mg/day or equivalent, or budesonide 9 mg/day): CCI [redacted]

[9c] AZA, 6-MP, or MTX: CCI [redacted]

[9d] CD-specific antibiotics: CCI [redacted]

Study Procedure Inclusion Criteria

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

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

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

[11a] Hematology:

CCI [redacted]

[11b] Chemistry:

CCI [redacted]

CCI [redacted]

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

5.2. Exclusion Criteria

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

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

Gastrointestinal Exclusion Criteria

[12] are participants who:

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

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

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

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

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

- might be anticipated to require surgery within CCI after screening,

OR

- could preclude the use of the SES-CD, CDAI, or PRO to assess response to therapy,

OR

- would possibly confound the ability to assess the effect of treatment.

Adenoma, Dysplasia, and Gastrointestinal Cancer Exclusion Criteria

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

[17] have any current sporadic adenoma without dysplasia that has not been removed. Once completely removed, the patient is eligible for study.

[18] have any evidence of colonic dysplasia.

Criteria for Discontinuing Prohibited Medications

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

[19a] corticosteroid enemas, corticosteroid suppositories, or a course of IV corticosteroids within CCI.

[19b] 5-ASA enemas or 5-ASA suppositories CCI

[19c] immunomodulatory medications, including oral cyclosporine, IV cyclosporine, tacrolimus, mycophenolate mofetil, thalidomide, or Janus kinase inhibitors CCI

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

[19d] anti-TNF antibodies (for example, infliximab, adalimumab, or certolizumab pegol) CCI.

[19e] anti-integrin antibodies (for example, vedolizumab) CCI .

[19f] agents that deplete B or T cells (for example, rituximab, alemtuzumab, or visilizumab) CCI Patients remain excluded if there is evidence of persistent targeted lymphocyte depletion at the time of screening endoscopy.

[19g] any investigational nonbiologic therapy CCI

[19h] any investigational biologic therapy CCI

[19i] leukocyte apheresis (leukapheresis, for example, Adacolumn) CCI

[19j] interferon therapy CCI

[19k] natalizumab CCI

[20] have ever received anti-IL-23p19 antibodies (for example, risankizumab [BI-655066], brazikumab [MEDI-2070], guselkumab [CNTO1959], or tildrakizumab [MK-3222]) for any indication, including investigational use.

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

Note: Participants who have received up to the IV induction dose and 1 SC dose of anti-IL 12/23p40 antibodies (e.g., ustekinumab), may be enrolled. However, these participants must have discontinued treatment for a nonclinical reason (e.g., change of insurance) and discontinued at least 16 weeks prior to screening endoscopy. Enrollment of participants meeting this criterion will be limited to approximately 10% of total enrollment.

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

Infectious Disease Exclusion Criteria

[23] are participants who

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

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

[23c] are diagnosed with latent tuberculosis infection (LTBI) at screening and/or have a past history of LTBI and have not started a course of an appropriate TB prophylaxis regimen (Section 8.2.7).

Participants diagnosed with LTBI at screening and/or history of LTBI without appropriate treatment (aligned with WHO/CDC guidance in place at the time of treatment) may be allowed to rescreen and may be eligible for the study, provided they fulfill all the criteria described in Section 8.2.7.

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

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

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

- positive for hepatitis B surface antigen (HBsAg+)

OR

- negative for hepatitis B surface antigen (HBsAg-) and positive for anti-hepatitis B core antibody (anti-HBc+) in conjunction with detectable HBV DNA (see Section 8.2.9).

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

- positive for hepatitis C antibody and detectable HCV RNA (see Section 8.2.10).

Note: Participants with a previous HCV infection that has been successfully treated with antiviral therapy are not excluded (see Section 8.2.10).

[28] have tested positive for *C. difficile* toxin or for other intestinal pathogens within CCI of screening endoscopy or test positive at screening for *C. difficile* toxin or for other intestinal pathogens. Participants with a confirmed diagnosis of cytomegalovirus-associated colitis should have adequate treatment and resolution of symptoms at least CCI prior to screening endoscopy. (See Section 8.2.6).

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

[29a] infections requiring IV antibiotics.

[29b] infections requiring hospitalization.

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

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

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

[30] have a current or recent acute, active nonserious extraintestinal infection for which signs and/or symptoms are present or treatment, if indicated, i CCI

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

General Exclusion Criteria

[32] have had lymphoma, leukemia, or any malignancy within the past 10 years.

Exceptions: The following conditions are not exclusionary:

a) basal cell or squamous epithelial carcinoma of the skin that has been adequately treated with no evidence of metastatic disease for 1 year.
b) cervical carcinoma in situ that has been adequately treated with no evidence of recurrence within the 3 years prior to baseline (Visit 2).

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

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

[35] are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

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

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

[38] CCI

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

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

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

[42] are unwilling or unable to comply CCI [redacted] for the duration of Study AMAM, or unable to complete other study procedures.

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

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

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

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

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

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

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

5.2.1. Rationale for Exclusion of Certain Study Candidates

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

Participants from 15 to <18 years of age at the time of screening will be eligible to be included in this study.

5.3. Lifestyle Considerations

Study participants should be instructed not to donate blood or blood products during the study and for CCI [redacted] following their last dose.

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

5.4. Screen Failures

Allowed Rescreening of Participants After Initial Screen Failure

CCI

CCI

For the reasons above, participants CCI

Participants who have failed screening because of Exclusion Criterion [23c] (if treated for LTBI for at least CCI and compliant with LTBI therapy while on study) may be rescreened 1 time. See Section 8.2.7.

Participants who have failed screening because of Exclusion Criterion [28] may be rescreened 1 time for *C. difficile* stool toxin. Additionally, a participant may be rescreened 1 time for stool culture or ova parasite. In either situation, participant rescreening should only occur after the reason for screen failure has resolved. It is recommended that the investigator confirms the participant has a negative *C. difficile* stool toxin/stool culture/stool ova parasite (as applicable) before performing additional rescreening investigations (see also Section 8.2.6 and Section 5.4.1). The start of rescreening is when the screen failure was first noted. The interval between rescreenings should be at least 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.

The interval between rescreening should be at least CCI after time/date of screen failure for participants because CCI

Participants who screen fail because they are unable to complete their endoscopy CCI will not be required to undergo repeat TB testing, chest X-ray (CXR) or computed tomography (CT), HIV, HBV, and HCV testing stool cultures, and *C. difficile* testing if these were normal or negative during screening. These tests should be repeated if based on the 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 Participants After Initial Screen Failure

CCI

5.4.1. Allowed Retesting of Screening Investigations

Retesting of screening investigations within a screening period (without a requirement for screen failure and rescreening) is allowed as described below. The following screening investigations may be retested 1 time at the discretion of the investigator.

Screening hematology and chemistry blood tests: CCI

Stool testing: if there is a technical difficulty in performing or reporting the *C. difficile* or stool culture assays (see Section 8.2.6).

Retesting or confirmatory testing with an interferon-γ release assay (IGRA): for example, QuantiFERON®-TB Gold or T-SPOT® assay, in selected participants as part of screening for LTBI (see Section 8.2.7 for details).

Endoscopy: where the endoscopist is unable to adequately visualize the mucosa (for example, due to poor bowel preparation, technical issues with equipment) or where the central readers are unable to determine the centrally read SES-CD score (for example, failure of the recording equipment).

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

6. Study Intervention

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

6.1. Study Intervention(s) Administered

The study interventions used in this study are:

- Mirikizumab administered by IV infusion (Induction), SC injection (Maintenance)

Packaging and Labeling

Clinical trial materials will be labeled according to the country's regulatory requirements. All investigational products will be stored, inventoried, reconciled, and destroyed according to applicable regulations. Clinical trial materials are manufactured in accordance with current Good Manufacturing Practices (GMP).

Study intervention will be supplied as:

- Single-use blinded solution vial containing mirikizumab, with study-specific labels.
  - CCI [redacted]
- Single-use blinded solution pre-filled syringe containing mirikizumab.
  - CCI [redacted]
  - CCI [redacted]

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

Preparation and Administration

Mirikizumab 900 mg will be administered intravenously every 4 weeks at Weeks 0, 4, and 8, then 300 mg subcutaneously every 4 weeks starting Week 12 until Week 48. Investigational product will be administered at the site by nurse, pharmacist, or other trained and qualified personnel as designated by the investigator.

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

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

Time of Doses

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

Investigator Responsibilities

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

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

6.2. Preparation/Handling/Storage/Accountability

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

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

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

Investigational products (interventions) will be supplied in accordance with current GMP and will be supplied with lot numbers, expiry dates, and certificates of analysis, as applicable.

6.3. Measures to Minimize Bias: Randomization and Blinding

Treatment Assignment

Treatment will be dispensed using an interactive web-response system (IWRS) as blinded study material. There will be no randomization, all adolescent patients will be assigned to mirikizumab.

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

6.4. Study Intervention Compliance

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

Every attempt will be made to select participants who have the ability to understand and comply with study instructions. The investigator is responsible for discussing methods to ensure high treatment compliance with the participant before randomization.

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

- the importance of complete bowel prep prior to colonoscopies,
- how to evaluate their CD symptoms CCI

and

- CCI

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

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

6.5. Concomitant Therapy

Recording of Information About Concomitant Medications

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

Use of Concomitant Medications During the Study

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

6.5.1. Permitted Therapy

Participants taking permitted CD concomitant medications are to keep doses stable unless modifications are needed due to AEs or for appropriate medical management. CCI

nstructions regarding guidance for use are detailed in Appendix 10.7.

6.5.2. Prohibited Therapy

Use of such medications should not be withheld if, in the opinion of the investigator, failure to prescribe them would compromise participant safety. Participants who require a prohibited medication to treat their CD should be discontinued from study drug as described in Section 7.1.1 and should complete an ETV and post-treatment follow-up visits as described in the SoA (Section 1.3). CCI

consult your medical monitor prior to discontinuing the participant.

Vaccinations

During the screening period, the investigator must review the study participant's vaccine record to confirm required vaccinations are up to date. If nonlive vaccination is needed, it should be performed during the screening period prior to the first dose of study drug. Use of BCG vaccination is prohibited throughout the duration of the study and for CCI after discontinuation of study drug.

Use of live, attenuated vaccines is prohibited CCI

Use of nonlive (killed, inactivated, subunit and RNA-based) vaccinations is allowed; CCI

For More Information

The list of prohibited medications is provided in Appendix 10.6.

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

6.5.3. Corticosteroid Taper

Participants who achieve clinical response (Section 8.1) and who are currently on corticosteroids CCI

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

CCI

6.5.4. Rescue Medicine

As noted in Section 6.5, participants who require a prohibited medication other than oral 5-ASA compounds or immunomodulators as described above to treat their CD should be discontinued

from study drug as described in Section 7.1.1 and should complete an ETV and post-treatment follow-up visits as described in the SoA (Section 1.3).

CCI , as all patients are assigned to active study drug.

6.6. Dose Modification

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

6.7. Intervention after the End of the Study

6.7.1. Study Extension

Participants who complete Study AMAM Adolescent Addendum through CCI will be assessed for eligibility to enter Study AMAZ. If a participant does not meet enrollment criteria for Study AMAZ or does not opt to continue into Study AMAZ, he or she will be asked to complete the post-treatment follow-up period, as described in the Schedule of Activities (Section 1.3), which will complete his or her study participation. At Week 52, patients may enter 3-year extension study or enter post-treatment follow-up CCI .

6.7.2. Treatment after Study Completion

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

6.7.3. Special Treatment Considerations

6.7.3.1. Premedication for Infusions

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

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

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

Hypersensitivity Events

If a participant experiences a systemic hypersensitivity reaction involving 2 or more organ systems (that is, mucocutaneous, respiratory, cardiovascular, or gastrointestinal systems), during or up to 6 hours after an infusion of study drug, the following guidance should be followed:

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

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

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

Other Infusion-Related Events

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

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

Injection Site Reactions or Infusion Site Reactions

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

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

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

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

These sections describe reasons for:

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

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

7.1. Discontinuation of Study Intervention

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

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

- ETV and,
- post-treatment follow-up visits CCI

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

7.1.1. Criteria for Permanent Discontinuation of Study Drug

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

Subject/Legal Guardian Decision

The participant or legal guardian requests to discontinue the study drug.

Disease Worsening

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

Safety Considerations

- The participant has a diagnosis of any of the following during the study:
  - cancer other than squamous cell or basal cell carcinoma of the skin.
  - intestinal dysplasia.
  - active TB (Section 8.2.7).
  - HIV/AIDS.
  - hepatitis B or development of detectable HBV DNA (Section 8.2.9).
  - hepatitis C or development of detectable HCV RNA (Section 8.2.10).
- The participant has a systemic hypersensitivity event or anaphylaxis to mirikizumab (Section 6.7.3.2). Study drug should be discontinued after a systemic hypersensitivity event or anaphylaxis.

- The participant has absolute lymphocyte count CCI
- The participant becomes pregnant. Pregnant participants will not undergo an endoscopy at the ETV (Section 8.1.1.2).
- Noncompliance with LTBI treatment (see Section 8.2.7).
- The participant has an AE or SAE which, in the opinion of the investigator or sponsor, would preclude the participant from continuing to receive study drug.
- It is recommended that the participant be assessed by an appropriately trained professional to assist in deciding whether the participant is to be discontinued if:

Other Reasons

- Treatment noncompliance: participant missed CCI of study drug (Section 6.4).

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

7.1.2. Criteria for Temporary Interruption (Withholding) of Study Drug

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

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

- The participant develops a clinically important intestinal or extraintestinal infection (including LTBI) during the study (see Section 5.2).
- The participant requires major surgery. Administration of study drug may be restarted only after adequate wound healing.
- The participant develops a confirmed CCI [redacted]
- Patients who develop an absolute lymphocyte CCI [redacted]
- The participant has laboratory abnormalities that may lead investigator to hold the study drug until resolution of the abnormalities.

7.1.3. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, the participant should be discontinued from study drug unless there are extenuating circumstances that make it medically necessary for the participant to continue on study drug. If the investigator and the sponsor agree that it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor to allow the inadvertently enrolled participant to continue in the study. Participants who are discontinued from study drug will complete AE and other follow-up as specified in Section 1.3 (Schedule of Activities), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events and Serious Adverse Events), including ETV and post-treatment follow-up visits (V801 and V802).

7.2. Participant Discontinuation/Withdrawal from the Study

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

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

- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- investigator decision
  - the investigator decides that the participant should be discontinued from the study
- subject decision
  - the participant requests to be withdrawn from the study
- Legal guardian decision
  - the legal guardian requests the participant to be withdrawn from the study

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

7.3. Lost to Follow-up

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

8. Study Assessments and Procedures

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

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

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

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

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 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.

8.1. Efficacy Assessments

The following table defines efficacy endpoints used in this study.

Endpoint	Definition
Endoscopic response	≥50% reduction from baseline in SES-CD total score
Endoscopic remission SES-CD ≤4 with ≥ 2 point reduction	SES-CD Total Score ≤4 and at least a 2-point reduction versus baseline and no subscore >1
Endoscopic remission SES-CD 0 to 2	SES-CD Total Score ≤2
Clinical remission by PRO	CCI
Clinical response by PRO	CCI
Clinical remission by CDAI	CDAI score <150
Clinical response by CDAI	A reduction in CDAI score by ≥100 points compared to baseline and/or being in clinical remission by CDAI
Clinical remission by CCI	CCI
Clinical response by CCI	CCI
Clinical response by CCI	CCI
Clinical remission by CCI	CCI

Abbreviations: AP = abdominal pain; CDAI = Crohn's Disease Activity Index; CCI [redacted]; PRO = patient-reported outcome; SES-CD = Simple Endoscopic Score for Crohn's Disease; CCI [redacted]

8.1.1. Primary Efficacy Assessment

The coprimary endpoint is clinical response by CCI [redacted]

Endoscopic Response

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

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

Refer to Sections 8.1.1.2 and 8.1.1.3 for more information on Endoscopy and Endoscopic Biopsies.

CCI [redacted]

8.1.1.1. Simple Endoscopic Score for Crohn's Disease

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

8.1.1.2. Endoscopy

An endoscopy will be performed on all patients during screening, prior to randomization. The endoscopy report and histopathology report (if biopsies sent to the local histopathology laboratory for histology confirmation for eligibility requirements) must be available in the source documents. Prior to performing the screening endoscopy, investigators should ensure that patients have clinically acceptable central laboratory test results. Stool culture and *C. difficile* must be negative at screening prior to randomization.

To ensure quality data and standardization, endoscopy will be performed locally at clinical sites per the study schedules and using the same endoscopist throughout the trial wherever possible. The endoscopist will be a licensed physician, who is qualified by education, training, and experience to perform colonoscopies. Investigators may delegate endoscopy to other members of the study team.

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

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

8.1.1.3. Endoscopic Biopsies

Biopsies will be collected during the endoscopy procedure. Biopsies will be used for the assessment of exploratory biomarkers where permitted (Section 8.8) and to support assessment of the histopathology endpoints (Section 8.1.3.2). The biopsy samples will be sent to the central study laboratory for processing. To ensure quality data and standardization, bowel tissue histopathologic scoring will be performed by blinded central readers. The details of biopsy sample collection will be provided in both the imaging manual and laboratory manual. A detailed endoscopy and histopathology charter will outline the procedures to be used for secure specimen transfer, processing, slide preparation, and digitization of slides for histopathologic scoring. These results will not be made available to study sites during the study.

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

CCI [redacted]

8.1.2. Secondary Efficacy Assessments

8.1.2.1. Clinical Remission by PRO

CCI [redacted]

CCI [redacted]

8.1.2.2. Crohn's Disease Activity Index

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

8.1.2.3. Patient Reported Outcomes

The following PROs will be collected:

CCI [redacted]

As noted in Section 6.4, the investigator is responsible for ensuring that study participants receive adequate training on and have appropriate understanding of how CCI [redacted]

See Appendix 10.8 for details on the above PROs.

8.1.2.4. Inflammatory Biomarkers

High-sensitivity C-Reactive Protein

High-sensitivity C-reactive protein (hsCRP) is an acute phase protein expressed by hepatocytes in response to inflammatory cytokines, particularly IL-6, TNF, and IL-1β (Sands 2015).

High-sensitivity CRP will be obtained at time points described in the Schedule of Activities (Section 1.3). Investigators will be blinded to hsCRP results.

Fecal Calprotectin

Fecal calprotectin is a complex consisting of the calcium-binding proteins S100A8 and S100A9 (Sands 2015). It is expressed by activated neutrophils (and to a lesser extent by macrophages and monocytes), and fecal calprotectin levels correlate with the number of neutrophils in the gut. It is used as a biomarker of intestinal inflammation in clinical practice. Fecal calprotectin will be obtained at time points described in the Schedule of Activities (Section 1.3). Investigators will be blinded to fecal calprotectin results.

8.1.2.5. Extraintestinal Manifestations

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

8.1.2.6. Fistulas

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

8.1.3. Exploratory Assessments

Exploratory endpoints will be defined in the statistical analysis plan (SAP).

8.1.3.1. Disease Severity Index – Crohn's Disease

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

This assessment will only be performed at screening.

CCI [redacted]

[redacted]

8.2. Safety Assessments

Visits and Order of Safety Assessments

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

- Height
- Weight
- Vital signs

- ECG (if applicable)
- Blood sampling

Adverse event collection should occur before the collection of the CCI [redacted]

Data Collection and Reporting

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

Safety Monitoring

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

8.2.1. Growth Monitoring

CCI [redacted]

8.2.2. Vital Signs

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

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

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

8.2.3. Physical Examinations

Physical examinations are mandated and will be performed as specified in the SoA (Section 1.3). Physical examinations can also be performed at the discretion of the investigator at any additional time points, for example, to assist in the evaluation of a new symptom during the study.

At screening, 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 visual examination of the skin. For participants with a risk factor, a thorough exam to evaluate for TB will be performed (Section 8.2.7).

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

8.2.4. Electrocardiograms

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

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

Electrocardiograms will be read locally.

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 participant receives the first dose of study drug should be reported to Lilly or its designee as an AE via eCRF.

8.2.5. Chest Radiography

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

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

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

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

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

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

8.2.6. Stool Testing

Stool Culture

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

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

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

- the participant has been adequately treated, and
- repeat central *C. difficile* toxin lab is negative (a local test may be completed prior to repeat central test)

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

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

C. difficile Toxin

A stool sample for *C. difficile* toxin will be obtained at screening. This assay tests for the presence of *C. difficile* toxin protein, followed by a confirmatory test for *C. difficile* toxin gene expression in the stool sample. In order to be assigned to treatment, participants must have a negative test result.

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

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

- the participant has been adequately treated, and repeat central *C. difficile* toxin lab is negative (a local test may be completed prior to repeat central test)

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

8.2.7. Tuberculosis Testing

Initial Screening

All participants will be screened for active TB and LTBI.

Screening for LTBI will include the following:

- thorough medical and social history to determine risk factors for TB infection over lifetime, symptoms or signs of active TB, and physical examination, including body temperature measurement and assessment of peripheral lymph nodes, as described in Section 8.2.2 and Section 8.2.3,
- CXR or CT, as described in Section 8.2.5, and
- a test 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), or
  - Tuberculin skin test (TST, also called a purified protein derivative [PPD] or Mantoux test).

Tests for Immune Response to Mycobacterial Antigens

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

Participants with documentation of a "negative" IGRA or TST within 3 months before initial screening may not need to repeat TB testing at screening, based on judgment of the investigator. Source documentation must include the original laboratory report (for IGRA) or a record of the size in millimeters of the induration response (for TST). A TST recorded as "negative" without documenting the size of induration in millimeters will not be acceptable and will require a retest. There must be a minimum of 2 weeks between initial TST and retest.

Interpretation of Screening Tests for LTBI

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

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

Participants with a diagnosis of LTBI, based on a positive IGRA test result or a positive TST response, and no evidence of active TB on medical history, physical examination, and CXR or CT, may be rescreened once, as indicated in Section 5.4.

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

- no history of risk of re-exposure since their treatments were completed,
- have received at least 4 weeks of appropriate ongoing prophylactic therapy for LTBI, based on national or international guidelines, for example, (CDC 2016) or (WHO 2018), with documentation of having completed the appropriate TB prophylaxis regimen,
- no evidence of reactivation of LTBI, and
- have no evidence of hepatotoxicity (ALT and AST levels must remain ≤2 × AA ULN) upon retesting of serum ALT and AST levels before randomization.

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

Retesting and Confirmatory Testing

One retest is allowed for participants with an "indeterminate" QuantiFERON-TB Gold assay or "borderline" T-SPOT assay, as stated in Section 5.4.1. Patients with 2 indeterminate QuantiFERON-TB Gold assays or 2 borderline T-SPOT assays will require a TST test and CXR; if both are negative, the participant may enroll.

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

- no risk factors for LTBI,
- no risk factors for increased likelihood of progressing from LTBI to active TB, and
- have never resided in a high-burden country, as detailed in Appendix 10.4.

If the confirmatory test is positive, the participants will be excluded from the study unless he or she completes at least 4 weeks of appropriate therapy for LTBI, based on national or international guidelines (as defined above) and has no evidence of hepatotoxicity (ALT and AST levels must remain ≤2 × ULN) upon retesting of serum ALT and AST levels after at least 4 weeks of LTBI treatment. Such participants must continue and complete appropriate full course of LTBI therapy during the course of the study to remain eligible to participate. If the confirmatory test is negative, these results will be discussed with the medical monitor in order to determine eligibility for the study.

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

Monitoring for TB During the Study

For all participants, monitoring for TB is to be continuous throughout the study. Every 3 months, the participants will be assessed for risk factors for TB (Appendix 10.4). If the participant has a risk factor, the investigator should conduct a thorough exam to evaluate for TB, including examination of peripheral lymph nodes and documentation of body temperature.

If the participant has a risk factor(s), the investigator should conduct a thorough exam to evaluate for TB, including examination of peripheral lymph nodes and documentation of body temperature. If there are relevant physical findings, an IGRA and CXR or CT should be performed.

Diagnosis of LTBI During the Study

Participants diagnosed with LTBI during the study must be temporarily discontinued from study drug (Section 7.1.2). If treatment for LTBI is considered to be appropriate, the participant must complete at least 4 weeks of appropriate therapy for LTBI, based on national or international guidelines (as defined above), and have no evidence of hepatotoxicity (ALT and AST levels must remain ≤2 × ULN) upon retesting of serum ALT and AST levels after at least 4 weeks of LTBI treatment. Such participants may then resume study drug and must continue with and complete a full course of treatment for LTBI in order to continue on the study drug.

Noncompliance with LTBI treatment during the study is a reason for permanent discontinuation from study drug (Section 7.1.1).

Household Contact

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

Prior Treatment for LTBI

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

Active TB

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

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

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

8.2.8. Clinical Laboratory Tests

Visits and Times

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

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

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

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

Central and Local Testing

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

Provision of Laboratory Test Results

With the exception of laboratory test results that may unblind the study (Section 8.1.2.4), Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor.

Investigator Responsibilities

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

Investigators must document their review of each laboratory safety report.

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

8.2.8.1. Pregnancy Testing

Pregnancy testing is to be performed on all female patients. Participants who are pregnant will be discontinued from the study (Section 7.1.1).

Visits and Times

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

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

8.2.8.2. Immunogenicity Assessment

Visits and Times

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

- CCI
- CCI

To aid interpretation of these results, CCI

CCI

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.CCI

Sample Retention

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

8.2.9. Hepatitis B Testing

HBV Screening and Interpretation

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

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

Exclusion Based on HBV Serology and HBV DNA Testing

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

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

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

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

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

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

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

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

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

Management of Participants with Detectable HBV DNA During the Study

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

If HBV DNA is detected during the study, the investigator should consider using 1 of the following terms to report the AE:

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

8.2.10. Hepatitis C Testing

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

Screening for HCV in this study is performed as follows: an initial test for HCV antibody, followed by a test for HCV RNA if the HCV antibody test is positive. Participants with a positive HCV antibody test and detectable HCV RNA will be excluded from the study (Section 5.2).

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

Participants who have spontaneously cleared hepatitis C infection, defined as:

- a positive HCV antibody test and
- a negative HCV RNA test, with no history of anti-HCV treatment,

may be eligible for inclusion in the study, provided they have no detectable HCV RNA on screening for this study.

Any participant with a history of hepatitis C infection who develops elevated ALT >3 times AA ULN within the study will be tested for HCV RNA.

Participants with a previous diagnosis of hepatitis C who have been treated with antiviral therapy and achieved a sustained virologic response (SVR) may be eligible for inclusion in the study, provided they have no detectable HCV RNA at screening. Sustained virologic response is defined as an undetectable HCV RNA level 24 weeks after completion of a full, documented course of an approved, potentially curative antiviral therapy for HCV.

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

CCI [redacted]

CCI

8.3. Adverse Events and Serious Adverse Events

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

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

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

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

After the ICF is signed, study site personnel will record via eCRF the occurrence and nature of each participant's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

In addition, site personnel will record any change in the condition(s), including exacerbation of CD, and any new conditions as AEs.

Investigators should record their assessment of the potential relatedness of each AE to protocol procedure or investigational product, via eCRF.

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

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

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

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

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

8.3.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization

- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent 1 of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the participant has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines (see Section 8.3.2) if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Participants with a serious hepatic AE should have additional data collected using the hepatic eCRF packet (see Section 8.2.11).

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

8.3.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 Code of Federal Regulations (CFR) 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidance 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 guidance.

8.3.2. Time Period and Frequency for Collecting AE and SAE Information

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

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

reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

CCI [redacted]

8.3.3. Follow-up of AEs and SAEs

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

8.3.5. Pregnancy Reporting

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

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

8.3.6. Cardiovascular and Death Events

Cardiovascular AEs and other events leading to death are collected as described in Section 8.3 and its subsections. See also Section 8.3.7.4.

8.3.7. Adverse Events of Special Interest

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

8.3.7.1. Opportunistic Infections

Infections will be categorized by Lilly as opportunistic according to *Opportunistic Infections and Biologic Therapies in Immune-Mediated Inflammatory Diseases: Consensus Recommendations for Infection Reporting during Clinical Trials and Postmarketing Surveillance* by Winthrop et al. (2015). See Appendix 10.5 for more information.

8.3.7.2. Systemic Allergic Reactions and Hypersensitivity Events

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

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

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

In case of a systemic hypersensitivity reaction involving 2 or more organ systems (that is, mucocutaneous, respiratory, cardiovascular, or gastrointestinal systems), additional blood samples for laboratory testing should be collected at the times specified in the SOA (Section 1.3). The lab results are provided to the sponsor via the central laboratory.

Site personnel should educate patients and/or caregivers about the symptoms and signs of hypersensitivity events and provide instructions on dealing with these events.

For recommendations on the management and follow-up of hypersensitivity events, see Section 6.7.3.2.

CCI [redacted]

[redacted]

[redacted]

[redacted]

8.3.8. Complaint Handling

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

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

8.4. Treatment of Overdose

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

8.5. Pharmacokinetics

Visits and Times

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

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

Collection, Handling, and Storage of Samples

Instructions for the collection and handling of blood samples will be provided by the sponsor. Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility

designated by the sponsor. Serum concentrations of mirikizumab will be determined using a validated enzyme-linked immunosorbent assay. It is not intended that samples collected from placebo-treated patients will be analyzed.

Additional Samples

A maximum of CCI In the case of systemic allergic/hypersensitivity reactions (Section 8.3.7.2), additional blood samples will be obtained, as described in the SoA.

Sample Retention

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

8.6. Pharmacodynamics

See Section 8.8 for biomarkers.

8.7. Pharmacogenomics

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

Sample Retention

Samples will be retained at a facility selected by Lilly or its designee for a maximum of CCI after the last participant visit for the study, or for a shorter period if local regulations and/or ERBs/investigational review boards (IRBs) impose shorter time limits. CCI

CCI [redacted]

8.8. Exploratory Biomarkers

CCI [redacted]

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

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

Sample Retention

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

8.9. Medical Resource Utilization and Health Economics

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

9. Statistical Considerations

9.1. Statistical Hypotheses

The primary efficacy objective is to summarize the efficacy of treatment of open-label mirikizumab in adolescents and placebo in adults from Study AMAM with regards to the coprimary endpoints of the rates of clinical response by CCI endoscopic response at CCI clinical response CCI and clinical remission CCI .

9.2. Sample Size Determination

The original sample size to be enrolled was at least 50 evaluable adolescent participants assigned to study intervention to provide CCI to detect a difference between mirikizumab-treated adolescents and placebo-treated adults for the coprimary endpoint of clinical remission by PRO and endoscopic response when comparing the corresponding 95% confidence intervals (CIs). Due to a change in the pediatric program, enrollment in this addendum has been stopped. CCI

All participants enrolled will be assigned to mirikizumab.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined.

Intent-to-Treat (ITT) Population

All enrolled patients, even if the participant does not receive treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Participants will be analyzed according to the treatment to which they were assigned.

Modified Intent-to-Treat (mITT) Population

All patients from ITT who take at least 1 dose of study drug.

Safety Population

Same as mITT Population.

9.4. Statistical Analyses

9.4.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. A detailed SAP describing the statistical methodologies will be developed by the sponsor or its designee. SAS (Version 9.2 or higher, SAS Institute, Cary, NC, USA) will be used for the statistical analysis.

Unless otherwise specified, efficacy analyses will be conducted on the mITT population, and safety analyses will be conducted on the safety population as described in Section 9.3.

Statistical analyses will include the following 3 participant cohorts:

1. Mirikizumab-treated adolescents: Adolescent participants in the addendum, ages 15 to less than 18 years old, assigned mirikizumab treatment as specified in Section 4.1.
2. Placebo-treated adults: Adult participants from Study AMAM, ages 18 years and up, assigned placebo treatment as described in Section 4.1.
3. Mirikizumab-treated adults: Adult participants from Study AMAM, ages 18 years and up, assigned mirikizumab treatment as described in Section 4.1.

For both induction and maintenance phases, the efficacy of mirikizumab-treated adolescent patients will be summarized alongside the adult placebo group and the adult mirikizumab group.

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

Full details of all a priori specified analyses for the amendment will be provided in a separate SAP, specific to the amendment. 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 amendment. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

9.4.1.1. Definition of Baseline

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

9.4.1.2. Estimand

The estimand (ICH 2019) is documented as follows:

The addendum will compare adolescents (15 to <18 years of age) receiving mirikizumab to adults on placebo in individuals with moderately to severely active CD. The specific treatment regimen is explained in Section 6.1. The study population is described in more detail in "Populations for Analysis" (Section 9.3) and the inclusion/exclusion criteria (Sections 5.1 and 5.2).

The primary summary of interest will include descriptive summary of adolescents assigned to the mirikizumab group and adults assigned to the placebo and mirikizumab groups separately for the CCI [redacted] as described in

Section 9.4.1. Additional information concerning the primary and secondary objectives is included in Section 3.

Patients will be considered nonresponders if they discontinue treatment, increase mandatory stable medications, have a disease related surgery, or take prohibited medications prior to the time point of interest (composite approach). The nonresponder imputation (NRI) method will be used as the primary method of accounting for intercurrent events as summarized in "Missing Data Imputation" (Section 9.4.1.3).

Additional details will be provided in the SAP.

9.4.1.3. Missing Data Imputation

The missing data methods described will be used to address the intercurrent event strategies proposed for this study. Analysis of categorical efficacy and health outcomes variables will use a NRI method for missing data. A participant will be considered NR for the NRI-based analysis if he or she:

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

The NRI method may be used to address missingness when the estimand of interest uses the composite strategy for handling intercurrent events. In this strategy, participants with any of the intercurrent events stated above are defined to have failed study intervention for all subsequent timepoints.

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

9.4.1.4. Multiple Comparisons/Multiplicity

No multiplicity adjustment is planned for this trial.

9.4.2. Treatment Group Comparability

9.4.2.1. Participant Disposition

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

9.4.2.2. Participant Characteristics

Demographic and baseline characteristics will be summarized descriptively; no testing will be performed for baseline characteristics. For continuous measures, summary statistics will include

sample size, mean, standard deviation, median, minimum, and maximum. For categorical measures, summary statistics will include sample size, frequency, and percentages.

9.4.2.3. Concomitant Therapy

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

9.4.2.4. Treatment Compliance

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

9.4.3. Efficacy Analyses

Primary and secondary analyses will be based on the mITT population as defined in Section 9.3.

9.4.3.1. Primary Analyses

Primary Endpoint:

The coprimary endpoint is comprised of 2 separate endpoints in the proportion of participants achieving:

- clinical response CCI at Week 12 and endoscopic response by SES-CD at Week 52
- clinical response CCI at Week 12 and clinical remission CCI at Week 52

Refer to Section 8.1 for definitions of the following endpoints:

- CCI
- Endoscopic response
- CCI

Primary analyses will include descriptive summary of the clinical response CCI endoscopic response as described in Section 9.4.1. for mirikizumab-treated adolescents, adults assigned to the placebo group, and adults assigned to the mirikizumab group from Study AMAM.

9.4.3.2. Secondary Analyses

Secondary Endpoints

Refer to Section 8.1 for definitions of the following endpoints:

- Clinical remission by PRO
- Clinical remission by CDAI
- Endoscopic remission SES-CD ≤4
- Clinical remission CCI

Confidence intervals for all secondary endpoints will also be provided for adolescents assigned to mirikizumab and adults assigned to placebo treatment and are not intended to correspond to a statistical hypothesis test.

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

9.4.3.3. Tertiary Exploratory Analyses

Details of the analyses of exploratory endpoints, as well as any additional exploratory analyses will be described in the addendum SAP.

9.4.4. Safety Analyses

Safety will be assessed by evaluating the following: including, but not limited to, exposure, AEs, laboratory analytes, vital signs, growth and development (assessment of puberty), patient characteristics, and AESIs (Section 8.3.7).

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

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

In an overview table, the number and percentage of patients with at least 1 TEAE, SAE, fatal SAE, or discontinuation from study treatment due to an AE will be summarized. Treatment-emergent adverse events (all and by maximum severity), SAEs including deaths, and AEs that lead to treatment discontinuation will be summarized and analyzed by MedDRA system organ class (SOC) and preferred term (PT) or by PT alone.

Laboratory and vital signs measurements will be summarized using boxplot displays and treatment emergent shifts to low/high tables. Other data, including development, body weight, and height data, will be summarized. Weight, height, and BMI data will be merged to the CDC standard growth data by age and sex to compare subjects' growth with the standard. Other measures related to growth (e.g., occipital circumference measurement) will be evaluated. Further analyses may be performed as deemed necessary. Potential AESIs will be identified by 1 or more standardized MedDRA queries (SMQs) by a Lilly-defined MedDRA PT listing based upon the review of the most current MedDRA version, or by treatment-emergent relevant laboratory changes. Definitions of the AESIs and associated analyses will be described in the addendum SAP.

This study also includes assessment of tolerability and acceptability CCI [redacted] through the summarization of AEs reported as injection site reactions and pain, as well as treatment discontinuations as defined in the SAP. Reports of CCI [redacted] will include the assessment of severity (mild, moderate, or severe). Data from these assessments will be reviewed regularly throughout the study by the medical team as part of the trial level safety reviews, as well as presented to our external steering committee approximately twice a year for their independent evaluation.

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

9.4.5. Pharmacokinetic/Pharmacodynamic Analyses

Analyses of the PK of mirikizumab and relationships between exposure and the efficacy endpoints will be conducted.

The PK of mirikizumab will be characterized using graphical evaluations. The observed serum concentration data will be overlaid to the PK profile of adult patients with CD at the same dose for a comparison.

CCI [redacted]

Population PK modeling and model-based analysis for exposure response relationship may be conducted if deemed appropriate. Data from this study may be combined with other study data, if appropriate, for the modeling analysis.

9.4.6. Evaluation of Immunogenicity

Frequencies and percentages will be tabulated for the following:

- CCI [redacted]
- CCI [redacted]

CCI [redacted]

[redacted] dditional details will be provided in the addendum SAP.

9.4.7. Other Analyses

CCI [redacted]

CCI [redacted]

9.4.7.2. Subgroup Analyses

Subgroup analyses may be conducted for the coprimary and selected secondary endpoints. Subgroups to be evaluated may include sex, age, body weight, race, ethnicity, geographic region, baseline SES-CD category, baseline AP/SF category, corticosteroid use at baseline, duration of

disease, and disease location. A detailed description of the subgroup variables and analyses will be provided in the addendum SAP.

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

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

9.5. Interim Analyses

Adolescent pharmacokinetic (PK) and safety data from Study AMAM will be needed to inform dosing decisions for other pediatric mirikizumab trials. To accomplish this, a snapshot of the PK and safety data (including AEs, labs, and vital signs) will be taken of the adolescent patients when approximately CCI [redacted]. If the adolescent PK exposure models are inconsistent with previous adult PK exposure models, a second PK snapshot may be performed if more information is needed to sufficiently determine drug exposure in adolescent patients. The timing of the second snapshot will be based on how much information is still needed after the first snapshot. Additional details on the analysis are found in the PK/pharmacodynamic (PD) analysis plan.

A DMC consisting of members external to Lilly will be established for interim safety monitoring across all the sponsor's Phase 3 studies in patients with CD, as well as a specific Pediatric IBD DMC, also composed of members external to Lilly. See Appendix 10.1.4 for more information. Unblinding details can found in the unblinding plan. Analysis details can be found in the Population PK/PD Analysis Plan.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- Reporting cases of suspected child abuse and/or neglect according to local medical association (e.g., [American Academy of Pediatrics (AAP)] or health department guidelines].

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

10.1.2. Informed Consent Process

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

Participants must be informed that their participation is voluntary.

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

The medical record must include a statement that legally authorized representative (parent/legal guardian) consent and adolescent assent (if deemed appropriate by local ethics review) was obtained before the participant was enrolled in the study and the date the written consent was obtained. The medical record should also describe how the clinical investigator determined that the person signing the ICF was the participant's legally authorized representative (parent/legal guardian). The authorized person obtaining the informed consent must also sign the ICF(s).

Participants and their legally authorized representative (parent/legal guardian) must be re-consented and re-assented to the most current version of the ICF(s) during their participation in the study.

Minor participants must be reconsented if they reach the age of majority during the course of the study, in order to continue participating.

A copy of the ICF(s) must be provided to the participant or the participant's parent/legal guardian. A copy of the ICF(s) is kept on file.

Participants who are rescreened are required to sign a new ICF. A copy of the ICF(s) must be provided to the participant or the participant's parent/legal guardian. Obtain informed consent for continued participation from pediatric participants once a child reaches the age of legal consent.

10.1.3. Data Protection

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

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

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

10.1.4. Committees Structure

CCI [redacted]

[redacted]

Data Monitoring Committee

A DMC consisting of members external to Lilly will be established. The purpose of the DMC is to conduct periodic monitoring of clinical trial data for the Phase 3 CD program. The DMC will consist of a minimum of 5 members, including a physician with expertise in gastroenterology, pediatrics, and a statistician.

No member of the DMC will have contact with study sites. A statistical analysis center (SAC) will prepare and provide unblinded data to the DMC. The SAC members may be Lilly employees or from third-party organizations designated by Lilly. The SAC members will be external to the study team and will have no contact with sites and no privileges to influence changes to the ongoing studies. The timing and frequency of the periodic clinical trial data review by the DMC will be detailed in a DMC charter.

The DMC is authorized to evaluate unblinded interim efficacy and safety analyses. In addition, the DMC may request key efficacy data to put safety observations into context and to assess a reasonable benefit/risk profile for ongoing patients in the study. The DMC will make recommendation to the Lilly Research Laboratories Senior Management Designee, who may order the immediate implementation of the DMC recommendation, or may convene an internal review committee (IRC), which is independent from the study team, to review the recommendation according to standard Lilly policy. Study sites will receive information about interim results ONLY if it is required for the safety of their patients.

10.1.5. Dissemination of Clinical Study Data

Report Preparation

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

Public Access to Reports and Data

Reports

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

Data

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

Publications

For policies on publications, see Section 10.1.9.

10.1.6. Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate
- provide sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and verify data reported to detect potential errors

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

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

Data Capture System

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

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

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

CCI [redacted]

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

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

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

10.1.7. Source Documents

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

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

What constitutes source data is described in Section 10.1.6.

10.1.8. Study and Site Closure

10.1.8.1. Discontinuation of the Study

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

10.1.8.2. Discontinuation of Study Sites

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

10.1.9. Publication Policy

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

10.2. Appendix 2: Clinical Laboratory Tests

Clinical Laboratory Tests

CCI	
CCI	
	Other Tests[a]
	Hepatitis B core antibody[b,d]
	Hepatitis B surface antigen[b,d]
	HBV DNA[b,e]
Other Tests (Local)	Hepatitis C antibody[b,d,f]
Pregnancy test (urine[g])	HCV RNA[b,d,f]
T-SPOT[d] or TST[d]	HIV[b,d]
	Pregnancy test (serum[b,d])
CCI	CCI
	QuantiFERON-TB Gold test[d]
	CCI


CCI


CCI

10.4. Appendix 4: Risk Factors for Latent Tuberculosis Infection

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

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

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

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

Source: adapted from Horsburgh and Rubin 2011.

World Health Organization List of High Burden Countries		
Angola	India	Peru
Azerbaijan	Indonesia	Philippines
Bangladesh	Kenya	Russian Federation
Belarus	Kazakhstan	Sierra Leone
Botswana	Democratic People's Republic of Korea	Somalia
Brazil	Kyrgyzstan	South Africa
Cambodia	Lesotho	Swaziland
Cameroon	Liberia	Tajikistan
Central African Republic	Malawi	United Republic of Tanzania
Chad	Republic of Moldova	Thailand
China	Mozambique	Uganda
Congo	Myanmar	Ukraine
Democratic Republic of the Congo	Namibia	Uzbekistan
Ethiopia	Nigeria	Vietnam
Ghana	Pakistan	Zambia
Guinea-Bissau	Papua New Guinea	Zimbabwe

Source: WHO 2015

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

This table is provided to aid the investigator in recognizing infections that may be considered opportunistic in the context of biologic therapy, for the purposes of exclusion criteria. This list is not exhaustive. Investigators should use their own clinical judgement in determining if other infections may be considered opportunistic, for the purposes of exclusion criteria. Winthrop et al. (2015) consider TB and non-TB mycobacterial disease to be opportunistic infections in the context of biologic therapy.

Bacterial
Bartonellosis (disseminated disease only)
Campylobacteriosis (invasive disease only)
Legionellosis
Listeriosis (invasive disease only)
Nocardiosis
Tuberculosis
Nontuberculous mycobacterial disease
Salmonellosis (invasive disease only)
Shigellosis (invasive disease only)
Vibriosis (invasive disease due to *Vibrio vulnificus*)
Viral
BK virus disease including polyomavirus-associated nephropathy
Cytomegalovirus disease
Hepatitis B virus reactivation
Hepatitis C virus progression
Herpes simplex (invasive disease only)
Herpes zoster (any form)
Post-transplant lymphoproliferative disorder (Epstein-Barr virus)
Progressive multifocal leukoencephalopathy (PML), John Cunningham (JC) virus
Fungal
Aspergillosis (invasive disease only)
Blastomycosis
Candidiasis (invasive disease or oropharyngeal, esophageal. Not isolated lingual)
Coccidioidomycosis
Cryptococcosis
Histoplasmosis
Paracoccidioides infections
Penicilliosis
Pneumocystosis
Sporotrichosis
Other invasive molds: Mucormycosis (zygomycosis) (*Rhizopus*, *Mucor,* and *Lichtheimia*), *Scedosporium*/*Pseudallescheria boydii*, *Fusarium*
Parasites
Leishmaniasis (visceral only)
Strongyloidosis (hyperinfection syndrome or disseminated disease)
Microsporidiosis
Toxoplasmosis
Trypanosoma cruzi infection (Chagas' disease progression) (disseminated disease only)
Cryptosporidiosis (chronic disease only)

Source: Adapted from Winthrop et al. 2015.

10.6. Appendix 6: Prohibited Medications

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

Drug Class	Guidance for Use
Anti-TNF antibodies (for example, infliximab, adalimumab, or certolizumab pegol)	CCI
Anti-integrin antibodies: natalizumab	
Agents depleting B or T cells (for example, rituximab, alemtuzumab, or visilizumab)	
Immunomodulatory medications, including oral cyclosporine, IV cyclosporine, tacrolimus, mycophenolate mofetil thalidomide, or JAK inhibitors	
Rectally administered 5-ASA therapies (enemas or suppositories)	
Rectally administered corticosteroids (enemas or suppositories)	
IV corticosteroids	

Drug Class	Guidance for Use
Systemic corticosteroids for non-CD indications (oral or IV)	CCI
Any biologic investigational therapy	
Any nonbiologic investigational therapy	
Interferon therapy	
Leukocyte apheresis (leukapheresis, for example, Adacolumn)	
Anti-IL-23p19 antibodies (for example, risankizumab [BI-655066], brazikumab [MEDI-2070], guselkumab [CNTO1959], tildrakizumab [MK-3222]) for any indication, including investigational use	
Anti-IL 12/23p40 antibodies (for example, ustekinumab)	
Bacillus Calmette-Guerin (BCG) and live attenuated vaccines	
Medicinal and recreational marijuana (includes CDB oil)	

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

10.7. Appendix 7: Permitted Medications

Drug Class	Guidance for Use
Oral 5-ASAs (for example, mesalamine, balsalazide, olsalazine)	CCI
Oral corticosteroids (prednisone ≤30 mg/day or equivalent, or budesonide 9 mg/day)	
Corticosteroids for non-CD indications: corticosteroids to treat adrenal insufficiency, as premedication for investigational product infusion, or locally administered corticosteroids (e.g., inhaled, intranasal, intra-articular, topical)	
Immunomodulators (for example, AZA, 6-MP, or methotrexate)	
CD-specific antibiotics (for example: rifaximin, Cipro)	
Antidiarrheals (for example, loperamide, diphenoxylate with atropine)	
Non-live (killed, inactivated subunit and RNA-based) vaccines	
Homeopathic and alternative treatments	

Abbreviations: 5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; AZA = azathioprine; CD = Crohn's disease; IV = intravenous; RNA = ribonucleic acid.

CCI [redacted]

CCI [redacted]	[redacted]
[redacted]	[redacted]
CDAI-SF/Bristol Stool Scale (Reference to Types 6 and 7)	
CCI [redacted]	
[redacted]	
[redacted]	
[redacted]	[redacted]
[redacted]	
	[redacted]
	[redacted]
	[redacted]

CCI [redacted]

The following are descriptions of additional PRO instruments for this study, CCI [redacted] (listed in order of administration):

CCI [redacted]

CDAI- (SF, AP, and general well-being): CDAI is an 8-item disease activity measure that includes 3 patient reported items: AP (4-point scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe); SF (number of liquid or very soft stools); and general well-being (0 = generally well, 1 = lightly under par, 2 = poor, 3 = very poor, 4 = terrible). Patients will be provided with an

eDiary tool during screening to record information daily pertaining to their abdominal pain, frequency of liquid or very soft stools, and well-being.

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

CCI

CCI

[redacted]


CCI

10.10. Appendix 10: Contraceptive Guidance and Collection of Pregnancy Information

Females who are infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as Mullerian agenesis

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Collection of Pregnancy Information

Collection of pregnancy information is collected as described in Section 8.3.5.

10.11. Appendix 11: Definitions and Selected Abbreviations

Term	Definition
5-ASA	aminosalicylic acid
6-MP	6-mercaptopurine
AA	age adjusted
AAULN	age-adjusted upper limit of normal
ADA	anti-drug antibodies
ADR	adverse drug reactions
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse events of special interest (AESIs) are AEs which the sponsor specifies as being of special interest based on standard drug registration topics, safety findings from previous studies in the development program, potential risks associated with biologic immunomodulators as noted in product labels and published literature, and comorbidities and risk factors prevalent in the studied population.
AIDS	acquired immune deficiency syndrome
ALP	alkaline phosphate
ALT	alanine aminotransferase
Anti-HBc	anti-hepatitis b core antibody
Anti-HBc+	positive for anti-hepatitis b core antibody
AP	abdominal pain
AST	aspartate aminotransferase
AZA	azathioprine
BCG	Bacillus Calmette-Guerin
blinding	A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the participants are aware of the treatment received.
C_{avg}	average concentration
CBD	cannabidiol

Term	Definition
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CDAI-AP	Crohn's Disease Activity Index-Abdominal Pain
CDAI-SF	Crohn's Disease Activity Index-Stool Frequency
CDAI-well-being	Crohn's Disease Activity Index-Well-Being
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
CI	confidence intervals
CIOMS	Council for International Organizations of Medical Sciences
COA/eCOA	clinical outcome assessment/electronic clinical outcome assessment
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	case report form
CCI	[redacted]
CT	computed tomography
CXR	chest X-ray
DMC	data monitoring committee
DNA	deoxyribonucleic acid
CCI	[redacted]
eCRF	electronic case report form
EDC	electronic data capture system
CCI	[redacted]
EIM	extraintestinal manifestation
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been randomized and assigned to a treatment.

Term	Definition
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
ETV	early termination visit
GCP	good clinical practice
GMP	good manufacturing practices
HBsAg	hepatitis b surface antigen
HBsAg+	positive for hepatitis b surface antigen
HBsAg-	negative for hepatitis b surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
CCI [redacted]	[redacted]
[redacted]	[redacted]
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Conference for Harmonisation
IEC	Independent Ethics Committee
IGRA	interferon—γ release assay
IL-12	interleukin-12
IL-23	interleukin-23
Informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INR	international normalized ratio
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.

Term	Definition
intervention	See "study intervention."
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. See "study intervention."
IRB	Institutional Review Boards/Investigational Review boards
ITT	intent-to-treat
IV	intravenous
IWRS	interactive web-response system
LTBI	latent tuberculosis infection
LV	last visit
MedDRA	Medical Dictionary for Regulatory Activities
medical monitor	The sponsor's designated medical monitor for the study
mITT	modified intent-to-treat
MTX	methotrexate
NOAEL	no-observed-adverse-effect-level
NR	nonresponder, or nonresponse
NRI	nonresponder imputation
NRS	numeric rating scale
patient	See "participant" when used in the context of clinical studies.
participant	Equivalent to "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
CCI [redacted]	[redacted]
PD	pharmacodynamics
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PK	pharmacokinetics

Term	Definition
PRO	patient-reported outcomes
PT	preferred term
CCI	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
SAC	statistical analysis center
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.
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF	stool frequency
SoA	schedule of activities
study drug	See "study intervention"
study intervention	Any investigational intervention, marketed product, placebo, or medical device intended to be administered to a study participant according to the study protocol
SUSARs	suspected unexpected serious adverse reactions
TB	tuberculosis
TBL	total bilirubin level
TE-ADA+	treatment-emergent anti-drug antibodies positive
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TST	tuberculin skin test
UC	ulcerative colitis

Term	Definition
ULN	upper limit of normal
WHO	World Health Organization
CCI [redacted]	[redacted]

10.12. Appendix 12: 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 conditions in which notification is required. To protect the safety of study participants, urgent changes may be implemented before approval but need to be reported as soon as possible. All approvals 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

Additional consent from the participant and legal guardian will be obtained, if required, for:

- participation in remote visits, as defined in Section "Remote visits,"
- a change in the method of study intervention administration,
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

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. Further, the flexibilities outlined may not be available in each site location.

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

Remote visits

In source documents and the CRF, the study site should capture the visit method, with a specific explanation for any data missing because of missed in-person site visits.

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and product complaints remain unchanged. Furthermore, every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

Telemedicine:

Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to:

- Concomitant medication reviews
- Tobacco/nicotine use
- AE reviews
- CCI [redacted]
- Questionnaire administration
  - CCI [redacted]
- Product complaint (if applicable)
- Verification of negative pregnancy test (if applicable)
- Status/observation of self-administration/caregiver administration of IP where applicable

Mobile healthcare:

Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor. Procedures performed at such visits include, but are not limited to:

- Informed consent
- Concomitant medication reviews
- Tobacco/nicotine use
- Adverse event collection
- Vital signs (temperature, pulse rate, blood pressure), weight
- Laboratory assessments (including stool collections)

- CCI [redacted]
- Questionnaire administration (Must be collected by site via Telemedicine, see section above)
- Dosing (SC only)
- CCI [redacted]
- Delivery of required ancillary supplies CCI [redacted]
- Urine pregnancy test (as applicable)

The below may be performed by qualified personnel approved by the sponsor:

- Physical exam
- EIMs
- Fistula evaluation
- Clinician CDAI CCI [redacted]
- TB Monitoring

Other alternative locations:

The sponsor should be made aware of temporary site relocations as soon as possible. Alternate locations for study conduct must be approved for appropriateness considering participant privacy and participant/site staff safety.

- Study visits or assessments may be done at an alternate location under exceptional circumstances, if allowed by local authorities. Procedures that may be done at an alternate location in exceptional circumstances, are: Temporary Site Relocation: In instances where temporary relocation to another facility is required, sites may continue to perform all procedures as feasible. This will include utilizing alternate endoscopy suites and performing central laboratory collection, infusion of investigational agent, or subcutaneous injection of investigational agent by a trained healthcare professional.

- Alternate facilities for central laboratory collection: Where available, participants may utilize laboratory facilities affiliated with the studies central laboratory vendor to conduct testing closer to their home.

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. However, central laboratory testing must be retained for: CCI [redacted]. The local laboratory must be qualified in accordance with applicable local regulations.

- Investigators must document their review of each laboratory safety report and retain in the source documentation. Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the participant receives the first dose of study drug should be reported to Lilly or its designee as an AE via eCRF.

- Laboratory testing may be performed centrally or locally based on logistics related sample stability and feasibility to collect at alternate location. Local laboratory collections will be used for immediate patient management and safety but will not be included in the data for analysis.

Study intervention and ancillary supplies (including participant diaries)

When a participant is unable to go to the site to receive study supplies during normal on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include:

- asking the participant/legal guardian to go to the site and receive study supplies from site staff without completion of a full study visit,

- asking the participant's designee to go to the site and receive study supplies on a participant's behalf,

- arranging delivery of study supplies, and

- working with the sponsor to determine how study intervention that is typically administered on site will be administered to the participant; for example, during a mobile healthcare visit, at an alternate location such as an infusion center, CCI [redacted].

    - Dosing can proceed only if central or local safety labs have been performed CCI [redacted] (or within a shorter timeframe for participants with previous abnormal lab results, as medically indicated) prior to dosing, and lab results do not require study drug discontinuation or temporary interruption.

    - For participants who have had abnormal laboratory values at a prior lab collection, the investigator may ask the participant to have local or central labs obtained to confirm that protocol requirements for IP administration are met.

    - Any clinically significant laboratory abnormality should be discussed with the medical monitor before at-home administration can proceed.

These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.

- When delivering supplies to a location other than the study site (for example, participant's home), the investigator, sponsor, or both should ensure oversight of the shipping

process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).

- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

In addition, if study intervention will be administered to the participant during a mobile healthcare visit or at an alternate location, these additional requirements must be met:

- Only authorized study personnel may supply, prepare, or administer study intervention.
- If IV administration occurs at an alternate location, resuscitation equipment, emergency medications, and appropriately trained staff must be available during the infusion and monitoring period. All participants should be monitored for CCI or longer after IV dosing, according to investigator practice or local standard of care.
- Adherence to the detailed instructions for IP administration, including infusion rate and SC injections provided by the sponsor must continue to be followed. Maintaining accurate records of study drug dispensing and collection. Site staff will document the IP package numbers that are dispensed CCI .
  - CCI
  - CCI
- CCI
- CCI

Concomitant Therapy

Steroid Tapering: The PI should use clinical judgement of the benefit/risk of tapering for each individual subject and consider Gastrointestinal Society guidance, to determine if corticosteroid dosage adjustment is indicated for their participants during the exceptional circumstances. If the investigator believes steroid tapering is in the best interest of the participant, CCI .

Use of prohibited medications in exceptional circumstances may not result in discontinuation. Please consult your medical monitor.

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:

- Due to exceptional circumstances, a maximum of CCI can be allowed from the time of the endoscopy to the time of the randomization CCI [redacted].
  - The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay in the source documentation.
  - Due to the pause in screening, sites should also reconfirm the impacted participant's consent/legal guardian consent and document this confirmation in the source documentation.
- No extensions of greater than CCI from endoscopy to randomization and/or a total screening window of greater than CCI will be allowed. If either or both timeframes are exceeded: The participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. This screen fail is allowed in addition to the main protocol screen fail. The participant can reconsent and be rescreened as a new participant. The screening procedures per the usual SoA should be followed, starting at the screening visit to ensure participant eligibility by the randomization visit. Prior to rescreening, the PI should feel confident that the exceptional circumstance will no longer prohibit collection of assessments and procedures per protocol. The medical monitor may be consulted if needed regarding the decision to move forward with rescreening.

Adjustments to Visit Windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual SoA. 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.

IP dosing:

There are no plans for an increase in number of IP doses or increase in exposure to IP.

In order for IP to be administered, the following must be done at a minimum and in compliance with the protocol requirements:

- Urine pregnancy test complete with negative result
- Review of AEs
- Review of concomitant medications
- Review of previous labs obtained

- Safety labs must have been obtained and reviewed CCI . Collections may utilize either local or central labs.
- Follow the protocol regarding administration of IP, including temporary holding of IP for safety issues as per protocol

There must be a minimum of CCI between IP doses.

The following describes the allowed adjustments to visit windows. See Table 1 for additional details.

Visits 1 through 10, Visits 12, 14, 16, and 17

- We will allow the visit window to extend to the beginning of the next window. If the participant visit exceeds the extended window, the visit procedures and dosing must occur at the earliest opportunity. CCI .
- Timeframes for future participant visits must be adjusted to bring the participant back into compliance with the protocol defined visit windows.
- Study drug dosing must occur at least CCI apart and a urine pregnancy test (if applicable) must be obtained prior to IP administration.
- See Visits 7 and 17 below for further details.
- The overall length of exposure will not be extended for this trial.

Visits 11, 13, and 15

- Per protocol, dosing visits occur every CCI . We will allow the visit window to extend to the beginning of the next window.
- If the participant visit exceeds the extended visit window, the visit procedures and dosing will be considered missed, and the participant will proceed to the next visit.
- Study drug dosing must occur at least CCI apart, and a urine pregnancy test (if applicable) must be obtained prior to IP administration.
- The overall length of exposure will not be extended for this trial.
- NOTE: Per protocol, participants who miss CCI doses must be considered for early termination.

Visit 7

Endoscopy, study assessments, and nonresponder evaluation

Visit 7 procedures should occur within the extended window if possible.

- CCI
- Sites should remind patients to CCI .

Nonresponder evaluation:

CCI slate information should continue to be collected in order to review response status to assess corticosteroid tapering timing.

- Sites will still need to enter Visit 7 date (Week 12) on the slate. The date of Visit 7 can be entered in the slate prior to the next visit, regardless of when the next visit occurs, if needed.

Visit 17

Visit 17 procedures should occur within the extended window if possible.

- CCI
- CCI

Post-treatment Follow-up Visits 801 and 802

- Visit 801: Visit window may be extended up to CCI
- Visit 802: Visit window may be extended up to CCI If additional time is required, a discussion with the sponsor should take place.

Documentation

Changes to study conduct will be documented:

- Sites will identify and document the details of how participants, visit 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 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.

The table below describes the mitigations to allow for expanded visit windows during exceptional circumstances. See the section *Adjustments to Visit Windows* for further details. There must be a minimum of CCI between study drug doses.

Table 1 Extended Visit Windows for Exceptional Circumstances

Study Visit (Week)[a]	Protocol Specified Day	Protocol Specified Visit Interval Tolerance	Mitigation Extension of Visit Interval Tolerance	Mitigation Study Day Range[b]	Endoscopy Evaluation	Other Assessments
V1	CCI					
V2						
V3						
V4						
V5						
V6						
V7						
V8						

Study Visit (Week)[a]	Protocol Specified Day	Protocol Specified Visit Interval Tolerance	Mitigation Extension of Visit Interval Tolerance	Mitigation Study Day Range[b]	Endoscopy Evaluation	Other Assessments
V9	[redacted]					
V10						
V11						
V12						
V13						
V14						
V15						
V16						
V17						

CCI

Study Visit (Week)[a]	Protocol Specified Day	Protocol Specified Visit Interval Tolerance	Mitigation Extension of Visit Interval Tolerance	Mitigation Study Day Range[b]	Endoscopy Evaluation	Other Assessments
	CCI					
801						
802						

CCI

10.13. Appendix 13: Protocol Amendment History

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

Amendment 15.1: 15-Jan-2021

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

Overall Rationale for the Amendment:

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

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

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

Section # and Name	Description of Change	Brief Rationale
1.2 Schema	Updated Schema.	Dosing information was added.
1.3 Schedule of Activities	Added timepoints for various evaluation criteria to allow for additional optional data collection at Visit 997 or for unscheduled assessments during a scheduled visit (UA/SV). Changed Visit 5 to a phone visit. Updated list of abbreviations.	Updated to reflect all assessments that may be collected at the discretion of the investigator at scheduled or unscheduled visits. Aim to avoid risk of an unnecessary visit to the site during the coronavirus disease 2019 pandemic, and as participants do not receive study drug at Visit 5, on-site assessments are not required. To reflect changes to table.

Section # and Name	Description of Change	Brief Rationale
	Footnote g: Modified text.	Computed tomography (CT) scan can be performed as an alternative to the chest x-ray (CXR).
	Footnote k: Modified text.	Tuberculin skin tests (TST) are to be read by a qualified professional 48 to -72 hours after placement with results noted in source documentation.
	Footnote q: Modified text.	Clarified collection of stool sample prior to endoscopy and visits where endoscopy is not scheduled to be performed.
	Footnote x: Modified text.	Optional testing may be performed during unscheduled visits at the discretion of the investigator.
	Footnote y: Modified text.	Clarification that CT scan can be performed as an alternative to the CXR based on regional standard of practice.
	Footnote z: Modified text.	Unscheduled assessments may be performed at the discretion of the investigator.
	Footnote aa: Added.	For consistency with adult protocol.
2.2.5 Preclinical and Clinical Studies of Mirikizumab	Updated text describing clinical studies in Crohn's disease.	For consistency with adult protocol.
2.3 Benefit/Risk Assessment	Reworded the information on selection criteria with respect to age and weight.	Reworded text to improve clarity.
	Updated additional text.	For consistency with adult protocol.

Section # and Name	Description of Change	Brief Rationale
3. Objectives and endpoints	Additional and updated secondary endpoints: CCI [redacted] Revised objective regarding safety and tolerability of mirikizumab treatment from evaluation of to description of. Revised endpoint regarding tolerability and acceptability of SC injection volumes to indicate that it is descriptive.	For all: CCI [redacted] For both, clarification.
4.1 Overall Design	Modified text to note that placebo nonresponders (NRs) are used as the comparator.	To align with statistical analysis plan (SAP).
4.3 Justification for Dose	Revised information on safety considerations to reflect current information from completed and ongoing clinical studies.	To reflect the safety data collected from AMAG, AMAA, AMAD, AMAF, and AMAC studies.
5.1 Inclusion Criteria	Criterion [8a]: Updated text	Improved clarity relative

Section # and Name	Description of Change	Brief Rationale
	relative to conventional-failure: prior budesonide use, dose change for methotrexate (MTX) – from 25 mg to at least 15 mg, and oral MTX use.	to prior budesonide and MTX use.
5.2 Exclusion Criteria	Criterion [19e]: CCI [redacted]	For consistency with pediatric program.
	Criterion [19j]: Updated text relative to discontinuing interferon therapy from prior to baseline endoscopy to screening endoscopy.	For consistency with adult protocol language.
	Criterion [21]: CCI [redacted]	For consistency with adult protocol language.
	[redacted]	Timeframe extended to CCI [redacted] to rule out participants not responding to ustekinumab.
	Criterion [22]: Removed text allowing oral and intravenous (IV) corticosteroids as premedication in patients with prior investigational product or other previous biologic injection reactions from criterion for discontinuing prohibited medications.	For consistency with adult protocol language.
	Criterion [47]: Updated text regarding delivery of parenteral nutrition.	Parenteral and enteral nutrition as primary source of diet is excluded due to potential to confound efficacy assessments.

Section # and Name	Description of Change	Brief Rationale
	Criterion [48]: CCI [redacted] (Prohibited Medications) accordingly.	CCI [redacted]
5.4 Screen Failures	Removed restriction of only 1 rescreening permitted for entry Criteria [4], [5], and [6].	Criteria [4], [5], and [6]: To permit flexibility for multiple rescreening. Crohn's disease (CD) activity can change over time; thus, participants may qualify upon rescreening.
	Criterion [22]: Specified that rescreening is allowed if a participant is no longer receiving steroids and has met washout criteria.	Criterion [22]: Improve clarity.
	Added Criterion [28] to list of entry criteria with allowance for rescreening and updated text to include that rescreening may be permitted once for *C. difficile* and once for stool culture or ova parasite.	Criterion [28]: Added for consistency and clarity per questions that have come up in live AMAM trial regarding ova parasite.
	Added Criterion [43].	Added for consistency with adult protocol.
	Added Criterion [48] to list of entry criteria with allowance for rescreening provided participant CCI [redacted]	Criterion [48]: CCI [redacted]
	Updated text to specify assessments that will not be repeated at rescreening for patients who screen fail due to inability to complete endoscopy prior to Visit 2.	Participants may avoid CT, human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) retest within

Section # and Name	Description of Change	Brief Rationale
	Modified text disallowing rescreening: Now allow rescreening for Criteria [22] and [43]. Disallow rescreening for Criterion [21].	a CCI timeframe provided there are no risk factors or signs/symptoms. Non-CD treatment can change. Added for consistency with adult protocol.
6.5.1 Permitted Therapy	Renamed from Concomitant Therapy to Permitted Therapy added text to include dose stabilization CCI for corticosteroids.	Correction/clarification.
6.5.2 Prohibited Therapy	Added exceptions to prohibited CD medications, CCI [redacted]	Allow more flexibility to prevent unnecessary discontinuation.
7.1.1 Criteria for Permanent Discontinuation of Study Drug	CCI [redacted]	Correct prior inadvertent errors in original protocol.
7.1.2 Criteria for Temporary Interruption (Withholding) of Study Drug	CCI [redacted]	Improve clarity and readability.
7.2 Participant Discontinuation/ Withdrawal from the Study	Removed text related to participant requiring prohibited medications.	Redundant.
8.1.1.3 Endoscopic Biopsies	Revised text referencing source of details of biopsy sample collection.	Clarification/correction.
8.1.2.3 Patient Reported Outcomes	CCI [redacted]	Correction to be consistent with Section 10.8.

Section # and Name	Description of Change	Brief Rationale
8.2.5 Chest Radiography	Clarified that a CT scan can be performed as an alternative to the CXR based on regional standard of practice.	Clarification.
8.2.6 Stool testing	Modified the conditions for rescreening of participants who have a "positive" stool culture result: Added that repeat central *C. difficile* toxin lab should be negative. Removed CCI [redacted] or since resolution of acute symptoms and signs.	For all, to simplify criteria.
8.2.7 Tuberculosis Testing	Clarified that CT scan can be performed as an alternative to the CXR. Revised text to remove that patients with 2 indeterminate QuantiFERON-TB Gold assays or 2 borderline T-SPOT assays will be excluded, and added that if the TST test and CXR are both negative, the participant may enroll.	For both, clarification and consistency with Section 8.2.5.
8.2.8.1 Pregnancy Testing	Revised text to replace women with female patients, and deleted women of childbearing potential.	Align with the adolescent study population.
8.2.8.2 Immunogenicity Assessment	CCI [redacted]	Gives more freedom; aligns with current/future analysis approach.
8.3.5 Pregnancy Reporting	Pregnancy details will be collected through CCI [redacted]	Clarification/correction.
8.7.1 Whole Blood Sample for Pharmacogenetic Research	CCI [redacted]	Clarification/correction.

Section # and Name	Description of Change	Brief Rationale
	[WWW]) that may be tested.	
8.8 Exploratory Biomarkers	Modified the section title.	Improve accuracy.
9.2 Sample Size Determination	Updated wording on sample size.	Clarification/correction.
9.4.1.2 Estimand	Deleted and reworded text because adolescent patients will not be randomized to placebo and updated composite approach when patients will be considered nonresponders.	Correcting an error in the original document.
9.4.1.3 Missing Data Imputation	Deleted bullets regarding status of mandatory stable medication use and taking of prohibited medications in defining a participant as a nonresponder. Added text relative to handling of concomitant CD medications and noted specifics will be provided in the SAP.	Revision to plan for missing data imputation. Revision to plan for missing data imputation.
9.4.6 Evaluation of Immunogenicity	CCI [redacted]	Clarification of sentence to align with analysis approach.
Section 10.2 Appendix 2: Clinical Laboratory Tests	Updated information on exploratory biomarker storage samples.	Separate exploratory biomarkers from nonexploratory biomarkers.
Section 10.6 Appendix 6: Prohibited Medications	Revised heading for Column 2 of table. CCI [redacted] Added text to include information on IV corticosteroid used for CD that may result in discontinuation. Revised guidance for use of systemic corticosteroids for	For consistency with adult protocol. For consistency with adult protocol. Allow medical discretion to prevent unnecessary discontinuation. Clarification.

Section # and Name	Description of Change	Brief Rationale
	non-CD indications. Added information about any nonbiologic investigational therapy. Revised text regarding anti-IL-23p19 antibodies. CCI [redacted] Updated abbreviations list.	Clarification. For consistency with adult protocol. CCI [redacted] To include new additions.
Section 10.7 Appendix 7: Permitted Medications	Revised table title and revised table column header for Column 2. Revised guidance for use for oral aminosalicylic acids (5-ASAs) and CD-specific antibiotics, oral corticosteroid stabilization, and updated type of permitted vaccines.	To align with development program. For consistency with adult protocol.
Section 10.10 Appendix 10 Contraceptive Guidance and Collection of Pregnancy Information	Revised text.	Clarification.
Section 10.11 Appendix 11: Definitions and Selected Abbreviations	Updated the list.	To include new additions.
Section 10.12 Appendix 12: Provisions for Changes in Study Conduct During Exceptional Circumstances	Added appendix.	Provides for temporary changes to procedures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

Section # and Name	Description of Change	Brief Rationale
Throughout	Minor typographical corrections, clarifications, or semantic changes.	Changes do not affect content.

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