Protocol Amendment I6T-MC-AMAX (e)

A Phase 3, Multicenter, Open-Label, Long-Term Extension Study to Evaluate the Long-Term Efficacy and Safety of Mirikizumab in Patients with Crohn's Disease

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Approval Date: 10-Sep-2024

Title Page

Protocol Title: A Phase 3, Multicenter, Open-Label, Long-Term Extension Study to Evaluate the Long-Term Efficacy and Safety of Mirikizumab in Patients with Crohn's Disease

Protocol Number: I6T-MC-AMAX

Amendment Number: e

Compound: Mirikizumab (LY3074828)

Brief Title: A Phase 3 Extension Study of Mirikizumab in Patients with Crohn's Disease

Study Phase: 3

Acronym: VIVID-2

Sponsor Name: Eli Lilly and Company, Inc.

Legal Registered Address: Lilly Corporate Center, Indianapolis, IN 46285

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Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
I6T-MC-AMAX(d)	*06-Feb-2023*
I6T-MC-AMAX(c)	*12-Jan-2023*
I6T-MC-AMAX(b)	*03-Aug-2022*
I6T-MC-AMAX(a)	*01-Jul-2021*
I6T-MC-AMAX	*13-Dec-2019*

Amendment [e]

This amendment is considered to be substantial.

The amendment is considered to be substantial because it is likely to have a significant impact on the safety or the rights of the study participants.

Overall rationale for the amendment

The main rationale for this amendment is to

- update the discontinuation language related to dysplasia, gastrointestinal lesions, and HBV DNA based on updated guidance, and
- add HBV DNA monitoring time points during Years 2 and 3 for participants with HBcAb-positive for consistency across study

The following table outlines a high-level description of all the changes, with a brief rationale.

Section # and Name	Description of Change	Brief Rationale
Title Page 1.1. Synopsis	Removed EudraCT number	Removed, as no longer applicable under EU CTR
1.1. Synopsis 3. Objectives and Endpoints	Subsection Objectives and Endpoints For AMAM participants CCI [redacted] • removed requirement of CCI [redacted] for the AMAX CCI [redacted] • added "(analyzed separately)" for the CCI [redacted] to be analyzed	To include all participants who CCI [redacted] For clarification
	For AMAM participants CCI [redacted] • corrected CCI [redacted] • added "(analyzed separately)" for the CCI [redacted] to be analyzed	For correction: This CCI [redacted] was intended to be updated when the primary endpoint and the CCI [redacted] were updated from PRO to CDAI in amendment (b) For clarification

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis 4.1. Overall Design	Subsections Overall Design and Intervention Groups and Duration: • added details on continued access period.	To update the study duration to account for continued access
1.2. Schema 10.13.2. Schema	Deleted "(no post-treatment follow-up period)"	This is already communicated in Footnote "a" of the schema
1.3.1. Visit 1 through Visit 9 CCI	Revised the following footnotes • Footnote "m": to update details for follow-up for participants with positive HBV DNA • Footnote "n": added "Additionally" • Footnote "o": to mention that the participants are allowed to take sample collection kits in advance for stool collections and return within 24 hours of producing the sample. • Footnote "x": to mention that vital signs should be performed prior to endoscopy if performed on same day.	To align with the updated HBV DNA language For clarification To clarify the order of procedures if performed on same day
1.3.2. Visit 10 through Visit 19 CCI	"HBV DNA monitoring" row • added "X" for V10, V11, V13, V15, and V17.	For more consistent frequency of HBV DNA testing
	Revised the following footnotes • Footnote "h": to update details for follow-up for participants with positive HBV DNA • Footnote "i": added "Additionally" • Footnote "j": to mention that the participants are allowed to take sample collection kits in advance for stool collections and return within 24 hours of producing the sample. • Footnote "m": to mention that vital signs should be performed prior to endoscopy if performed on same day.	To align with the updated HBV DNA language For clarification To clarify the order of procedures if performed on same day

Section # and Name	Description of Change	Brief Rationale
1.3.3. Early Termination, CCI Unscheduled Visits/Assessments, and Follow-up Visits	Added a row for "Tobacco/Nicotine use" and specified as optional for "V997" and "UASV"	To allow greater flexibility for collection of this information when deemed relevant
	Revised the following footnotes • Footnote "n": to clarify details related to performing HBV DNA testing at ETV and to update details for follow-up for participants with positive HBV DNA	To clarify and to align with the updated HBV DNA language
	• Footnote "o": added "Additionally" • Footnote "r": to mention that the participants are allowed to take sample collection kits in advance for stool collections and return within 24 hours of producing the sample.	For clarification
	• Footnote "u": added a statement for returning of the 14-Day paper diary for ETV, if the participant has pending diary return.	For clarification
	• Footnote "w": to mention that vital signs should be performed prior to endoscopy if performed on same day.	To clarify the order of procedures if performed on same day
2.2.5. Preclinical and Clinical Studies of Mirikizumab	Subsection Clinical Studies in CD: • revised to include objectives and results for Study AMAM	To update the available results for Study AMAM
2.3. Benefit/Risk Assessment	Replaced the citations, "D'Haens et al. 2019; D'Haens et al. 2022; Dubinsky et al. 2022" with "D'Haens et al. 2023"	To update reference from conference abstracts to journal publication
	Deleted the sentence, "In the Phase 2 CD study… …moderately to severely active CD."	To avoid redundancy
	Added "and Phase 3 studies" with citation "Ferrante et al. 2024"	To update available Phase 3 results
	Subsection Overall Benefit/Risk Conclusion • revised to include Phase 3 AMAM details	

Section # and Name	Description of Change	Brief Rationale
3. Objectives and Endpoints	Tertiary/Exploratory • CCI [redacted]	For clarification
6. Study Intervention	Updated the definition of study intervention	To align with EU CTR requirements
6.1. Study Intervention(s) Administered	Table, Dosage Level(s) row: • categorized the dosage level based on the originator study of the participants	For clarification
	Table, authorization row: • updated "Not authorized in EU" to "Authorized in EU and not used according to the marketing authorization"	Per current status of mirikizumab in EU (mirikizumab received EU authorization for treatment of ulcerative colitis in May 2023)
	Subsection Packaging and Labeling: • updated to describe that study intervention will be supplied by the sponsor and labeled as appropriate for country requirements	To align with EU CTR requirements
6.7. Management of Hypersensitivity, Infusion-Related Events, Infusion Site Reactions, and Injection Site Reactions	Subsection Hypersensitivity Events • Last paragraph, added "severe/generalized" and "(e.g., diffuse rash)"	For better clarity
	Subsection Injection Site Reactions or Infusion Site Reactions • deleted the last bullet point on premedication.	Clarified in subsequent section "Premedication for Infusions or Injections".
6.7.1. Premedication for Infusions or Injections	Updated the heading to include "or Injections"	For correction
6.8.1. Treatment after Study Completion	Revised to mention that mirikizumab will be made available to eligible participants after Visit 19 through the optional Continued Access Period	To clarify availability of mirikizumab after Visit 19
7.1.2. Permanent Discontinuation	Revised the safety considerations related to dysplasia, gastrointestinal lesions, and HBV DNA	For clarification and based on current recommendations.
8.1.1.2. Endoscopy	Revised to mention that vital signs should be performed prior to endoscopy if performed on same day	To clarify the order of procedures if performed on same day

Section # and Name	Description of Change	Brief Rationale
8.1.2.1. Clinical Remission by PRO	Deleted statement regarding PROs being used as primary endpoint	For correction: The endpoints and objectives were updated in amendment (b), such that PRO is no longer part of the primary endpoint. However, this sentence was not updated at that time.
8.2.8. Hepatitis B Testing	• Revised the language on HBV DNA testing • Added guidance for management of participants with detectable HBV DNA.	For clarification and based on current recommendations.
8.2.10 Hepatic Safety Monitoring	Subsection Close hepatic monitoring • Last paragraph, added a language to capture results from local hepatic monitoring tests in the corresponding CRFs	For reminder
8.3.1.1. Suspected Unexpected Serious Adverse Reactions	• Replaced "Directive 2001/20/EC" with "Regulation 536/2014 [submission of SUSARs to the EudraVigilance database]" • Revised the statement on processing of safety reports	Per current EU CTR requirements
8.3.4. Regulatory Reporting Requirements for SAEs	Revised the SAE regulatory reporting requirements	Per current EU CTR requirements and feedback
CCI		
9.4.1. General Considerations	A statement has been added to describe the handling of missing, unused, and spurious data	To align with EU CTR requirements
9.4.1.1. Analyses	Replaced "intervention received in Study AMAM" and related text with "as defined in the SAP"	To add reference to SAP for details of treatment groups used in the analysis model.
	Replaced "the change from baseline in endoscopic scores for Study AMAM endoscopic responders" with "continuous endpoints with more than 1 postbaseline timepoint"	To clarify where the described methodology will be applied
	Deleted ", and geographic region (North America, Europe or Other)"	To clarify that the geographic region is not considered as one covariate in the model.
	Deleted "with a single postbaseline time point"	For correction

Section # and Name	Description of Change	Brief Rationale
9.4.1.4. Missing Data Imputation	Nonresponder imputation: • revised the third bullet point to explain the reasons for discontinuation to consider participants as nonresponder for the NRI analysis • deleted last bullet point on concomitant CD medications	For clarification
	Mixed-model for repeated measures: • deleted "primary"	To clarify the primary analytic approach for continuous endpoints is ANCOVA.
	Replaced "No additional imputation methods will be applied to the MMRM analysis" with "Additional details will be provided in the SAP"	For correction to align with planned estimand for this study.
	Added a bullet point for modified baseline observation carried forward with ANCOVA	To clarify the missing data imputation approach used for ANCOVA.
	Added a paragraph "Methodology to address… … will be addressed in the SAP."	To clarify the methodology to address additional types of missing data
9.4.2.1 Participant Disposition	revised "ITT population" with "mITT/PAS population"	For correction
10.1.4. Data Protection	Clarifications have been added about the informed consent process and sponsor processes to ensure information security, data integrity, and data protection	To align with EU CTR requirements
10.1.9. Study and Site Start and Closure	Updated the heading and included the language on Study start and first act of recruitment	To clarify regarding the first act of recruitment for this study
10.2. Appendix 2: Clinical Laboratory Tests	Table, Hypersensitivity Tests row • replaced "may" with "should" • added ", or severe/generalized non-systemic hypersensitivity reactions involving a single organ system (Section 6.7)"	For consistency with Section 6.7, which was clarified in this amendment.
10.3.1.2. Events Meeting the AE Definition	• Deleted the bullet point related to the overdose of study intervention. • Added a bullet point related to medication error, misuse or abuse of IMP.	To align with EU CTR requirements
10.3.5. Reporting of SAEs	Added a reference for Section 8.3.4.	To cross refer the regulatory reporting requirements for SAEs

Section # and Name	Description of Change	Brief Rationale
10.7. Appendix 7: Prohibited Medications	Merged the rows "IV corticosteroids" and "Systemic corticosteroids for non-CD indications (oral, IM, or IV)" and updated the drug class to read "Corticosteroids"	For greater clarity
	Medicinal and recreational marijuana row: • revised the guidance to read "Marijuana use is prohibited ~~for the duration~~ through the end of the long-term extension period of the study. If use is identified ~~during the trial~~ prior to this time, it may…"	For clarification with the continued access
10.9. Appendix 9: Patient-Reported Outcome Instruments	Subsection IBDQ • revised IBDQ score from ">170" to "≥170" • revised the citation from "Irvine et al. 1994" to "Irvine 2008"	To update the IBDQ score with latest reference used.
10.11. Appendix 11: Abbreviations and Definitions	Added abbreviation for "CFR"	Editorial update
10.13.3. Schedule of Activities for Continued Access Period	Subsection, Continued Access Treatment (Visit 501 to last dosing visit) • Added language to describe potential timing scenarios for V19 and V501 activities.	For clarification
	Revised the following footnotes: • Footnote "a": to include "Additional AMAX SoA procedures may be… …contact your monitor for questions." • Footnote "k": to update details for follow-up for participants with positive HBV DNA	To align with updated HBV DNA guidance
	• Footnote "o": to include "Changes cannot be made to dispensing and… …changes to safety lab testing schedule)."	For clarification
10.13.5 Overall Design	• Deleted "all"	For clarification

Section # and Name	Description of Change	Brief Rationale
10.13.6.1. Inclusion Criteria	Criterion 33: • deleted "all" Criterion 34: • revised to state the recommended duration to be no more than 8 weeks between last dose of long-term extension period and dosing in continued access.	For clarification
10.13.7. Study Intervention	Added language to clarify that the caregiver or participant can administer injections at the study site if needed during the Continued Access Period.	

10.13.8. Discontinuation of Study Intervention and Participant Discontinuation from the Continued Access Period	• Revised the sixth bullet point to read, "mirikizumab is locally commercially available and reimbursable (this includes patient access programs when and where available)".
	• Last bullet point,
	  ○ deleted "for CD"
	  ○ added "worldwide for the indication in this protocol".	

10.14.2 Inclusion Criteria	Last paragraph, added CCI [redacted]	To refer to the CCI [redacted]
10.14.3. Study Intervention	Last paragraph, added CCI [redacted] and "(non-site staff)"	For clarification
10.14.3.1. Participant Training and Administration	Subsection Participant training • Paragraph 2, added "and will administer the first injection" and "the second injection of the" Subsection Reporting requirements • added "for remote retraining" Subsection Remote training • added "If retraining needs to be performed and is conducted remotely,"	

Section # and Name	Description of Change	Brief Rationale
	Subsection CCI forms • replaced "all visits" with "each CCI • added "(at the training visit, the CCI Subsection Independent self-administration period • added "/caregivers" CCI table, Footnote "e" • added "If the retraining is performed remotely, a telemedicine visit must be conducted."	
10.15.3. Czech Republic 10.15.4. Hungary	Updated the appendix to align with changes to the main protocol.	Clarifications and to align with the updates to the main protocol
10.16. Appendix 16: Protocol Amendment History	Added amendment (d) summary of changes table	To update amendment history
11. References	Updated the list of references.	Editorial consistency
Throughout the Protocol	Minor formatting and editorial changes	For correction/clarification. Minor, therefore not detailed

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 3, Multicenter, Open-Label, Long-Term Extension Study to Evaluate the Long-Term Efficacy and Safety of Mirikizumab in Patients with Crohn's Disease

Brief Title: A Phase 3 Extension Study of Mirikizumab in Patients with Crohn's Disease

Regulatory Agency Identifier Numbers:

IND: 130052

EU Trial Number: 2022-502841-91-00

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 in Crohn's disease (CD). Study I6T-MC-AMAX (AMAX) is a Phase 3 long-term extension study designed to evaluate the long-term efficacy and safety of mirikizumab in treating participants from the Phase 3 study, I6T-MC-AMAM (AMAM) and the Phase 2 study, I6T-MC-AMAG (AMAG) who meet all of the AMAX inclusion criteria and none of the exclusion criteria.

Objectives and Endpoints

Objectives	Endpoints
Primary	
CCI	
• To assess the effect of mirikizumab on clinical remission by CDAI and endoscopic response CCI	• Proportion of participants achieving clinical remission by CDAI CCI at Week 52 of AMAX • Proportion of participants achieving endoscopic response (defined by CCI in SES-CD Total Score) at Week 52 of AMAX
Secondary	
CCI	
• To assess the long-term effect of mirikizumab on endoscopic, PRO, and CDAI endpoints that are not included in the primary objective in participants CCI	• Proportion of participants with CCI in AMAX at: ○ CCI ○ Week 52 ○ CCI ○ CCI • Proportion of participants with clinical remission by CDAI in AMAX at: CCI • Proportion of participants achieving endoscopic response in AMAX at: ○ CCI • Proportion of participants achieving endoscopic remission (defined as SES-CD Total Score CCI in AMAX at: ○ Week 52 ○ CCI • Proportion of participants with clinical response by PRO (CCI) in AMAX at: ○ Week 52 ○ CCI ○ CCI

Objectives	Endpoints
	• Proportion of participants CCI [redacted] in AMAX at: ○ Week 52 ○ CCI ○ CCI
• To evaluate the effect of mirikizumab in CCI [redacted] in participants from CCI [redacted]	The following scores over time during AMAX: • [redacted] • IBDQ in AMAX at CCI Week 52, CCI [redacted] • CCI [redacted] • CCI [redacted]
CCI [redacted]	
• To assess the effect of mirikizumab CCI [redacted] endoscopic response CCI [redacted]	• Proportion of participants achieving endoscopic response in AMAX at: ○ Week 52 ○ CCI
• To assess the effect of mirikizumab CCI [redacted] endoscopic remission CCI [redacted]	• Proportion of participants achieving endoscopic remission in AMAX at: ○ Week 52 ○ CCI
• To assess the effect of mirikizumab CCI [redacted] of clinical response by PRO CCI [redacted]	• Proportion of participants achieving clinical response by PRO in AMAX at: ○ Week 52 ○ CCI ○ CCI
• To assess the effect of mirikizumab CCI [redacted]	• Proportion of participants achieving CCI [redacted] in AMAX at: ○ Week 52 ○ CCI ○ CCI

Objectives	Endpoints
• To evaluate the effect of mirikizumab CCI	• Proportion of participants achieving CCI in AMAX at: ○ CCI ○ Week 52 ○ CCI ○ CCI
• To evaluate the effect of mirikizumab CCI CDAI remission CCI	• Proportion of participants achieving clinical remission by CDAI in AMAX at: ○ CCI ○ Week 52 ○ CCI ○ CCI
• To assess the effect of mirikizumab CCI endoscopic response CCI	• Proportion of participants achieving endoscopic response in AMAX at: ○ Week 52 ○ CCI
• To assess the effect of mirikizumab CCI endoscopic remission CCI	• Proportion of participants achieving endoscopic remission in AMAX at: ○ Week 52 CCI
• To assess the effect of mirikizumab CCI clinical response by PRO CCI	• Proportion of participants achieving clinical response by PRO in AMAX at: ○ Week 52 ○ CCI ○ CCI
• To assess the effect of mirikizumab CCI	• Proportion of participants achieving CCI in AMAX at: ○ Week 52 ○ CCI ○ CCI
• To evaluate the effect of mirikizumab CCI clinical remission by CDAI or endoscopic remission in participants CCI ○ CCI ○ CCI	• Proportion of participants who achieve clinical remission by CDAI or endoscopic remission (analyzed separately) at AMAX Week 52 CCI • Proportion of participants who achieve clinical remission by CDAI or endoscopic remission (analyzed separately) CCI

Objectives	Endpoints
CCI	
• To assess the effect of mirikizumab in the achievement of endoscopic response CCI	• Proportion of participants achieving endoscopic response in AMAX at: ○ Week 52 ○ CCI
• To assess the effect of mirikizumab in the achievement of endoscopic remission CCI	• Proportion of participants achieving endoscopic remission in AMAX at: ○ Week 52 ○ CCI
• To assess the effect of mirikizumab on clinical response by PRO CCI	• Proportion of participants achieving clinical response by PRO in AMAX at: ○ Week 52 ○ CCI ○ CCI
• To assess the effect of mirikizumab on CCI	• Proportion of participants achieving clinical remission by PRO in AMAX at: ○ Week 52 ○ CCI ○ CCI
• To evaluate the effect of mirikizumab on CCI	• Proportion of participants achieving clinical response by CDAI in AMAX at: ○ CCI ○ Week 52 ○ CCI ○ CCI
• To evaluate the effect of mirikizumab on CDAI remission CCI	• Proportion of participants achieving clinical remission by CDAI in AMAX at: ○ CCI ○ Week 52 ○ CCI ○ CCI
• To assess the effect of mirikizumab on inflammatory biomarkers and CCI	To evaluate the following endpoints in AMAX: • C-reactive protein at Week 12 • Fecal calprotectin at Week 12 • CCI • CCI

Objectives	Endpoints
• To assess the effect of mirikizumab in the achievement of endoscopic response [redacted]	• Proportion of participants achieving endoscopic response in AMAX at: ○ Week 52 ○ [redacted]
• To assess the effect of mirikizumab in the achievement of endoscopic remission [redacted]	• Proportion of participants achieving endoscopic remission in AMAX at: ○ Week 52 ○ [redacted]
• To assess the effect of mirikizumab in the achievement of clinical response by PRO [redacted]	• Proportion of participants achieving clinical response by PRO in AMAX at: ○ Week 52 ○ [redacted] ○ [redacted]
• To assess the effect of mirikizumab in the achievement of [redacted]	• Proportion of participants achieving clinical [redacted] in AMAX at: ○ Week 52 ○ [redacted] ○ [redacted]
• To evaluate the effect of mirikizumab in achieving [redacted] or endoscopic remission [redacted]	• Proportion of participants achieving [redacted] or endoscopic remission (analyzed separately) in AMAX at: ○ Week 52 ○ [redacted]

Abbreviations: AP = abdominal pain; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; [redacted] IBDQ = Inflammatory Bowel Disease Questionnaire; [redacted] PRO = patient-reported outcome; SC = subcutaneous; SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency; [redacted]

Overall Design

Study AMAX is a Phase 3, multicenter, long-term extension study evaluating the efficacy and safety of mirikizumab in participants with moderately-to-severely active CD who have participated in an originator adult mirikizumab CD study, inclusive of the Phase 3 Study AMAM and the Phase 2 Study AMAG.

Participants who are CCI [redacted] will receive open-label mirikizumab subcutaneously (SC) for an extended period of time (up to 3 years) and then enter a 12- to 16-week posttreatment follow-up period. Participants who are CCI [redacted] will receive CCI [redacted] of mirikizumab CCI [redacted] After completion of the long-term extension period, if mirikizumab is not yet locally commercially available and reimbursable, eligible participants will be provided with an option of continued access to open-label mirikizumab, followed by a CCI [redacted] follow-up period. The duration of the continued access will differ by participant and country.

Participants who meet all of the inclusion criteria and none of the exclusion criteria of AMAX, and who, in the opinion of the investigator, would receive benefit from open-label treatment with mirikizumab are eligible for enrollment into Study AMAX. It is possible that some participants enrolling from Study AMAM may have received placebo only in the originating study. These participants will receive mirikizumab for the first time in Study AMAX.

Brief Summary:

This is a long-term extension treatment study with participants who have been previously or are currently diagnosed with moderately-to-severely active CD.

Participants from Study AMAM: All incoming participants irrespective of AMAM treatment assignment (mirikizumab, ustekinumab, or placebo) are CCI [redacted]

- CCI [redacted]
- CCI [redacted]

CCI [redacted]

Study Population:

In general, an individual may take part in Study AMAX if the individual

- has completed the last visit of participation in Study AMAG, remained on mirikizumab treatment in either the maintenance dosing period or in Study AMAG extension period, and in the opinion of the investigator, would derive clinical benefit from continued treatment with mirikizumab, OR
- has completed Week 52 of Study AMAM, including the Week 52 endoscopy CCI [redacted], and in the opinion of the investigator, would derive clinical benefit from treatment with mirikizumab.

Number of Participants:

The final sample size of Study AMAX will be determined by the number of participants who enroll in Study AMAX from the preceding studies (AMAM and AMAG). It is anticipated that approximately 50% to 70% of the participants from Studies AMAM and AMAG will enroll, leading to approximately 640 to 900 participants in Study AMAX.

Intervention Groups and Duration:

Duration of Treatment: The planned maximum duration of treatment for each participant through the end of the long-term extension period is 3 years, until the participant discontinues from the study, or until mirikizumab is commercially available in the country in which the participant resides, whichever occurs first. After completion of the long-term extension period, if mirikizumab is not yet locally commercially available and reimbursable, eligible participants will be provided with an option of continued access to open-label mirikizumab, and then enter a 4-week follow-up period. The duration of the continued access will differ by participant and country.

CCI [redacted]. Participants from Study AMAM will be eligible to enroll in Study AMAX after completing protocol-required procedures and assessments at Week 52, including endoscopy. Participants from Study AMAG will be eligible to enroll into Study AMAX after completing protocol-required Study AMAG procedures.

Treatment Period through end of Long-Term Extension: 3 years maximum per participant.

Dose Regimens:

Participants CCI [redacted]

- Participants CCI [redacted]: At trial entry in Study AMAX, participants will receive CCI [redacted] during the treatment phase beginning with a dose at Week 0 per the Schedule of Activities.
- Participants CCI [redacted]: At trial entry in Study AMAX, participants will receive CCI [redacted]
  - All participants CCI [redacted] during the treatment phase of the AMAX study.
  - If the participant CCI [redacted], then the participant is to discontinue from the study CCI [redacted] and enter the 12- to 16-week posttreatment follow-up period.

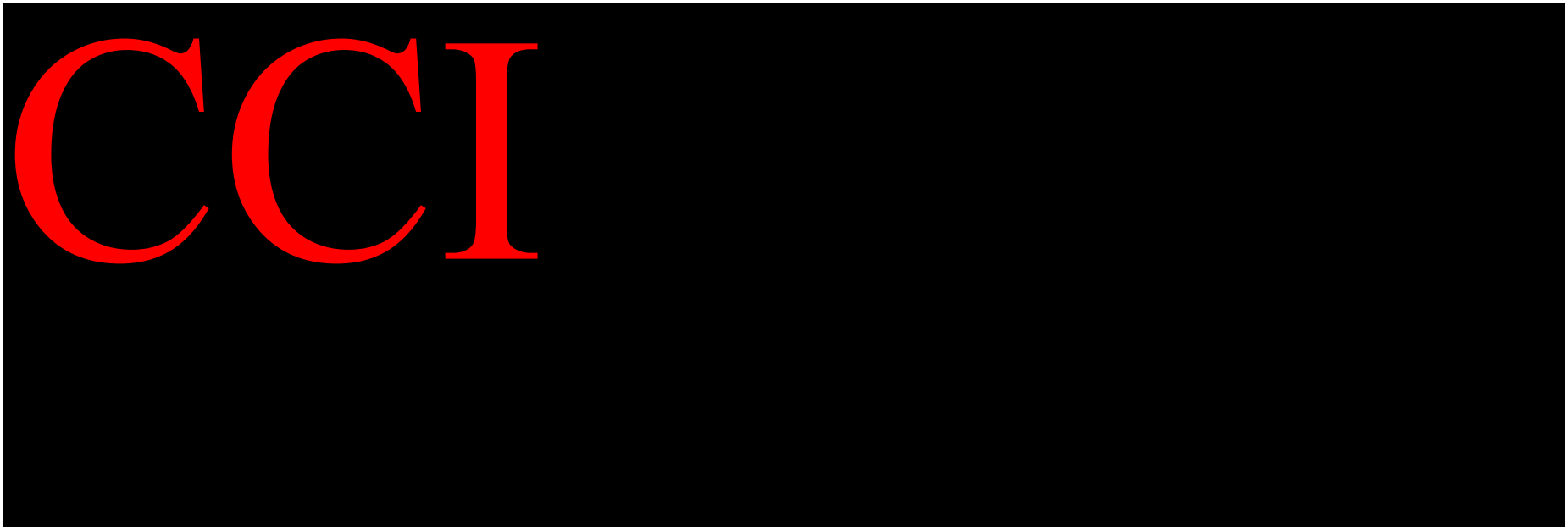
Participants CCI [redacted]: Participants who CCI [redacted] will CCI [redacted] receive CCI [redacted] the treatment phase of Study AMAX.

Ethical Considerations of Benefit/Risk:

The efficacy and safety data from the Phase 2 CD Study AMAG support the continued clinical development of mirikizumab as a treatment for patients with CD, inclusive of the Phase 3 CD Study AMAM and Study AMAX.

Data Monitoring Committee: Yes


CCI


CCI

1.3. Schedule of Activities (SoA)

1.3.1. Visit 1 through Visit 9 CCI

Table AMAX.1-1. Schedule of Activities - Visit 1 through Visit 9 CCI

Procedures	Schedule of Activities[a]											
Visit Number	V1[b]		V2	V3	V4		V5	V6	V7	V8	V9	
Visit Type	Office – Screening/ V1[a]	Office - Dosing/V1[b]	Office	Office	Phone	Office	Office	Office	Office	Office	Phone	Office
Week Relative to Study Drug Start[c]	CCI											
Day with Visit Tolerance Interval (VTI)												
All Participants (X); AMAM Rollover Participants Only (M); AMAG Rollover Participants Only (G); Optional (Opt) (See footnotes for additional key details)												
Informed consent	X											
Preexisting conditions	X	X										
Inclusion/Exclusion Criteria	X											
Concomitant medications	X[ae]	X	X	X		X	X	X	X	X		X
Tobacco/Nicotine use	X[f]					X						X
Demographics	X[f]											
AEs[g] (See Section 8.3)	X[ae]	X	X	X		X	X	X	X	X		X
Phone Reminder[e]					X						X	
Physical Evaluation												
Vital signs (T, PR, BP) (See Section 8.2.1.)	X[ae, ag]	X[ag]	X	X		X	X	X	X	X		X
Weight	X[af]					X						X
Physical examination[h] (See Section 8.2.2.)	X[ae]	X	X	X		X	X	X	X	X		X
CCI	X[f]	X[ah]	X	X		X	X	X	X	X		X
CCI	X[f]	X[ah]	X	X		X	X	X	X	X		X
Clinician CDAI (See Section 8.1.2.1.)	X[af]	X[ah]				X						X
TB Risk Assessment Monitoring[i]	X[af]	X[ah]	X			X	X	X	X	X		X

Procedures	Schedule of Activities[a]											
Visit Number	V1[b]		V2	V3	V4		V5	V6	V7	V8	V9	
Visit Type	Office – Screening/ V1[a]	Office - Dosing/V1[b]	Office	Office	Phone	Office	Office	Office	Office	Office	Phone	Office
Week Relative to Study Drug Start[c]	CCI											
Day with Visit Tolerance Interval (VTI)												
Laboratory Tests												
Chemistry	X[af]	X[ah]	X	X		X	X	X	X	X		X
Hematology	X[af]	X[ah]	X	X		X	X	X	X	X		X
Urine Pregnancy (local)[j] (See Section 8.2.7.1.)	X	X	X	X		X	X	X	X	X		X
Urinalysis	X[k]											
HIV testing	X											
HBV screening[l] (Section 8.2.8.)	X											
HBV DNA monitoring[m]	X[af]	X[ah]	X			X	X	X	X	X		X
HCV testing (See Section 8.2.9.)	X											
PK sample[n]	X[af]	X[ah]				X			X			X
Immunogenicity (ADA) samples[n]	X[af]	X[ah]				X			X			X
CCI	X[f]	X[ah]				X			X			X
Stool Samples (Note: Additional local stool testing [for example, ova and parasites] is allowed at the investigator's discretion.)												
Fecal calprotectin[o]	X[f]	X[ah]				X			X			X
Dispense stool collection kit[o]										M		
Take Home Patient Diary (Electronic)[p]												
Patient electronic diary dispensed[q]	M											
Patient electronic diary returned[r]						M						
Take Home Patient Diary (Paper)[p]												
Patient 14-Day paper diary dispensed[s,t]				G						X		
Patient 14-Day paper diary returned						G						X
On-Site Questionnaires (Paper)												
Patient 1-Day paper diary (24-hour recall)[t]	G		G	G			X	X	X	X		
CCI (See Section 8.1.2.2.)	M[u]	M[ah]				M						

Procedures	Schedule of Activities[a]											
Visit Number	V1[b]		V2	V3	V4		V5	V6	V7	V8	V9	
Visit Type	Office – Screening/ V1[a]	Office - Dosing/V1[b]	Office	Office	Phone	Office	Office	Office	Office	Office	Phone	Office
Week Relative to Study Drug Start[c]	CCI											
Day with Visit Tolerance Interval (VTI)												
CCI (See Section 8.1.2.2.)	M[u]	M[ah]	M	M		M						
CCI (See Section 8.1.2.2.)	M[u]	M[ah]				M						
IBDQ	X[v]	X[ah]				X						X
CCI	X[v]	X[ah]				X						X
CCI	X[v]	X[ah]				X		X				X
CCI (See Section 8.2.11.)	X											
CCI												
CCI												
CCI												

Abbreviations: ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; CCI AP = abdominal pain; CCI ; BP = blood pressure; CDAI = Crohn's Disease Activity Index; CDAI-AP = Crohn's Disease Activity Index – Abdominal Pain; CDAI-SF = Crohn's Disease Activity Index – Stool Frequency; CCI CT = computed tomography; CXR = chest x-ray; CCI CCI ; HBcAb = hepatitis B core antibody; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; CCI IBDQ = Inflammatory Bowel Disease Questionnaire; IGRA = interferon gamma release assay; IP = investigative product; IV = intravenous; NA = Not applicable; NRS = numeric rating scale; CCI ; PI = principle investigator; PK = pharmacokinetic; PR = pulse rate; CCI SC = subcutaneous; CCI SoA = Schedule of Activities; T = temperature; TB = tuberculosis; TST = tuberculin skin test; V = Visit; VTI = visit tolerance interval; CCI .

a Please see detailed instructions provided by the sponsor for calculation of visit dates. Also, note that unscheduled assessments can be performed during scheduled visits, see Table AMAX.1-3 for details.

b V1 is a split visit, occurring on at least 2 office visits on different dates. Screening procedures are to be performed at the first part of V1, called Screening/V1a, in order to have results available to confirm eligibility prior to dosing. For AMAM-originating participants, it is recommended that V1a screening procedures be on the same date as AMAM V17. V1 dosing is performed at the Dosing/V1b visit. For both AMAM and AMAG-originating participants, the timing for AMAX V1a and V1b must allow for first AMAX dosing (V1b) within no more than CCI from the last dosing in the originating study. It is required that all screening assessments, including laboratory test results are reviewed to confirm eligibility from both the final visit of the originating study as well as AMAX V1a, as applicable, prior to dosing at V1b. For participants originating from AMAM, the CCI Note that some assessments may be required at both V1a and V1b. Refer to footnotes for details. To accommodate potential lab delays and/or needs for retesting, please plan for at least 10 business days to obtain lab results after initial samples are received at the laboratory, and up to 5 business days for endoscopy results after receipt of video.

c All activities should be completed prior to any study drug administration unless otherwise stated.

d See footnote b for definitions of the V1 Screening visit (V1a) and the V1 Dosing visit (V1b). V1 dosing (V1b) is defined as Day 1. All V1 screening activities need to be performed prior to dosing, including all assessment retesting (if needed), with results available prior to dosing such that the total interval from last dose in the originating study to first dose in AMAX is no more than CCI . Please see detailed instructions provided by the sponsor for calculation of subsequent visit dates.

e Site to remind participant to complete 14-Day diary and/or bowel prep, as appropriate. Phone reminder must occur at least 15 days prior to actual next visit date to ensure the participant begins the collection of diary data in time.

f Data should be collected at V1 from the AMAG originating participants. Demographic data from the originator study can be used for AMAM participants. For all other items with AMAM participants: if data were collected at the final visit in AMAM, those data can be used in AMAX; otherwise, data should be collected at V1a.

g For AESIs, additional data are collected (Section 8.3.7).

h Includes a symptom-directed evaluation as well as examination of eyes, heart, lungs, abdomen, and visual examination of the skin (Section 8.2.2).

i At V1 and throughout the study, participants will be assessed for risk factors for TB (Section 10.5, Appendix 5). If the participant has a risk factor(s) or any TB-related signs or symptoms identified as part of the discussions of preexisting conditions or AEs, or as part of the standard physical exam, 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 or other factors that the investigator feels requires testing and imaging, an IGRA or TST and a CXR should be performed (Table AMAX.1-3 Unscheduled assessments). A CT scan can be performed as an alternative to the CXR, based on regional standard of practice (Section 8.2.6).

j To be performed only on women of child-bearing potential. Done locally and at screening, as well as prior to each dosing (Section 8.2.7.1).

k Data should be collected from the AMAM originating participants. If data were collected at the final visit in AMAG for AMAG-originating participants, they can be used, and there is no need to recollect at V1 in AMAX.

l Participants testing HBcAb+ in the originator study do not need to have HBV full screening at V1 but they will need to have HBV DNA testing at screening and continue HBV DNA monitoring throughout the trial. All other participants should have the full HBV screening at V1a.

m Perform only if participant had ongoing monitoring for HBV DNA during their originator study, or for participants who were found to be HBcAb+ in AMAX and met the requirements to continue in the study as described in Section 8.2.8. Such participants will undergo monitoring of HBV DNA at specified intervals. Any participants not meeting the requirements to continue in the study at any time must be discontinued from the study and receive appropriate follow-up medical care (Section 8.2.8).

n Samples will be collected predose on the days specified in the SoA. Additionally, in the event of a systemic allergic/hypersensitivity event, blood samples will be collected for PK, ADA,[redacted] at the following time points: as close as possible to: (1) the onset of the systemic allergic/hypersensitivity event, (2) the resolution of the systemic allergic/hypersensitivity event, [redacted]

o Participants must adhere to proper stool incubation requirements and return stool to site within 24 hours of producing sample. AMAG and AMAM participants dispensed pre-endoscopy stool collection kit per SoA. AMAG participants should also receive stool collection kit at the visit prior to the endoscopy performed at [redacted]. Instruct participants to collect stool samples up to 3 days prior to beginning bowel prep for endoscopy. For stool collection for testing associated with other visits, the sample collection kits may be sent home in earlier visits. This allows the participants to collect samples within 24 hours prior to their visit and bring to the site on the day of visit. If samples are not collected before or on the day of the visit, the collection kit should be sent home with the participant on the day of the visit, and sample should be collected as soon as possible and returned to the site within 24 hours of producing the sample. For AMAG-originating participants at V1, the collection may be performed at the first day of screening and must be collected prior to dosing.

p Visits will differ for participant collections via paper diary or electronic diary capture. See Section 8.1.2.2 for instructions.

q Dispensed at V1a to AMAM participants only. Includes [redacted] CDAI-SF with Bristol Stool Scale, CDAI-AP, CDAI well-being, [redacted] (See Section 8.1.2.2).

r Collected only from AMAM participants.

s The CCI endoscopy should be performed for AMAG-originating participants CCI (See Table AMAX.1-3) and is notated here under V1 only as a reminder, since it could occur over a wide window of time within the AMAX schedule. At the visit prior to the CCI endoscopy, the site should provide the participant with one 14-Day paper diary to be returned at the next regularly scheduled office visit. The 14-Day diary should be completed in the 14 days leading up to the next regularly scheduled office visit and may begin before or after the endoscopy, depending on endoscopy timing (See Table AMAX.1-3)

t The 14-Day paper diaries and 1-Day paper diaries both include: CCI CDAI-SF with Bristol Stool Scale, CDAI-AP, CDAI well-being, CCI (See Section 8.1.2.2.).

u Collections required only for participants from AMAM. Collect at AMAX V1a if data were not collected at the final visit in the originator study.

v Collect at AMAX V1a if data were not collected at the final visit in the originator study.

w At V1a of AMAX, participants from AMAM should be administered the CCI. Participants from AMAG should be administered the CCI

x

y

z Visit procedures and assessments must be completed prior to dosing. For both AMAM and AMAG-originating participants, dosing at V1b should occur no later than CCI after the participant's last dose in the originator study.

aa Dispense study drug at each office visit for the next CCI dose(s) as needed, noting that the visit schedule changes from every CCI Also, see Table AMAX.1-4 and Section 6.1 regarding timing for administrations between scheduled office visits and participants who choose not to self-administer. At Visit 4, provide ancillary supplies. Continue to dispense ancillary supplies at each visit as needed. Note that any used or unused study drug may be returned as an optional unscheduled activity at subsequent visits (Table AMAX.1-3).

ab Site to complete training with the participant using the *Patient Study Drug Administration Training Log* at Visit 4. If training does not occur at Visit 4, the participant should be trained at the earliest opportunity based on the PI's discretion. Additionally, participants may be retrained on how to self-administer the investigational product, if needed.

ac Site to complete and dispense *Patient Study Drug Administration Log*. Provide syringes for next dosing, inform participant of dosing date for self-injection, and provide ancillary supplies to participant.

ad Participant to return the *Patient Study Drug Administration Log* at the next visit.

ae Assessments are scheduled to be performed at the last visit of the originating study and will only need to be performed separately for AMAX V1a if these visits do not occur on the same date.

af Collect/assess at AMAX V1a if not performed at the last visit of the originator study.

ag Vitals should be assessed at both V1a and V1b. However, only vitals data from V1b should be entered into Inform for V1.

ah If more than CCI will have elapsed between last collection/assessment and the first AMAX dosing, additional procedures must be performed again prior to the V1b dosing. See sponsor guidance regarding sample collection kits or data entry for items that need to be collected again at V1b. Investigator medical judgment should be used regarding whether the repeat lab results should be available and reviewed prior to dosing (review prior to dosing not needed for PK, immunogenicity, CCI or fecal calprotectin).

1.3.2. Visit 10 through Visit 19 CCI [redacted]

Table AMAX.1-2. Schedule of Activities - Visit 10 through Visit 19 CCI [redacted]

Procedures	Schedule of Activities[a]													
Visit Number	V10	V11	V12		V13	V14		V15	V16		V17	V18	V19[r]	
Visit Type	Office	Office	Phone	Office	Office	Phone	Office	Office	Phone	Office	Office	Office	Phone	Office
Week Relative to Study Drug Start[b]	CCI [redacted]													
Day with Visit Tolerance Interval (VTI)														
All Participants (X); AMAM Rollover Participants Only (M); AMAG Rollover Participants Only (G); Optional (Opt) (See footnotes for additional key details)														
Concomitant medications	X	X		X	X		X	X		X	X	X		X
Tobacco/Nicotine use							X							X
AEs[d] (See Section 8.3)	X	X		X	X		X	X		X	X	X		X
Phone Reminder[e]			X			X			X				X	
Physical Evaluation														
Vital signs (T, PR, BP) (See Section 8.2.1.)	X	X		X	X		X	X		X	X	X		X
Weight				X			X			X				X
Physical examination[e] (See Section 8.2.2.)	X	X		X	X		X	X		X	X	X		X
CCI [redacted] .)	X	X		X	X		X	X		X	X	X		X
CCI [redacted]	X	X		X	X		X	X		X	X	X		X
Clinician CDAI (See Section 8.1.2.1.)				X			X			X				X
TB Risk Assessment Monitoring[f]	X	X		X	X		X	X		X	X	X		X

Procedures	**Schedule of Activities[a]**													
Visit Number	**V10**	**V11**	**V12**		**V13**	**V14**		**V15**	**V16**		**V17**	**V18**	**V19[r]**	
Visit Type	**Office**	**Office**	**Phone**	**Office**	**Office**	**Phone**	**Office**	**Office**	**Phone**	**Office**	**Office**	**Office**	**Phone**	**Office**
Week Relative to Study Drug Start[b]	CCI													
Day with Visit Tolerance Interval (VTI)														
Laboratory Tests														
Chemistry	X	X		X	X		X	X		X	X	X		X
Hematology	X	X		X	X		X	X		X	X	X		X
Urine pregnancy (local)[g] (See Section 8.2.7.1.)	X	X		X	X		X	X		X	X	X		X
HBV DNA monitoring[h]	X	X		X	X		X	X		X	X	X		X
PK sample[i]				X			X			X				X
Immunogenicity (ADA) samples[i]				X			X			X				X
CCI				X			X			X		X		X
Stool Samples (Note: Additional local stool testing [for example, ova and parasites] is allowed at the investigator's discretion.)														
CCI				X			X			X		X		X
Dispense stool collection kit[j]												X		
Take Home Patient Diary (Paper)														
Patient 14-Day paper diary dispensed[k,l]		X			X			X				X		
Patient 14-Day paper diary returned				X			X			X				X
On-Site Questionnaires (Paper)														
Patient 1-Day paper diary (24-hour recall)[l]	X	X			X			X			X	X		X
CCI							X							X
							X							X
				X			X			X		X		X

Procedures	Schedule of Activities[a]													
Visit Number	V10	V11	V12		V13	V14		V15	V16		V17	V18	V19[r]	
Visit Type	Office	Office	Phone	Office	Office	Phone	Office	Office	Phone	Office	Office	Office	Phone	Office
Week Relative to Study Drug Start[b]	CCI													
Day with Visit Tolerance Interval (VTI)														
CCI														

Abbreviations: ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; ACCI ; BP = blood pressure; CDAI = Crohn's Disease Activity Index; CDAI-AP = Crohn's Disease Activity Index – Abdominal Pain; CDAI-SF = Crohn's Disease Activity Index – Stool Frequency; CT = computed tomography; CXR = chest x-ray; CCI ETV = early termination visit; CCI ; HBcAb = hepatitis B core antibody; HBV = hepatitis B virus; CCI ; IBDQ = Inflammatory Bowel Disease Questionnaire; IGRA = interferon gamma release assay; IP = investigational product; CCI ; PK = pharmacokinetic; PR = pulse rate; CCI SoA = Schedule of Activities; T = temperature; TB = tuberculosis; TST = tuberculin skin test; V = visit.

a Please see detailed instructions provided by the sponsor for calculation of visit dates. Also, note that unscheduled assessments can be performed during scheduled visits, see Table AMAX.1-3 for details. Please refer to Section 10.13.3 for continued access period details.

b All activities should be completed prior to any study drug administration unless otherwise stated.

c Site to remind participant to complete 14-Day diary and/or bowel prep, as appropriate. Phone reminder must occur at least 15 days prior to actual next visit date to ensure the participant begins the collection of diary data in time.

d For AESIs, additional data are collected (See Section 8.3.7).

e Includes a symptom-directed evaluation as well as examination of eyes, heart, lungs, abdomen, and visual examination of the skin (Section 8.2.2).

f Throughout the study, participants will be assessed for risk factors for TB (Section 10.5, Appendix 5). If the participant has a risk factor(s) or any TB-related signs or symptoms identified as part of the discussions of AEs or as part of the standard physical exam, 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 or other factors that the investigator feels warrant testing and imaging, an IGRA or TST and CXR should be performed (Table AMAX.1-3 Unscheduled assessments). A CT scan can be performed as an alternative to the CXR based on regional standard of practice (Section 8.2.6).

g To be performed only on women of child-bearing potential. Done locally and prior to dosing (Section 8.2.7.1). Between visits, urine pregnancy tests are to be performed prior to monthly at-home dosing.

h Perform only if participant had ongoing monitoring for HBV DNA during their originator study, or for participants who were found to be HBcAb+ in AMAX and met the requirements to continue in the study as described in Section 8.2.8. Such participants will undergo monitoring of HBV DNA at specified intervals. Any participant not meeting the requirements to continue in the study at any time must be discontinued from the study and receive appropriate follow-up medical care (Section 8.2.8).

i Samples will be collected predose on the days specified in the SoA. Additionally, in the event of a systemic allergic/hypersensitivity event, blood samples will be collected for PK, ADA, CCI [redacted] at the following time points: as close as possible to: (1) the onset of the systemic allergic/hypersensitivity event, (2) the resolution of the systemic allergic/hypersensitivity event, CCI [redacted]

j Participants must adhere to proper stool incubation requirements and return stool to site within 24 hours of producing sample. AMAG-originating participants should receive stool collection kits in AMAX at the visit CCI [redacted], AMAG- and AMAM-originating participants are dispensed a stool collection kit per SoA. Instruct participants to collect stool samples up to 3 days prior to beginning bowel prep for endoscopy. For stool collection for testing associated with other visits, the sample collection kits may be sent home in earlier visits. This allows the participants to collect samples within 24 hours prior to their visit and bring to the site on the day of visit. If samples are not collected before or on the day of the visit, the collection kit should be sent home with the participant on the day of this visit, and sample should be collected as soon as possible and returned to the site within 24 hours of producing the sample.

k At the visit CCI [redacted], the site should provide the participant with one 14-Day paper diary to be collected at the next regularly scheduled office visit. The 14-Day diary should be completed in the 14 days leading up to the next regularly scheduled office visit and may begin before or after the endoscopy, depending on endoscopy timing (see Table AMAX.1-3).

l The 14-Day paper diaries and 1-Day paper diaries both include: CCI [redacted] CDAI-SF with Bristol Stool Scale, CDAI-AP, CDAI well-being, CCI [redacted] (See Section 8.1.2.2.)

m [redacted]

n Visit procedures and assessments must be completed prior to dosing.

o Dispense study drug at each office visit for the next [redacted] as needed, noting that the visit schedule changes from every [redacted] Also, see Table AMAX.1-4 and Section 6.1 regarding timing for administrations between scheduled office visits and participants who choose not to self-administer. Continue to dispense ancillary supplies at each visit as needed. Note that any used or unused study drug may be returned as an optional unscheduled activity at subsequent visits (see Table AMAX.1-3).

p Site to complete and dispense *Patient Study Drug Administration Log*. Provide syringes for next dosing, inform participant of dosing date for self-injection, and provide ancillary supplies to participant.

q Participant to return the *Patient Study Drug Administration Log* at the next visit.

r Participants who are eligible for continued access should move directly from Visit 19 to Visit 501, on the same day, if possible. Visit 801 and Visit 802 should not be performed for these participants.

1.3.3. Early Termination, CCI Unscheduled Visits/Assessments, and Follow-up Visits

Table AMAX.1-3. Schedule of Activities - Early Termination, CCI, Unscheduled Visits/Assessments, and Follow-up Visits

Procedures		Schedule of Activities[a]						
Visit Number	ETV	CCI			V997[c]	UASV[d]	V801[y]	V802[y]
Visit Type	Office	CCI						
Visit Tolerance Interval	N/A							
All Participants (X); AMAM Rollover Participants Only (M); AMAG Rollover Participants Only (G); Optional (Opt) (See footnotes for additional key details)								
Concomitant Medications	X				X		X	X
Tobacco/Nicotine use					Opt	Opt		
AEs[e] (Section 8.3.7.)	X				X		X	X
Phone Reminder[f]		G						
Physical Evaluation								
Vital signs (T, PR, BP) (See Section 8.2.1.)	X				Opt		X	X
Weight	X			G	Opt	Opt		
Physical examination[g] (See Section 8.2.2.)	X				Opt		X	X
CCI	X				Opt		X	X
CCI	X				Opt		X	X
Clinician CDAI (See Section 8.1.2.1)	X			G				
12-lead ECG (local) (See Section 8.2.3.)					Opt	Opt		
TB Risk Assessment Monitoring[h]					Opt	Opt		
CXR (local)[i]					Opt	Opt		

Procedures		**Schedule of Activities[a]**						
Visit Number	**ETV**		CCI		**V997[c]**	**UASV[d]**	**V801[y]**	**V802[y]**
Visit Type	**Office**	**Phone**	**Endoscopy**	**Office**	**Office**	**Office**	**Office**	**Office**
Visit Tolerance Interval	CCI							
Laboratory Tests								
Chemistry	X				Opt	Opt	X	X
Hematology	X				Opt	Opt	X	X
Hematocrit Only				G[j]	Opt	Opt		
Lipid panel (fasting)					Opt	Opt		
FSH					Opt	Opt		
Urine pregnancy (local)[k] (See Section 8.2.7.1.)	X				Opt	Opt	X	X
Urinalysis					Opt	Opt		
TB testing[l] (Section 8.2.6.)					Opt	Opt		
HIV testing					Opt	Opt		
HBV screening[m] (See Section 8.2.8.)					Opt	Opt		
HBV DNA monitoring[n]	X				Opt	Opt		X
HCV testing (See Section 8.2.9.)					Opt	Opt		
PK sample[o]	X				Opt	Opt		X
Immunogenicity (ADA) sample[o]	X				Opt	Opt		X
CCI	X			G[j]	Opt	Opt		
Hypersensitivity kit (tryptase, PK, and immunogenicity)					See footnote[p]	See footnote[p]		
Hepatic kit					See footnote[q]	See footnote[q]		

Procedures		**Schedule of Activities[a]**						
Visit Number	**ETV**		CCI		**V997[c]**	**UASV[d]**	**V801[y]**	**V802[y]**
Visit Type	**Office**	**Phone**	**Endoscopy**	**Office**	**Office**	**Office**	**Office**	**Office**
Visit Tolerance Interval	CCI							
Stool Samples (Note: Additional local stool testing [for example, ova and parasites] is allowed at the investigator's discretion.)								
Stool culture					Opt	Opt		
CCI								
	X		G		Opt	Opt		
Dispense stool collection kit[r]			G		Opt	Opt		
Take Home Patient Diary (Electronic)[s]								
Patient electronic diary returned[t]	M							
Take Home Patient Diary (Paper)[s]								
Patient 14-Day paper diary dispensed[u,v]								
Patient 14-Day paper diary returned[u]	X			G				
On-Site Questionnaires (Paper)								
Patient 1-Day paper diary (24-hour recall)[v]	X			G	Opt	Opt		
CCI	X							
	X							
	X				Opt	Opt		
	CCI							

Procedures		Schedule of Activities[a]						
Visit Number	ETV	CCI			V997[c]	UASV[d]	V801[y]	V802[y]
Visit Type	Office	Phone	Endoscopy	Office	Office	Office	Office	Office
Visit Tolerance Interval	CCI							

Abbreviations: ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; CCI BP = blood pressure; CDAI = Crohn's Disease Activity Index; CDAI-AP = Crohn's Disease Activity Index – Abdominal Pain; CDAI-SF = Crohn's Disease Activity Index – Stool Frequency; CRF = case report form; CT = computed tomography; CXR = chest x-ray; ECG = electrocardiogram; CCI ; ETV = early termination visit; CCI FSH = follicle-stimulating hormone; HBcAb = hepatitis B core antibody; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; CCI ; IBDQ = Inflammatory Bowel Disease Questionnaire; IGRA = interferon gamma release assay; IP = investigative product; LV = last visit; N/A = not applicable; CCI ; PK = pharmacokinetic; PR = pulse rate; CCI SoA = Schedule of Activities; T = temperature; TB = tuberculosis; TST = tuberculin skin test; UASV = Unscheduled Assessments during a Scheduled Visit; V = Visit.

a Please see detailed instructions provided by the sponsor for calculation of visit dates. Please refer to Section 10.13.3 for continued access period details.

b The CCI should be associated in the electronic data capture system with the next regularly scheduled office visit. The 14-Day diary should be completed in the *14 days leading up to that next office visit* and may begin before or after CCI

c Unscheduled visits (997) may be performed at the discretion of the investigator between protocol visits. During all unscheduled 997 visits, concomitant medications and AEs must be completed. Other assessments are considered optional (defined as Opt) and if performed, require documentation via the appropriate standard (CRF, laboratory requisition or source documentation).

d 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).

e For AESIs, additional data are collected (Section 8.3.7).

f Site to remind participant to complete 14-Day diary, stool collection, CCI [redacted]. Phone reminder must occur CCI [redacted] at least 15 days prior to *actual next office visit date* to ensure the participant begins each item in time.

g Includes a symptom-directed evaluation as well as examination of eyes, heart, lungs, abdomen, and visual examination of the skin (Section 8.2.2).

h At the discretion of the investigator, participants may be assessed for risk factors for TB (Section 10.5, Appendix 5) as an additional optional assessment. If the participant has a risk factor(s) or any TB-related signs or symptoms identified as part of the discussions of AEs or as part of the standard physical exam, 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 TB-related physical findings or other factors that the investigator feels warrant testing and imaging, an IGRA or TST and CXR should be performed. See Footnotes i and l for additional details. A CT scan can be performed as an alternative to the CXR based on regional standard of practice.

i If there are relevant TB-related physical findings or other factors that the investigator feels warrant testing and imaging, a CXR should be performed. A CT scan can be performed as an alternative to the CXR. An IGRA or TST should also be performed (see footnote l).

j Sample to be collected for CCI [redacted] office visit occurs at a regularly scheduled visit that does not already collect that sample.

k To be performed only on women of child-bearing potential. Done locally and prior to dosing.

l TB testing is required for participants who have relevant physical findings or other factors that the investigator feels warrant testing and imaging. Participants who had a TST must return 48 to 72 hours after placement to have their test results read (Section 8.2.6). A CXR should also be performed (see Footnote i).

m Participants previously testing HBcAb+ do not need to be retested for HBV serology (Section 8.2.8).

n Perform at ETV only if participant had ongoing monitoring for HBV DNA previously or was found to be HBcAb+ by the time of the ETV. Any enrolled participant who is HBcAb+ and meets the requirements to continue in the study as described in Section 8.2.8 will undergo monitoring of HBV DNA at specified intervals. Any participant not meeting the requirements to continue in the study at any time must be discontinued from the study and receive appropriate follow-up medical care (Section 8.2.8).

o Samples will be collected predose per the SoA. Additionally, in the event of a systemic allergic/hypersensitivity event (Section 6.7), blood samples will be collected for PK, ADA, CCI [redacted] at the following time points: as close as possible to: (1) the onset of the systemic allergic/hypersensitivity event, (2) the resolution of the systemic allergic/hypersensitivity event, CCI [redacted]

p In the event of a systemic allergic/hypersensitivity event, blood samples will be collected for PK, ADA, CCI at the following time points: as close as possible to: (1) the onset of the systemic allergic/hypersensitivity event, (2) the resolution of the systemic allergic/hypersensitivity event, CCI

q CCI

r Participants must adhere to proper stool incubation requirements and return stool to site within 24 hours of producing sample. AMAG-originating participants should receive stool collection kits in AMAX at the visit CCI Instruct participants to collect stool samples CCI . Fecal calprotectin is only tested at the CCI office visit does not coincide with a regularly scheduled visit that already collects this lab. For stool collection at the ETV and at optional timepoints, the sample collection kits may be sent home in earlier visits. This allows the participants to collect the samples within 24 hours prior to their visit and bring to the site on the day of visit. If samples are not collected before or on the day of the visit, the collection kit should be sent home with the participant on the day of the visit, and sample should be collected as soon as possible and returned to the site within 24 hours of producing the sample.

s Visits will differ for participant collections via paper or electronic diary capture (Section 8.1.2.2).

t Collected from AMAM participants only.

u Return of the 14-Day paper diary only applies for the ETV if participant has a pending diary return. At the visit prior to CCI , the site should provide the participant with one 14-Day paper diary to be collected at the next regularly scheduled office visit (also see Footnote b).

v The 14-Day paper diaries and 1-Day paper diaries both include: CCI CDAI-SF with Bristol Stool Scale, CDAI-AP, CDAI well-being, CCI (See Section 8.1.2.2.).

w CCI , as indicated in the table. For each visit with an endoscopy, it is recommended that the endoscopy be performed on a separate day from the vital signs and study questionnaires, and IP administration, within the visit window, with the endoscopy preceding the other activities. However, if they must be performed on the same day due to logistical issues, the following period order of procedures must be followed: (1) Measurement of vital signs and collection of responses to questionnaires; (2) Administration of IP with protocol-specific observation (at least 1 hour); (3) Performance of endoscopy with or without sedation. An ETV endoscopy should only be performed if the ETV occurs at least 16 weeks after the last endoscopy. An ETV endoscopy will not be performed during the follow-up period.

x Participant to return the *Patient Study Drug Administration Log* at the next visit.

y Participants who are eligible for continued access should move directly from Visit 19 to Visit 501, on the same day, if possible. Visit 801 and Visit 802 should not be performed for these participants.

1.3.4. Study Drug Self-Administration

Table AMAX.1-4. Table for Study Drug Self-Administration not Associated with an Office Visit

Procedures	
Name of Visit Interval CCI [redacted]	CCI [redacted]
Week Relative to Study Drug Start	
Days Relative to Study Drug Start and Visit Interval Tolerance (Days)	
Study Drug Self-Administration[b]	

a CCI [redacted]

b Complete *Patient Study Drug Administration Log* at time of administration. Also, see Section 6.1 regarding participants who choose not to self-administer. In this case, the *Patient Study Drug Administration Log* must still be completed, and dose administrations would be performed on these specified weeks in the office by site staff.

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-AMAX (AMAX) is an open-label, long-term extension for adult participants in studies I6T-MC-AMAM (AMAM) and I6T-MC-AMAG (AMAG). Study AMAX is a Phase 3 clinical trial designed to evaluate the long-term safety and efficacy of mirikizumab in participants with moderately-to-severely active Crohn's disease (CD) who have previously participated in Studies AMAM and AMAG.

2.2. Background

2.2.1. Disease State and Treatment Goals

Crohn's disease 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, is a normal characteristic for CD (Baumgart and Sandborn 2007). Symptoms include chronic diarrhea (often bloody and containing pus or mucus), abdominal pain (AP), weight loss, fever, fatigue, anemia, rectal bleeding, and a feeling of fullness in the abdomen. Symptoms depend on the severity of the disease and location of the disease, with most patients experiencing an abscess, fistula, stricture, or an obstruction requiring surgical intervention. Relapsing–remitting symptoms, meaning that many patients have intermittent disease flares that are interspersed with periods of remission, are very common in CD (Lichtenstein et al. 2018).

Treatment goals in clinical practice are control of symptoms and healing of the intestinal mucosa. In clinical trials, these goals are reflected by assessing induction of response (typically within a 6-week to 12-week period) and maintenance of remission in the longer term (over 52 weeks and beyond 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 includes endoscopy to assess improvement in the endoscopic appearance of the mucosa and healing of ulcers.

2.2.2. Currently Available Treatments and Unmet Need

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

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

2.2.3. IL-23 as a Therapeutic Target in CD

The contribution of IL-12 and IL-23 in driving the pathophysiology of CD has 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 blocking IL-23 alone may be a more effective strategy than blocking both IL-12 and IL-23.

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

The relative contribution of IL-12 and IL-23 to disease pathology in IBD has been explored in several studies. The results of these studies would indicate that IL-23, but not IL-12, promotes intestinal inflammation (Hue et al. 2006; Kullberg et al. 2006; Uhlig et al. 2006; Yen et al. 2006). Data from murine models of psoriasis demonstrating a protective role in dermatologic inflammation (Kulig et al. 2016), as well as clinical trials (Blauvelt et al. 2017; Reich et al. 2019), 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, inclusive of long-term efficacy and safety.

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

The efficacy of IL-23p19 blockade in CD has been demonstrated in Phase 2 studies evaluating the short-term efficacy and safety of different IL-23p19 monoclonal antibodies, including brazikumab induction (Sands et al. 2017), guselkumab induction and maintenance (Danese et al. 2022; Sandborn et al. 2022), and recent Phase 3 studies of risankizumab induction and maintenance (D'Haens et al. 2022; Ferrante et al. 2022). The data from these studies showed significant efficacy of anti-IL-23 p19 biologics in patients with moderately to severe Crohn's disease with favorable safety profiles.

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-23 receptor, 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.

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

Clinical Studies in UC

Study I6T-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 remained in clinical remission at Week 52. There were few serious adverse events (SAEs) and few discontinuations due to AEs over 52 weeks (D'Haens et al. 2019).

The Phase 3 LUCENT program comprises of Study I6T-MC-AMAN (AMAN), a 12-week double-blind, placebo-controlled, Phase 3 induction study of mirikizumab in participants with moderate to severe UC who had failed conventional and/or biologic treatments (D'Haens et al. 2022) and Study I6T-MC-AMBG, a double-blind, randomized withdrawal maintenance study in patients who responded to mirikizumab induction therapy in AMAN (Dubinsky et al. 2022). In Study AMAN, mirikizumab met the primary endpoint of clinical remission at Week 12 compared to placebo ($p<.0001$). At Week 12, mirikizumab when compared to placebo also achieved highly statistically significant p-values, including reduced bowel urgency, clinical response, endoscopic remission, symptomatic remission, and improvement in endoscopic histologic inflammation.

The incidence of TEAEs and SAEs among participants treated with mirikizumab was consistent with that of the previous Phase 2 mirikizumab study in UC and studies with the anti-IL-23p19 antibody class. The most common AEs ≥3% in any treatment group included nasopharyngitis, anemia, and headache for both placebo and mirikizumab-treated participants (D'Haens et al. 2022).

The Phase 3 LUCENT program also includes I6T-MC-AMAP (mirikizumab open-label extension) in patients with moderately-to-severely active UC; this study is ongoing at the time of this writing.

Clinical Studies in CD

Study I6T-MC-AMAG (AMAG) was a Phase 2, placebo-controlled, double-blind clinical trial of mirikizumab in participants with active CD. Unblinded results are available from the completed 12-week induction period and 52-week maintenance data. The primary efficacy objective is to test the hypothesis that treatment with mirikizumab is superior to placebo in the proportion of patients with endoscopic response at Week 12, defined as a 50% reduction from baseline in Simple Endoscopic Score for Crohn's Disease (SES-CD) Total 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% 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; placebo: 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 combined IV group and the SC group, 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 AEs in the mirikizumab groups were similar to placebo. 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 TEAEs were similar across all groups. Frequencies of SAEs and discontinuations due to AEs were higher in the nonrandomized maintenance cohort, consisting of Week 12 endoscopic nonimprovers, and participants who received placebo in the first 12 Weeks followed by mirikizumab for the remainder of the trial. 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. 2022).

Study AMAM was a Phase 3, multicenter, randomized, double-blind, double-dummy, parallel group, and active- and placebo-controlled, treat-through clinical trial of mirikizumab in participants with moderately to severely active CD. Participants who had an inadequate response to, loss of response to, or were intolerant to corticosteroid or immunomodulator therapy for CD (termed "conventional-failed"), and those who had an inadequate response to, loss of response to, or were intolerant to biologic therapy for CD (termed "biologic-failed") were included in the study. The primary objective was to test the hypothesis that mirikizumab is superior to placebo as assessed by the following co-primary endpoints:

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

A significantly greater percentage of participants achieved both co-primary endpoints at Week 52 in the mirikizumab group (endoscopic response: 38.0%, 220 of 579 participants, p<0.000001; clinical remission: 45.4%, 263 of 579 participants, p<0.000001) compared with the placebo group (endoscopic response: 9.0%, 18 of 199 participants; clinical remission: 19.6%, 39 of 199 participants).

Thus, mirikizumab demonstrated statistically significant and clinically meaningful improvements for both co-primary endpoints compared to placebo. Overall, higher frequencies of TEAEs were reported in the placebo group compared with the mirikizumab group. Most TEAEs were mild-to-moderate in severity. Frequency of SAEs and discontinuation due to AEs were higher in placebo group compared with the mirikizumab group. Three participant deaths were reported in this study (1 in the placebo group due to pulmonary embolism, 1 in the ustekinumab group due to sepsis, and 1 due to CD in the placebo nonresponder group who switched to mirikizumab at Week 12).

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

2.3. Benefit/Risk Assessment

At the time of the last benefit/risk assessment, evaluation of unblinded safety data from the completed or ongoing clinical studies has not revealed any dose-related safety or tolerability concerns. Mirikizumab has demonstrated efficacy in blinded, placebo-controlled Phase 2 and Phase 3 studies in psoriasis (Reich et al. 2019; Papp et al. 2020), Phase 2 and 3 studies in UC (Sandborn et al. 2018; D'Haens et al. 2023), and Phase 2 and Phase 3 studies in CD (Sands et al. 2022; Ferrante et al. 2024). Evaluation of unblinded safety data in studies in psoriasis, UC, and CD with dose regimens of up to 1000 mg IV Q4W for up to 52 weeks and up to 300 mg SC Q4W for up to 104 weeks have shown a safety profile generally consistent with the IL-23 antibody class. These data are summarized in the IB. Given the data from the Phase 2 and Phase 3 studies in CD and data from other clinical studies completed to date, potential benefits to participants who receive mirikizumab while participating in Study AMAX are reasonably anticipated.

In Phase 2 mirikizumab studies where mirikizumab in a lyophilized solution was administered intravenously over no less than 30 minutes, immediate hypersensitivity reactions, including 2 reports of immediate, infusion-related hypersensitivity events consistent with anaphylaxis and AEs that resulted in study drug discontinuation, were reported. In response, the duration of mirikizumab administration was increased. After this change was implemented, no additional events consistent with anaphylaxis were reported, and no anaphylactic reactions have been reported in participants who received the current Phase 3 formulation of mirikizumab (planned for commercial use). Infusion-related hypersensitivity reaction is an ADR for mirikizumab. Based on unblinded Phase 3 data, the following additional ADRs have been identified: injection site reactions, upper respiratory tract infections, alanine amino transferase increased, aspartate aminotransferase increased, headaches, and rashes. Consult the IB for information regarding ADRs and potential risks with mirikizumab.

Adverse events of special interest (AESIs), which are not necessarily ADRs but are of special interest based on standard drug registration topics, safety findings from previous studies in development program, potential risks associated with biologic immunomodulators as noted in product labels and published literature, and comorbidities and risk factors prevalent in the studied populations, are noted in Section 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 (Section 10.1.5). This independent assessment of clinical trial data will contribute to the overall ongoing evaluation and management of potential risks associated with mirikizumab administration.

Overall Benefit/Risk Conclusion

In summary, the efficacy and safety data from the Phase 2 CD Study AMAG and the Phase 3 CD Study AMAM support the continued clinical development of mirikizumab as a treatment for patients with CD in the ongoing Phase 3 CD Study AMAX.

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

Objectives	Endpoints
Primary	
CCI	
• To assess the effect of mirikizumab on clinical remission by CDAI and endoscopic response CCI	• Proportion of participants achieving clinical remission by CDAI CCI at Week 52 of AMAX • Proportion of participants achieving endoscopic response (defined by CCI SES-CD Total Score) at Week 52 of AMAX
Secondary	
CCI	
• To assess the long-term effect of mirikizumab on endoscopic, PRO, and CDAI endpoints that are not included in the primary objective in participants CCI	• Proportion of participants with CCI in AMAX at: ○ Week 12 ○ Week 52 ○ CCI ○ CCI • Proportion of participants with clinical remission by CDAI in AMAX at: CCI • Proportion of participants achieving endoscopic response in AMAX at: ○ CCI • Proportion of participants achieving endoscopic remission (defined as SES-CD Total Score ≤4 CCI in AMAX at: ○ Week 52 ○ CCI • Proportion of participants with clinical response by PRO CCI in AMAX at: ○ Week 52 ○ CCI ○ CCI

Objectives	Endpoints
	• Proportion of participants CCI [redacted] in AMAX at: ○ Week 52 ○ CCI ○ CCI
• To evaluate the effect of mirikizumab in CCI [redacted] in participants CCI [redacted]	The following scores over time during AMAX: • [redacted] • IBDQ in AMAX at CCI Week 52, • [redacted]
CCI [redacted]	
• To assess the effect of mirikizumab CCI [redacted] endoscopic response CCI [redacted]	• Proportion of participants achieving endoscopic response in AMAX at: ○ Week 52 ○ CCI
• To assess the effect of mirikizumab CCI [redacted] endoscopic remission CCI [redacted]	• Proportion of participants achieving endoscopic remission in AMAX at: ○ Week 52 ○ CCI
• To assess the effect of mirikizumab CCI [redacted] clinical response by CCI [redacted]	• Proportion of participants achieving clinical response by PRO in AMAX at: ○ Week 52 ○ CCI ○ CCI
• To assess the effect of mirikizumab CCI [redacted]	• Proportion of participants CCI [redacted] in AMAX at: ○ Week 52 ○ CCI ○ CCI

Objectives	Endpoints
• To evaluate the effect of mirikizumab CCI	• Proportion of participants achieving CCI in AMAX at: ○ CCI ○ Week 52 ○ CCI ○ CCI
• To evaluate the effect of mirikizumab CCI CDAI remission CCI	• Proportion of participants achieving clinical remission by CDAI in AMAX at: ○ CCI ○ Week 52 ○ CCI ○ CCI
• To assess the effect of mirikizumab CCI endoscopic response CCI	• Proportion of participants achieving endoscopic response in AMAX at: ○ Week 52 ○ CCI
• To assess the effect of mirikizumab CCI endoscopic remission CCI	• Proportion of participants achieving endoscopic remission in AMAX at: ○ Week 52 ○ CCI
• To assess the effect of mirikizumab CCI clinical response by PRO CCI	• Proportion of participants achieving clinical response by PRO in AMAX at: ○ Week 52 ○ CCI ○ CCI
• To assess the effect of mirikizumab CCI	• Proportion of participants achieving CCI in AMAX at: ○ Week 52 ○ CCI ○ CCI
• To evaluate the effect of mirikizumab CCI clinical remission by CDAI or endoscopic remission in participants CCI : ○ CCI ○	• Proportion of participants who achieve clinical remission by CDAI or endoscopic remission (analyzed separately) at AMAX Week 52 CCI • Proportion of participants who achieve clinical remission by CDAI or endoscopic remission (analyzed separately) CCI

Objectives	Endpoints
AMAM participants not achieving endpoints at Week 52 of AMAM:	
• To assess the effect of mirikizumab in the achievement of endoscopic response [redacted]	• Proportion of participants achieving endoscopic response in AMAX at: ○ Week 52 ○ [redacted]
• To assess the effect of mirikizumab in the achievement of endoscopic remission [redacted]	• Proportion of participants achieving endoscopic remission in AMAX at: ○ Week 52 ○ [redacted]
• To assess the effect of mirikizumab on clinical response by PRO [redacted]	• Proportion of participants achieving clinical response by PRO in AMAX at: ○ Week 52 ○ [redacted] ○ [redacted]
• To assess the effect of mirikizumab [redacted]	• Proportion of participants achieving clinical remission by PRO in AMAX at: ○ Week 52 ○ [redacted] ○ [redacted]
• To evaluate the effect of mirikizumab on [redacted]	• Proportion of participants achieving clinical response by CDAI in AMAX at: ○ [redacted] ○ Week 52 ○ [redacted] ○ [redacted]
• To evaluate the effect of mirikizumab on CDAI remission [redacted]	• Proportion of participants achieving clinical remission by CDAI in AMAX at: ○ [redacted] ○ Week 52 ○ [redacted] ○ [redacted]
• To assess the effect of mirikizumab on inflammatory biomarkers [redacted]	To evaluate the following endpoints in AMAX: • C-reactive protein at Week 12 • Fecal calprotectin at Week 12 • [redacted]

Objectives	Endpoints
• To assess the effect of mirikizumab in the achievement of endoscopic response [redacted]	• Proportion of participants achieving endoscopic response in AMAX at: ○ Week 52 ○ [redacted]
• To assess the effect of mirikizumab in the achievement of endoscopic remission [redacted]	• Proportion of participants achieving endoscopic remission in AMAX at: ○ Week 52 ○ [redacted]
• To assess the effect of mirikizumab in the achievement of clinical response by PRO [redacted]	• Proportion of participants achieving clinical response by PRO in AMAX at: ○ Week 52 ○ [redacted] ○ [redacted]
• To assess the effect of mirikizumab in the achievement of [redacted]	• Proportion of participants achieving [redacted] in AMAX at: ○ Week 52 ○ [redacted] ○ [redacted]
• To evaluate the effect of mirikizumab in achieving [redacted] endoscopic remission [redacted]	• Proportion of participants achieving [redacted] or endoscopic remission (analyzed separately) in AMAX at: ○ Week 52 ○ [redacted]
[redacted]	


CCI

CCI

CCI

Abbreviations: AP = abdominal pain; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CCI ; IBDQ = Inflammatory Bowel Disease Questionnaire; CCI PRO = patient-reported outcome; SC = subcutaneous; SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency; CCI

4. Study Design

4.1. Overall Design

Study AMAX is a long-term study of adult participants completing studies AMAM or AMAG (see schema in Section 1.2).

Two intervention groups will be studied in participants with moderate-to-severe CD:

- Mirikizumab CCI
- Mirikizumab CCI .

CCI

Study participants will receive mirikizumab for an extended period of time (approximately 3 years or until commercial availability of mirikizumab, whichever comes first) and then enter a 12- to 16-week posttreatment follow-up period. After completion of long-term extension period, if mirikizumab is not yet locally commercially available and reimbursable, eligible participants will be provided with an option of continued access to open-label mirikizumab, and then enter a CCI follow-up period (Section 10.13, Appendix 13). The duration of the continued access will differ by participant and country.

AMAM participants will require an endoscopy to be performed at Week 52, CCI) in the AMAX study.

AMAG participants who are entering AMAX after completing CCI into AMAX. Participants who have not yet completed CCI

See Section 8.1.1.2 for details.

4.2. Scientific Rationale for Study Design

Study AMAX is designed to accumulate data on the long-term safety of mirikizumab and evaluate the efficacy of mirikizumab in CCI for up to 3 years of treatment in participants with moderately-to-severely active CD. The primary objective of Study AMAX is to evaluate the long-term effect of mirikizumab in clinical remission and endoscopic response at Week 52 of treatment in Study AMAX. Clinical remission is defined as achieving CCI . Endoscopic response is defined as CCI

Endpoints

To evaluate the effect of mirikizumab on clinical improvement of CD and decreasing intestinal mucosa inflammation, the following measures will be used for the primary objectives of Study AMAX: CDAI and SES-CD Total Score.

For participants transitioning from AMAM, the SES-CD will be determined at Week 52 of AMAM, at Week 52 (Year 1) of AMAX, CCI), with evaluation of endoscopic response CCI) at Week 52 AMAX as a primary endpoint. CCI

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

To assess the effect of mirikizumab on SF and AP, CCI will be measured in Study AMAX at time points detailed in the Schedule of Activities (SoA) (Section 1.3). Participants transitioning from AMAM will be provided with an electronic daily diary during Week 0-Week 12 of the study to record their signs and symptoms on a daily basis.

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

4.3. Justification for Dose

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

Safety Considerations

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

Single IV doses of up to CCI mg were evaluated in Study AMAA (healthy participants and participants with psoriasis) and up to CCI 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 no-observed-adverse-effect levels (NOAELs) established in studies in monkeys. The margins of safety for the CCI dose regimens proposed relative to the NOAEL level in the 6-month nonclinical toxicology study in cynomolgus monkeys are CCI , respectively, based on area under the plasma concentration versus time curve.

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 900 mg IV induction dose in the ongoing phase 3 AMAM study is expected to produce near-maximal effect based on this exposure-response analysis. CCI

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 responseCCI [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]

In summary, the totality of the available data for both efficacy and safety supports the proposed CCI [redacted]

4.4. End of Study Definition

The end of the study is the date of the last visit or last scheduled procedure shown in the SoA (Section 1.3) for the last participant.

5. Study Population

Study AMAX is a continuation of originator Studies AMAM and AMAG. Adult participants may enter into Study AMAX directly from Studies AMAM and AMAG after they sign a study-specific Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent. A participant is considered enrolled into the study once the eligibility of the participant is verified (see Section 8). Participants who sign informed consent to enter Study AMAX but do not meet eligibility criteria should return to the originator trial for safety follow-up (see Section 5.4). Data collected during the last visit of the originator studies, including laboratory evaluations, endoscopy, and patient-reported data, may be used to review entry criteria, assess the suitability of a participant for entering this long-term extension trial, and serve as part of Visit 1 for AMAX. (Note that AMAX V1 is a split visit. See SoA Table AMAX.1-1 footnote d for additional details.) Prior to study entry, participants who do not meet 1 or more hepatic or hematologic laboratory enrollment criteria may have these blood measures repeated 1 time at the investigator's discretion to assess participant eligibility.

Participants who discontinued from Study AMAM for any reason are not eligible to enter study AMAX. AMAG participants who discontinued from the AMAG study or addendum or permanently discontinued treatment prior to the time of enrollment in Study AMAX are not eligible to enter Study AMAX.

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

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply. Criteria below apply to all AMAX participants, regardless of their originating study, unless a specific originator study (AMAM or AMAG) is specified:

Informed Consent

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

Type of Participant and Disease Characteristics

[2] Participants from the Phase 2 Study **AMAG** who:

- completed the last visit of participation in the AMAG study and remained on mirikizumab treatment in either the maintenance dosing period 3 or in the AMAG extension period, and
- in the opinion of the investigator, would derive clinical benefit from continued treatment with mirikizumab.

  It is recommended that participants receive the first dose of AMAX study drug within approximately[redacted] of the last dosing visit in AMAG. A maximum of[redacted] will be allowed between the last dose in AMAG and the first dose in AMAX to accommodate situations where due to circumstances outside the patient's control, a patient may not be able to complete all required assessments within the recommended shorter window.

OR

[3] Participants from the Phase 3 Study **AMAM** who:

- completed Week 52 of the AMAM study, including the Week 52 endoscopy CCI [redacted], and in the opinion of the investigator would derive clinical benefit from treatment with mirikizumab.

  It is recommended that participants receive the first dose of AMAX study drug within approximately CCI [redacted] after the last dosing visit in AMAM. A maximum of CCI [redacted] will be allowed between the last dose in AMAM and the first dose in AMAX to accommodate situations where due to circumstances outside the patient's control, a patient may not be able to complete all required assessments within the recommended shorter window.

Note: Participants who have completed the AMAM adolescent addendum are not eligible for the AMAX trial, but may be eligible for the pediatric IBD long-term extension trial.

Participant Characteristics

[4] Are willing and able to complete the scheduled study assessments, including endoscopy, self-administer investigational product (or have caregiver administer investigational product), and complete patient electronic and paper diary (See Section 8.1.2.2).

Note: Self-administration is a key long-term convenience factor for participants, and it is important that participants are well-supported in becoming comfortable with learning to take this step toward greater independence. Additional support will be available for training if participants express concerns about self-administration. The sponsor may approve exceptions regarding self-administration, depending on circumstances. Please contact your medical monitor. Patients who cannot carry out or do not feel comfortable with self-administration of study drug will not be excluded from participation in this trial.

[5] Have clinically acceptable central laboratory test results at study entry which would not have resulted in permanent discontinuation of treatment in the originator study.

Prior to study entry, patients whose hepatic or hematologic laboratory values meet discontinuation criteria in the originator study may have these blood measures repeated 1 time at the investigator's discretion to assess participant's eligibility for AMAX.

Participants with a diagnosis of Gilbert's syndrome (requires source documentation showing isolated unconjugated hyperbilirubinemia, with no evidence of hemolysis) can be included with elevated serum total bilirubin levels.

[6] Contraception: Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male Participants:

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

b. Female Participants:

Women of **childbearing potential** (WOCBP, defined as all adult females unless they are WNOCBP as defined below) may participate if they meet the following criteria:

A. must test negative for pregnancy prior to initiation of treatment as indicated by a negative urine pregnancy test at Visit 1/Week 0 of this study

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 a combination of 2 effective methods of contraception or 1 highly effective method of contraception for the entirety of the study. Abstinence or contraception must continue following completion of study drug administration for **16 weeks**.

i. Effective methods of contraception may include barrier methods such as male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges (which usually are made with spermicide). The barrier method must include use of a spermicide to be counted as one effective method.

ii. Highly effective (<1% failure rate) methods of contraception include

- female sterilization
- combination oral contraceptive pill
- progestin-only contraceptive pill (mini-pill)
- implanted contraceptives
- injectable contraceptives
- contraceptive patch (only women <198 pounds or 90 kg)
- vasectomy (if only sexual partner)
- fallopian tube implants (if confirmed by hysterosalpingogram)
- combined contraceptive vaginal ring, or
- intrauterine devices.

iii. Ineffective forms of contraception, whether used alone or in any combination, include

- spermicide alone
- periodic abstinence
- fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal)
- withdrawal
- postcoital douche, or
- lactational amenorrhea.

Women **not of childbearing potential** (WNOCBP) may participate and include those who are:

A. infertile due to surgical sterilization (total hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, bilateral oophorectomy, or tubal ligation)[a], have a congenital anomaly such as Müllerian agenesis,

OR

B. postmenopausal[b] – defined as either:

i. a woman at least 40 years of age with an intact uterus, not on hormone therapy, who has had either:
   - cessation of menses for at least 1 year, without an alternative medical cause
   - at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone (FSH) level >40 mIU/mL

ii. a woman 55 years or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea, or

iii. a woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

[a] Note that if it has been less than 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, she will be required to use contraception until she has reached 6 weeks since the procedure.

[b] For the purpose of defining the length of time of amenorrhea to determine postmenopausal status, only count time in which the woman was not taking medications such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, SERMs, or chemotherapy that could induce transient amenorrhea.

5.2. Exclusion Criteria

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

Type of Participant and Disease Characteristics

[7] Exclusion criterion [7] has been deleted due to redundancy with Inclusion Criteria [2] and [3].

[8] Exclusion criterion [8] has been deleted due to redundancy with Inclusion Criterion [3].

[9] Had a reported SAE in originator study or developed other condition prior to AMAX Week 0 that would disqualify them from treatment with mirikizumab according to originator study criteria.

[10] Had permanently discontinued study drug in the originator study or had a temporary interruption of study drug in originator study such that, in the opinion of the investigator or sponsor, restarting of mirikizumab would pose an unacceptable risk for the participant in Study AMAX.

Medical Conditions

[11] Presence of significant uncontrolled neuropsychiatric disorder or judged at risk of suicide in the opinion of the investigator

OR

marked "yes" to CCI [redacted] on ideation prior to dosing at Week 0

OR

marked "yes" to suicide behaviors prior to dosing at Week 0

AND

the ideation or behavior occurred within the past month.

[12] Have an unstable or uncontrolled illness, including, but not limited to, cerebro-cardiovascular, respiratory, gastrointestinal (excluding CD), hepatic, renal, endocrine, hematologic or neurological disorders, or abnormal laboratory values that developed prior to dosing at Visit 1 that, in the opinion of the investigator or sponsor, would pose an unacceptable risk to the participant if investigational product continues to be administered.

[13] Are diagnosed with any medical condition (or signs or symptoms thereof), including developing malignancy or suspicion of active malignant disease prior to dosing at Visit 1 of AMAX, which would have precluded enrollment in the prior originator study or would have required discontinuation.

[14] Have been diagnosed with serious infection (including, but not limited to, hepatitis B, hepatitis C, human immunodeficiency virus (HIV), and active tuberculosis [TB]) during the originator study or prior to dosing at Visit 1 of AMAX.

Note: Participants with a history of active TB with documentation of treatment by the World Health Organization (WHO) and/or Centers for Disease Control and Prevention (CDC) criteria prior to the originator study are not excluded from the study.

[15] Have been diagnosed with latent tuberculosis infection (LTBI) during an originator study or prior to dosing at Visit 1 of AMAX and is not willing to comply with completing TB treatment as appropriate (see Section 8.2.6 for TB prophylaxis details).

[16] Have a known hypersensitivity to any component of mirikizumab or has experienced an acute systemic hypersensitivity event with previous study drug administration in the originating study that precludes mirikizumab therapy.

[17] Have any other condition that, in the opinion of the investigator, renders the participant unable to understand the nature, scope, and possible consequences of the study or precludes the participant from attending study visits, completing study procedures, or adhering to prohibited concomitant medication requirements (See Section 10.7, Appendix 7).

General Exclusion Criteria

[18] Are pregnant, lactating, or planning to become pregnant while enrolled in the study or within 16 weeks after receiving the last dose of study drug.

[19] Exclusion criterion [19] has been deleted since surgical interventions of concern during originator trials would have been addressed previously.

[20] Intend to receive a Bacillus Calmette Guerin (BCG) vaccination or a live attenuated vaccine during the study.

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

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

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

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

*Note: except for low-grade sporadic colonic adenomatous polyp[a] ≤10 mm once completely removed (per [22] above)

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

[24] 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.

[25] 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.

[26] Are a Lilly employee, employee of a third-party organization involved with the study, or investigator site personnel directly affiliated with this study and/or their immediate families.

[27] 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. This includes participants who use marijuana (both recreational and medicinal uses [including cannabidiol oil]). Marijuana use must be stopped prior to screening and is prohibited for duration of the long-term extension period of the study.

5.3. Lifestyle Considerations

In order to participate in the study, the participants must agree to the contraception, reproduction, and breastfeeding criteria detailed in the inclusion and exclusion criteria. Study participants should be instructed not to donate blood or blood products during the study or for 16 weeks following study drug administration.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study due to failing one or more eligibility criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Participants who sign informed consent to enter Study AMAX but do not subsequently enroll should receive safety follow-up per the originator trial protocol.

6. Study Intervention

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

6.1. Study Intervention(s) Administered

The doses and routes of administration reflect the multipart study design (Section 4.1).

This table lists the intervention used in this clinical study

Intervention Name	Mirikizumab
Dosage Level(s)	CCI
Route of Administration	IV infusion or SC injection
Authorized as defined by EU Clinical Trial Regulation	Authorized in EU and not used according to the marketing authorization

Packaging and Labeling

Study interventions will be supplied by the sponsor in accordance with current Good Manufacturing Practice. Study interventions will be labeled as appropriate for country 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.

- Single-use solution vial containing mirikizumab with study-specific labels.
  - The CCI vial of mirikizumab is manufactured to deliver CCI
- Single-use solution prefilled syringe containing mirikizumab.
  - The CCI syringe of mirikizumab is manufactured to deliver CCI
  - The CCI syringe of mirikizumab is manufactured to deliver CCI

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

Preparation and Administration

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

Detailed instructions for investigational product administration will be provided by the sponsor, and the investigational product will be administered at the site only by clinical staff until Visit 4, at which time site staff will train participants on self-injection and will provide them with a log to track their doses at home. If the participant or caregiver is not able or willing to administer any dose throughout the study, the study site staff may administer that injection. Also, as noted in Inclusion Criterion 4, the sponsor may approve a general exception for self-administration for a participant depending on circumstances. In this situation, the reason will be documented. Participants will return to the site for administration by site staff, and will complete the *Patient Study Drug Administration Log.*

For those participants who choose self-administration of syringes, at Visit 4, site personnel will administer the first injection, and then the participant/caregiver will administer the second injection with guidance from the site personnel. Following Visit 4, injections will be self-administered SC by the participant or caregiver as specified in the SoA (Section 1.3). Participants will self-administer CCI [redacted]. Following training, injections will be self-administered per the study schedule without clinical intervention and participants will document information related to dosing in the provided Patient Study Drug Administration Log. The log will collect information including whether the participants were able to successfully self-administer the full dose of mirikizumab CCI [redacted]). Participants will record the time when each of the 2 injections were administered.

In the AMAX clinical study, a product usability study is being conducted on a subset of participants to assess the effectiveness of self-administration of mirikizumab by participants or caregivers in a home/office setting.

Refer to the appropriate *Manual Syringe Directions for Use* provided by the sponsor for the investigational product. Note that in the case a study drug injection is performed in an arm, it is not to be given in the same arm from which participant blood samples, including PK samples, are drawn at relevant visits.

Study Drug Administration Logs will be dispensed to each participant for recording pertinent data about each injection; details of the use of these logs are provided in Section 6.1.1. Possible injection sites are identified in the *Manual Syringe Directions for Use*. The injection site may be rotated to another area for subsequent doses.

Time of Doses

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

Investigator Responsibilities

The investigator or his or her designee is responsible for the following, in addition to the study intervention responsibilities listed in Sections 6.1.1, 6.2, and 6.4:

- explaining the correct use of the investigational interventions to the site personnel
- ensuring that participants are dosed with the correct CCI [redacted] Please refer to the supplemental training materials.

- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection, and
- 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.

6.1.1. Study Drug Administration Log

Training for self-administration will begin at Visit 4 (or earliest opportunity if not at Visit 4). A paper Study Drug Administration Training Log will be completed at training. Subsequent injections will be self-administered SC by the participant or caregiver as specified in the SoA (Section 1.3). If the participant or caregiver is not able to administer any dose throughout the study, the study site staff may administer that injection.

If an injection is missed, sites should contact their clinical research associate for further instructions.

A paper Study Drug Administration Log (or Study Drug Administration Training Log for the training visit) will be completed for each injection from Week 12 of study participation. The data from the Log must be transcribed into the eCRF by site personnel.

Participants will be instructed to contact their study site in the event of an injection problem. In addition, site personnel will review all Study Drug Administration Logs at each visit to identify any product complaints, and they will complete a product complaint form for each operation failure reported on a Study Drug Administration Log (see Section 8.3.8 for additional instructions regarding complaint handling).

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 when applicable. 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, and
- 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

This is an open-label study.

6.4. Study Intervention Compliance

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

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.

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

- the importance of complete bowel prep prior to colonoscopies
- how to evaluate their CD symptoms and to record them on the eDiary, paper diary, or questionnaires.
- the importance of being compliant with the daily eDiary or paper diary recording, and
- SC self-administration by the participant or caregiver.

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

If, in consultation with Lilly or its designee, the noncompliance is deemed to be significant or if further noncompliance occurs, the participant may be discontinued. See Section 7.1.2 for treatment noncompliance leading to permanent discontinuation from study drug.

6.5. Concomitant Therapy

Recording of Information about Concomitant Medications

All concomitant medications, including vaccinations and endoscopy preparation medications taken during the study, must be recorded on the Concomitant Medication eCRF. This includes concomitant medications for CD, underlying conditions or diseases, and 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 (Section 10.7, Appendix 7).

6.5.1. Permitted Therapy

Participants taking permitted CD concomitant medications other than oral corticosteroids are recommended to keep doses stable unless modifications are needed due to AEs or for appropriate medical management. For participants entering AMAX on corticosteroids for CD, corticosteroids should remain stable until Week 12 unless modifications are needed due to medical necessity.

After Week 12, corticosteroid tapering will occur as described in Section 6.5.3. Instructions regarding guidance for use are detailed in Section 10.8, Appendix 8.

6.5.2. Prohibited Therapy

Use of prohibited medications should not be withheld if, in the opinion of the investigator, failure to prescribe them would compromise participant safety. Participants who require a prohibited medication should be discontinued from study drug as described in Section 7.1.2 and should complete an early termination visit (ETV) and posttreatment follow-up visits as described in the SoA (Section 1.3). Some exceptions (IV corticosteroid, systemic corticosteroids for non-CD indications, and marijuana) may not necessarily result in discontinuation. Consult the medical monitor prior to discontinuing the participant (see Section 10.7, Appendix 7).

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

Vaccinations

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

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

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

For More Information

The list of prohibited medications is provided in Section 10.7, Appendix 7.

The list of permitted medications with dose stabilization guidance is provided in Section 10.8, Appendix 8.

6.5.3. Corticosteroid Taper

For participants who enter AMAX on corticosteroids, corticosteroid tapering as described below should be initiated or continued for participants who at the discretion of the investigator have achieved clinical response at Week 12. Instructions regarding guidance for use are detailed in Section 10.8, Appendix 8. For participants who cannot tolerate the corticosteroid taper without recurrence of clinical symptoms, corticosteroid taper may be paused and/or corticosteroid dose may be increased up to the original dose at baseline. The oral corticosteroid dose, however, may not be increased above the baseline dose in originator study unless due to medical necessity.

For participants who previously have tapered off corticosteroids but have recurrence of symptoms during study AMAX necessitating reintroduction of corticosteroids, this is allowed, however the dose may not be increased above the baseline dose in originator study, unless due to medical necessity.

Additionally, for participants who were not on oral corticosteroids during the originator study, oral corticosteroids may not be initiated, unless due to medical necessity.

For participants who have not begun corticosteroid tapering at Week 12 or participants who start corticosteroids after Week 12, tapering should be considered over the course of the study as soon as the participant demonstrates clinical response. Investigators must contact the Study Medical Monitor to discuss any participant who does not initiate CS tapering upon achieving clinical response.

The recommended tapering schedule for oral corticosteroids (other than budesonide) is as follows; however, investigators may taper steroids as clinically feasible and appropriate:

- Dose >10 mg/day prednisone or equivalent: taper daily dose by 5 mg/week until receiving 10 mg/day, and then continue tapering at 2.5 mg/week until 0 mg/day.
- Dose ≤10 mg/day prednisone or equivalent: taper daily dose by 2.5 mg/week until 0 mg/day.

For participants receiving oral budesonide, the recommended tapering schedule is having their dose tapered by 3 mg every 3 weeks until 0 mg/day.

6.7. 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).

Note: Results from PK, immunogenicity, CCI [redacted] are not intended for participant management and will not be provided to investigative sites. The participant should be monitored until resolution or stabilization of the symptoms, as clinically appropriate.

- Study drug should be discontinued (Section 7.1.2). The participant should undergo an ETV and posttreatment follow-up procedures after study drug discontinuation.

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

Other Infusion-Related Events

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

- The study drug infusion should be interrupted, and appropriate medical care should be administered (for example, non-steroidal anti-inflammatory drugs, antipyretics, or antihistamines).
- Blood samples should be obtained as described in Section 8.3.7.2 or 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 edema 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.

6.7.1. Premedication for Infusions or Injections

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). Systemic corticosteroids may be permitted if deemed necessary by the investigator.

6.8. Intervention after the End of the Study

6.8.1. Treatment after Study Completion

Mirikizumab will be made available by sponsor to eligible study participants, who complete Visit 19 CCI [redacted] through the optional Continued Access Period until local commercial availability of mirikizumab and reimbursement, including patient access programs, when and where available. Refer to Section 10.13 for more information on continued access.

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 Section 10.1.9.

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 ET procedures, which include:

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

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

7.1.1. Liver Chemistry Stopping Criteria

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

Interrupting study drug based on elevated liver tests

The study drug should be **interrupted** and CCI [redacted] if one or more of these conditions occur:

Elevation	Exception
ALT or AST >8x ULN	
ALT or AST >5x ULN for more than 2 weeks	
ALT or AST >3x ULN and either TBL >2x ULN or INR >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL>2x ULN.
ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >3x ULN, when the source of increased ALP is the liver	
ALP >2.5x ULN and TBL > 2x ULN	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL>2x ULN.
ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 and other consensus guidelines, with minor modifications	

Resuming study drug after elevated liver tests

Resumption of the study drug can be considered only in consultation with the Lilly-designated medical monitor and only if the liver test results return to baseline and if a self-limited non-drug etiology is identified. Otherwise, the study drug should be discontinued.

7.1.2. Permanent Discontinuation

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

Subject Decision

- The participant requests to discontinue the study drug.

Disease Worsening

- The participant requires treatment with a specified prohibited CD medication (Section 10.7, Appendix 7).
- The participant undergoes surgery for CD (with the exception of drainage of a perianal or other cutaneous abscess or seton placement).

Safety Considerations

- The participant has a diagnosis of any of the following during the study:
  - cancer other than squamous cell or basal cell carcinoma of the skin
  - any colonic adenomatous polyp with low grade dysplasia, not completely removed,
  - any adenomatous polyp with high grade dysplasia
  - evidence of dysplasia in non-polypoid mucosa (indefinite for dysplasia, low grade, or high-grade dysplasia) in the GI tract
  - active TB (Section 8.2.6)
  - HIV/acquired immunodeficiency syndrome (AIDS)
  - hepatitis B or development of detectable hepatitis B virus (HBV) DNA under specified circumstances (Section 8.2.8), or
  - hepatitis C or development of detectable hepatitis C virus (HCV) RNA (Section 8.2.9).
- If the investigator determines that a systemic hypersensitivity reaction has occurred related to study intervention administration, the participant may be permanently discontinued from the study intervention, and the sponsor's designated medical monitor should be notified. If the investigator is uncertain about whether a systemic hypersensitivity reaction has occurred and whether discontinuation of study intervention is warranted, the investigator may consult the sponsor.
- The participant has absolute lymphocyte count $<0.5 \times 10^3/\mu L$ after retesting (see Section 7.1.3).
- The participant has liver chemistry levels outside acceptable ranges that fail to meet the criteria for resumption of study drug as described in Section 7.1.1.
- 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 8.2.6).
- The participant has an AE or SAE which, in the opinion of the investigator or sponsor, would preclude the participant from continuing to receive study drug.
- It is recommended that the participant be assessed by an appropriately trained professional to assist in deciding whether the participant is to be discontinued if:
  - CCI [redacted]
  - the participant reports suicidal ideation or suicidal behaviors during the study.

Other Reasons

- Treatment noncompliance: CCI [redacted] (Section 6.4).
- Study participants and physicians may discontinue the study participation if they perceive no clinical benefit.

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

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

Cases that may merit temporary withholding of study drug must 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 of study drug include, but are not limited to:

- The participant develops a clinically important intestinal or extraintestinal infection (including LTBI) during the study (see Section 5.2).
- The participant requires major surgery. Administration of study drug may be restarted only after adequate wound healing.
- The participant develops a confirmed absolute neutrophil count $<1 \times 10^9$/L ($<1 \times 10^3$/μL or <1 GI/L (2 assessments below this threshold).
- A participant who develops an absolute lymphocyte count <500 cells/μL ($<0.5 \times 10^3$/μL or <0.50 GI/L) will be retested every 2 weeks for up to 8 weeks unless the lymphocyte count becomes $\geq 0.5 \times 10^3$/μL or ≥0.50 GI/L.
  - Azathioprine, methotrexate, or 6-mercaptopurine must be discontinued, if applicable, after the first retest confirming absolute lymphocyte count $<0.5 \times 10^3$/μL (second assessment below threshold), and the next dose of study drug held. The participant must be retested in approximately 2 weeks.
  - The third retest (fourth assessment below threshold) should occur prior to the next monthly dosing and if still below $<0.5 \times 10^3$/μL, the next dose of study drug should also be held. The participant must be retested in approximately 2 weeks.

    - After the fourth retest (fifth assessment below threshold), the participant may be permanently discontinued. Consult the medical monitor. White blood cell and lymphocyte counts will be followed for these participants until they return to an acceptable level.
- The participant has laboratory abnormalities that may lead the investigator to hold the study drug until resolution of the abnormalities.

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)
- the investigator decides that the participant should be discontinued from the study
- all participants from originator Study AMAM CCI [redacted] and enter the 12- to 16-week posttreatment follow-up period, or
- the participant requests to be withdrawn from the study.

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

7.3. Lost to Follow up

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

8. Study Assessments and Procedures

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

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

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

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

All screening criteria evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Timing to receive results and to retest if needed should be considered when scheduling. If the available screening laboratory results are from samples taken more than CCI prior to Visit 1 dosing, new labs should be collected again prior to dosing. 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.

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

8.1. Efficacy Assessments

The following table defines efficacy endpoints used in this study.

Endpoint	Definition
Endoscopic response	CCI
Endoscopic remission CCI	
Clinical remission by PRO	
Clinical response by PRO	
Clinical remission by CDAI	
CCI	

Abbreviations: CCI ; CDAI = Crohn's Disease Activity Index; PRO = patient-reported outcome; CCI .

8.1.1. Primary Efficacy Assessment

The primary endpoints are clinical remission by CDAI and endoscopic response by SES-CD at Week 52 of AMAX.

Clinical Remission

The CDAI is an 8-item disease activity measure comprised of a composite of 3 patient-reported and 5 physician-reported/laboratory items (physical signs and a laboratory parameter [hematocrit]). 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 Section 10.9, Appendix 9, for additional descriptions of PROs (CDAI-SF, CDAI-AP, and CDAI-well-being).

Endoscopic Response

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

The SES-CD tool will be utilized by central readers to evaluate the endoscopy video that is collected during the participant's 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.

8.1.1.1. Simple Endoscopic Score for Crohn's Disease

The SES-CD (Daperno et al. 2004) is an endoscopic scoring system for CD based on 4 endoscopic variables (presence and size of ulcers, proportion of surface covered by ulcers, proportion of surface affected by disease, and presence and severity of stenosis) which are assessed in 5 ileocolonic bowel segments (ileum, right colon, transverse colon, 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

The endoscopy completed at Week 52 of AMAM CCI [redacted]

Endoscopies will be performed on all AMAM participants at Week 52 aCCI [redacted] of Study AMAX.

AMAG participants who are entering AMA CCI [redacted] participants will have an endoscopy performed CCI [redacted] of Study AMAX.

Investigators may use these endoscopies to perform surveillance for dysplasia or colorectal cancer locally, according to national and international guidelines.

For both AMAG and AMAM participants, an ET endoscopy should only be performed if the visit occurs CCI after the last endoscopy. An ET endoscopy will not be performed during the follow-up period.

Unscheduled endoscopies can be performed at the principal investigator's discretion if deemed clinically appropriate.

To ensure quality data and standardization, endoscopy will be performed locally at clinical sites per the study schedules and use 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.

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

For each visit with an endoscopy, it is recommended that the endoscopy be performed on a separate day from the vital signs and study questionnaires, and IP administration, within the visit window, with the endoscopy (with or without sedation) preceding the other activities. However, if they must be performed on the same day due to logistical issues, the following order of procedures must be followed: (1) Measurement of vital signs and collection of responses to questionnaires; (2) Administration of IP with protocol-specific observation period (at least 1 hour); (3) Performance of endoscopy with or without sedation.

If a participant 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 to support assessment of the CCI (Section 8.1.3). The biopsy samples will be sent to the central study laboratory for processing. To ensure quality data and standardization, bowel tissue CCI The details of biopsy sample collection will be provided in both the imaging manual and laboratory manual. Detailed endoscopy and CCI charters outline the procedures to be used for secure specimen transfer, CCI
These results will not be made available to study sites during the study.

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

Samples will be retained at a facility selected by Lilly or its designee for a maximum 15 years after the last participant visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits.

8.1.2. Secondary Efficacy Assessments

CCI

8.1.2.2. PROs

Participants Originating from AMAM

The following PROs will be collected from Week 0 through Week 12:

- Daily via patient eDiary
  - CCI
  - CDAI-SF

    Note: Bristol Stool Scale is used as a reference to complete CDAI-SF
  - CDAI-AP
  - CDAI-well-being
  - CCI
- At scheduled visits via paper questionnaire
  - CCI
  - Inflammatory Bowel Disease Questionnaire (IBDQ)
  - CCI

Participants Originating from AMAG

The following PROs will be collected at scheduled visits from Week 0 through Week 12:

- via patient 1-Day and/or 14-Day paper diary or paper questionnaire
  - CCI
  - CDAI-SF

    Note: Bristol Stool Scale is used as a reference to complete CDAI-SF.
  - CDAI-AP
  - CDAI-well-being
  - CCI
  - IBDQ.

All Participants from AMAG and AMAM

The following PROs will be collected at scheduled visits from Week 16 through study completion:

- via patient 1-Day and/or 14-Day paper diary or paper questionnaire
  - CCI
  - CDAI-SF

    Note: Bristol Stool Scale is used as a reference to complete CDAI-SF.
  - CDAI-AP
  - CDAI-well-being
  - CCI
  - IBDQ.

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

See Section 10.9, Appendix 9 for details on the above PROs.

8.1.2.3. Inflammatory Biomarkers

High-Sensitivity C-Reactive Protein

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

Investigators will be blinded to high-sensitivity C-reactive protein results until after AMAM database lock.

Fecal Calprotectin

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

Investigators will be blinded to fecal calprotectin results until after AMAM database lock.

CCI

CCI

8.1.3. Exploratory Assessments

Other exploratory endpoints, including CCI , will be defined in the statistical analysis plan (SAP).

8.2. Safety Assessments

Visits and Order of Safety Assessments

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

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

Adverse event collection should occur before the collection of the CCI (Section 8.2.11 and Section 8.3.2.1).

Data Collection and Reporting

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

Safety Monitoring

The sponsor will periodically review evolving aggregate safety data within the study by appropriate methods. In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the individual or group level, additional analyses of the safety data can be performed by members of the DMC (Section 10.1.5, Appendix 1) or by the sponsor through its internal review committee process.

8.2.1. Vital Signs

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

Sitting blood pressure and pulse rate should be measured after the participant has been sitting for at least 5 minutes. Sitting blood pressure and pulse rate should be obtained at approximately the same time of day as ECG measurements and/or blood sampling. When multiple assessments are scheduled for the same visit, the preferred order of completion is: Vital signs, ECG (if applicable), then blood sampling.

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

8.2.2. Physical Examinations

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

Physical examinations should include a symptom-directed evaluation as well as an examination of eyes, heart, lungs, abdomen, and a visual examination of the skin.

For participants with a risk factor, a thorough exam to evaluate for TB will be performed (Section 8.2.6).

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

8.2.3. Electrocardiograms

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

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

Electrocardiograms will be read locally.

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

8.2.4. Chest Radiography

A posterior-anterior chest x-ray (CXR), interpreted and reported by a radiologist or pulmonologist, will be obtained if there are relevant TB-related physical findings or other factors that the investigator feels warrant testing and imaging, as specified in the SoA (Section 1.3) and Section 8.2.6. A lateral CXR can also be obtained if, in the opinion of the investigator, a lateral view is indicated. A computed tomography (CT) scan can be performed as an alternative to the CXR based on regional standard of practice. An IGRA or TST should also be performed (Section 8.2.6).

8.2.5. Stool Testing

Stool Culture

Stool culture/testing is allowed at the investigator's discretion.

C. difficile Toxin

A stool sample for *C. difficile* toxin (toxins A and B, and glutamate dehydrogenase, with reflex to polymerase chain reaction testing as needed) is allowed at the investigator's discretion.

8.2.6. Tuberculosis Testing

Initial Screening

All participants will be evaluated for risk factors for LTBI at rollover from their originator studies during the AMAX Visit 1 (Section 10.5, Appendix 5). If the participant has risk factors or any TB-related signs or symptoms are identified as part of the discussions of preexisting conditions or as part of the standard physical exam, the investigator should conduct a thorough physical examination, including body temperature measurement and assessment of peripheral lymph nodes. For participants with relevant TB-related physical findings or other factors that the investigator feels warrant testing and imaging:

- a TB test should be performed:
  - IGRA (for example, QuantiFERON-TB Gold or TSPOT.TB), or
  - Tuberculin skin test (TST; also called a purified protein derivative [PPD] or Mantoux test).

  Note: 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.

  If participant has a history of positive TB test result with prophylaxis, TB testing should not be performed unless advised to do so based on local guidelines (See also section on Prior Treatment for LTBI).
- a CXR should be performed, as described in Section 8.2.4. A CT scan may be performed as an alternative to the CXR based on regional standard of practice.

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 the TST. Interferon gamma release assay is also the preferred screening test for LTBI in participants who have received a BCG vaccination. In countries where the TST is available and is preferred (in the judgment of the investigator) as an alternative screening test for LTBI, that test may be used instead of an IGRA for appropriate participants.

Interpretation of 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.

Retesting and Confirmatory Testing

One retest is allowed for participants with an "indeterminate" QuantiFERON-TB Gold assay or "borderline" T-SPOT.TB assay. Participants with 2 indeterminate QuantiFERON-TB Gold assays, 2 borderline T-SPOT.TB assays, or 1 indeterminate QuantiFERON-TB Gold assay plus 1 borderline T-SPOT.TB assay will be excluded.

Confirmatory testing with an IGRA is allowed for selected participants who have a positive QuantiFERON-TB Gold assay, positive T-SPOT.TB assay, or positive TST who meet all 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 Section 10.5, Appendix 5.

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 (see TB Screening Outcomes and Enrollment below). 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.

TB Screening Outcomes and Enrollment

Participants who are negative for LTBI and active TB may be enrolled in the trial (Section 5.2).

Participants diagnosed with LTBI at screening, based on a positive IGRA test result or a positive purified protein derivative response ≥5 mm of induration, and no evidence of active TB, may be enrolled in the study if treatment with mirikizumab is initially withheld and 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, United States CDC (2016) or the WHO (2018), with documentation of having completed the appropriate TB prophylaxis regimen
- no evidence of reactivation of LTBI, and
- 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 prophylaxis, before mirikizumab dosing.

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.

Participants diagnosed with active TB at screening will be excluded (see Active TB section below).

Monitoring for TB during the Study

For all participants, monitoring for TB is to be continuous throughout the study. Every 2 to 3 months as indicated in the SoA, the participants will be assessed for risk factors for TB (Section 10.5, Appendix 5). If the participant has a risk factor or any TB-related signs or symptoms identified as part of the AE discussions or standard physical exam, 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 or other factors that the investigator feels warrant testing and imaging, an IGRA OR TST and CXR should be performed. A CT scan can be performed as an alternative to the CXR, based on regional standard of practice.

Participants diagnosed with active TB during the study will be discontinued and should be referred for appropriate treatment (see Active TB section below).

Diagnosis of LTBI During the Study

Participants diagnosed with LTBI after enrollment in the study, based on a positive IGRA test result or a positive purified protein derivative response ≥5 mm of induration, and no evidence of active TB, will temporarily discontinue investigational product and be offered treatment, if clinically appropriate. These participants can be considered for resumption of investigational product after completing the first 4 weeks of appropriate ongoing prophylactic therapy for LTBI based on national or international guidelines (for example, United States CDC [2016] or the WHO [2018]) and if they have no evidence of treatment hepatotoxicity (ALT and AST levels must remain ≤2 × ULN). These participants must continue with and complete a full course of treatment for LTBI in order to continue investigational product. Noncompliance with LTBI treatment during the study is a reason for permanent discontinuation from study drug.

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 7.1.2), and the participant will undergo an ETV and then enter the 12- to 16-week posttreatment follow-up period. The participant should also be referred by the investigator for appropriate TB treatment and follow-up.

8.2.7. Clinical Safety Laboratory Assessments

Visits and Times

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

Retesting for study entry is allowed 1 time prior to dosing at Visit 1 of Study AMAX.

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, 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 originator Study AMAM (Section 8.1.2.3), Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor.

Investigator Responsibilities

The investigator must review the laboratory reports in a timely manner throughout the study. Investigators must document this review and record any clinically relevant changes occurring after the participant receives the first dose of study drug in the AE section of the CRF.

The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. All laboratory tests with values considered clinically significantly abnormal during participation in the study or during the 12- to 16-week follow-up period should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

All protocol-required laboratory assessments, as defined in Section 10.2, Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. If laboratory values from nonprotocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (for example, SAE, AE, or dose modification), then the results must be recorded in the case report form (CRF).

8.2.7.1. Pregnancy Testing

Pregnancy testing is to be performed on all women unless they meet the criteria describing women not of childbearing potential, as outlined in Section 5.1. Participants who are pregnant will be discontinued from the study (Section 7.1.2).

Visits and Times

Urine pregnancy testing will be performed locally during designated scheduled visits through Week 156. The urine pregnancy test must be "negative" within 24 hours prior to administration of study drug.

Between visits, urine pregnancy tests are to be performed prior to monthly at-home dosing.

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 local serum pregnancy test is an acceptable alternative.

Assessment of follicle-stimulating hormone levels can assist in determining if a woman meets the definition of "postmenopausal" as outlined in Section 5.1. Follicle-stimulating hormone can be optionally obtained during study entry procedures at the discretion of the investigator. Follicle-stimulating hormone can also be optionally obtained during the study to determine postmenopausal status (see Section 1.3).

8.2.8. Hepatitis B Testing

HBV Screening and Interpretation

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

Screening for HBV in this study is performed as follows: an initial test for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb), followed by a test for HBV DNA in participants who are HBsAg-, HBcAb+. Participants testing HBcAb+ in the originator study do not need to have HBV full screening at Visit 1, but they will need to have HBV DNA testing at screening, as well as HBV DNA monitoring throughout the trial, as described below.

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 HBcAb result, or
- HBsAg-, HBcAb+ 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-, HBcAb-, or
- HBsAg-, HBcAb+ with no HBV DNA detected.

Management of participants with the following HBV serology from the originator study or at Week 0 of AMAX (or found to have the following serology at any time during AMAX) will undergo HBV DNA monitoring as described in the SoA (Section 1.3):

- HBsAg-, HBcAb+, HBV DNA not detected

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

Management of Participants with Detectable HBV DNA during the Study

Please contact medical monitor for any scenarios not covered below.

<table>
<tr><th colspan="2">If a participant develops detectable but not quantifiable HBV DNA:</th></tr>
<tr><td colspan="2">• Withhold the study drug.
• Repeat HBV DNA, HBsAg, ALT, AST, TBL within 2 weeks and again 2 weeks later, at the central laboratory, if possible. However, if central laboratory collection is not possible due to extenuating circumstances, and after consultation with the medical monitor, local laboratories may be used to facilitate the patient's compliance. Results should be reported in the Local Laboratory Tests CRFs under the Hepatic visit for tests where data collection fields exist.
• If the repeat HBV DNA is undetectable, or detectable but not quantifiable, on 2 consecutive retests (for a total of 3 consecutive tests), and the participant remains asymptomatic[a] with no elevation in liver tests[b], the study drug can be resumed with close monitoring of HBV DNA and liver tests.
• The investigator should wait for the results of both HBV DNA tests before making a decision on resuming the study drug.
• HBV DNA, ALT, AST, TBL should be monitored at least once-monthly in the 3 months after the last detectable HBV DNA result and every 3 months thereafter.
• If one of the subsequent HBV DNA results again becomes detectable and not quantifiable, but the participant remains asymptomatic with normal liver tests, continue the study drug, and increase monitoring frequency of HBV DNA, ALT, AST, and TBL to once-monthly.
• If one of the repeat HBV DNA results is detectable and quantifiable, follow the instructions below, for participants with detectable and quantifiable HBV DNA.</td></tr>
<tr><th colspan="2">If a participant develops detectable and quantifiable HBV DNA:</th></tr>
<tr><td>If the participant is asymptomatic[a] and liver tests are not elevated[b]:
• Withhold the study drug.
• Repeat HBV DNA, HBsAg, ALT, AST, and TBL within 2 weeks.
• Inform the Lilly-designated medical monitor.
• Refer to a hepatologist[c] for further management, including initiation of a nucleoside/nucleotide analog (NA).</td><td>If the participant is symptomatic[a], or if ALT, AST, or TBL are elevated[b]:
• Withhold the study drug.
• Repeat HBsAg, ALT, AST, and TBL within 48 to 72 hours to determine if the levels are increasing or decreasing.
• Continue monitoring liver tests 1 to 3 times weekly according to the protocol requirements for treatment-emergent abnormal liver tests.
• Inform the Lilly-designated medical monitor.</td></tr>
</table>

• Continue monitoring HBV DNA, HBsAg, ALT, AST, and TBL every 2 weeks. If HBV DNA is undetectable in 3 consecutive tests, and liver tests are not elevated[b], monitoring frequency can decrease to once every 1 to 2 months.	• Refer to a hepatologist for further management, including initiation of a nucleoside/nucleotide analog (NA). • Continue monitoring HBV DNA, and HBsAg, every 2 weeks. If liver tests are back to baseline, and HBV DNA is undetectable in 3 consecutive tests, monitoring frequency can decrease to once-monthly.

Resumption of the study drug in participants with detectable and quantifiable HBV DNA:

Resumption of the study drug after interruption for detectable and quantifiable HBV DNA, can be considered only:

- in asymptomatic[a] participants without concurrent elevated[b] liver tests, or in whom there was a clear alternative cause for the elevations, and they have returned to baseline
- in consultation with the Lilly-designated medical monitor, and
- only after the participant was seen by a hepatologist[c] and NA has been initiated.

If the above criteria are met:

- the study drug can be restarted 7 days after NA initiation.
- If NA was initiated and the study drug was resumed, HBV DNA, HBsAg, ALT, AST, and TBL should be monitored at least monthly initially.
- After HBV DNA is undetectable in 3 consecutive tests, monitoring frequency can be decreased to every 2 to 3 months.

Permanent discontinuation of the study drug in participants with detectable and quantifiable HBV DNA:

The study drug should be permanently discontinued if any of the following occurs:

- HBV DNA is detectable and quantifiable with concurrent elevation[b] of ALT, AST, or TBL for which there is no clear alternate cause.
- HBV DNA is detectable and quantifiable with concurrent symptoms[a] that are considered by the investigator to be related to HBV reactivation.
- HBV DNA viral load is >100 IU/mL on 2 or more tests.

HBV DNA is detectable and quantifiable, but participant does not start NA treatment.

Duration of HBV DNA monitoring and NA prophylaxis in participants with detectable and quantifiable HBV DNA:

- HBV DNA monitoring should continue for at least 6 months after the last dose of the study drug.
- If NA was initiated and the study drug was resumed, NA treatment and HBV DNA monitoring should continue for at least 6 months after the last dose of the study drug.
- The participant should be referred to a hepatologist[c] for continued follow-up and management after study participation.

a Symptoms may include worsening fatigue, nausea, vomiting, abdominal discomfort, jaundice, fever, or rash.

b ALT, AST, or TBL elevation refers to elevations ≥2x ULN in participants with normal baseline or near normal baseline (i.e., <1.5x ULN) or elevation ≥2x baseline in participants with elevated baseline (i.e., ≥1.5x ULN). In participants with Gilbert's syndrome, isolated hyperbilirubinemia may be up to 3x ULN provided that direct bilirubin is no higher than 30% of the total.

c A hepatologist may include a health care provider with recognized expertise in the assessment and management of viral hepatitis.

If the study drug must be discontinued per guidelines above, the participant will have an ETV. The participant will then enter the posttreatment follow-up period (Section 7.1). Prior to discontinuing investigational product (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 consultation has been completed and after discussion with the medical monitor. Such participants should also receive appropriate follow-up medical care.

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

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

8.2.9. Hepatitis C Testing

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

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

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

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

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

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

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

Participants with a previous diagnosis of hepatitis C who have been treated with antiviral therapy and achieved a sustained virologic response 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 posttreatment follow-up period (Section 7.1). Such participants should also receive appropriate follow-up medical care.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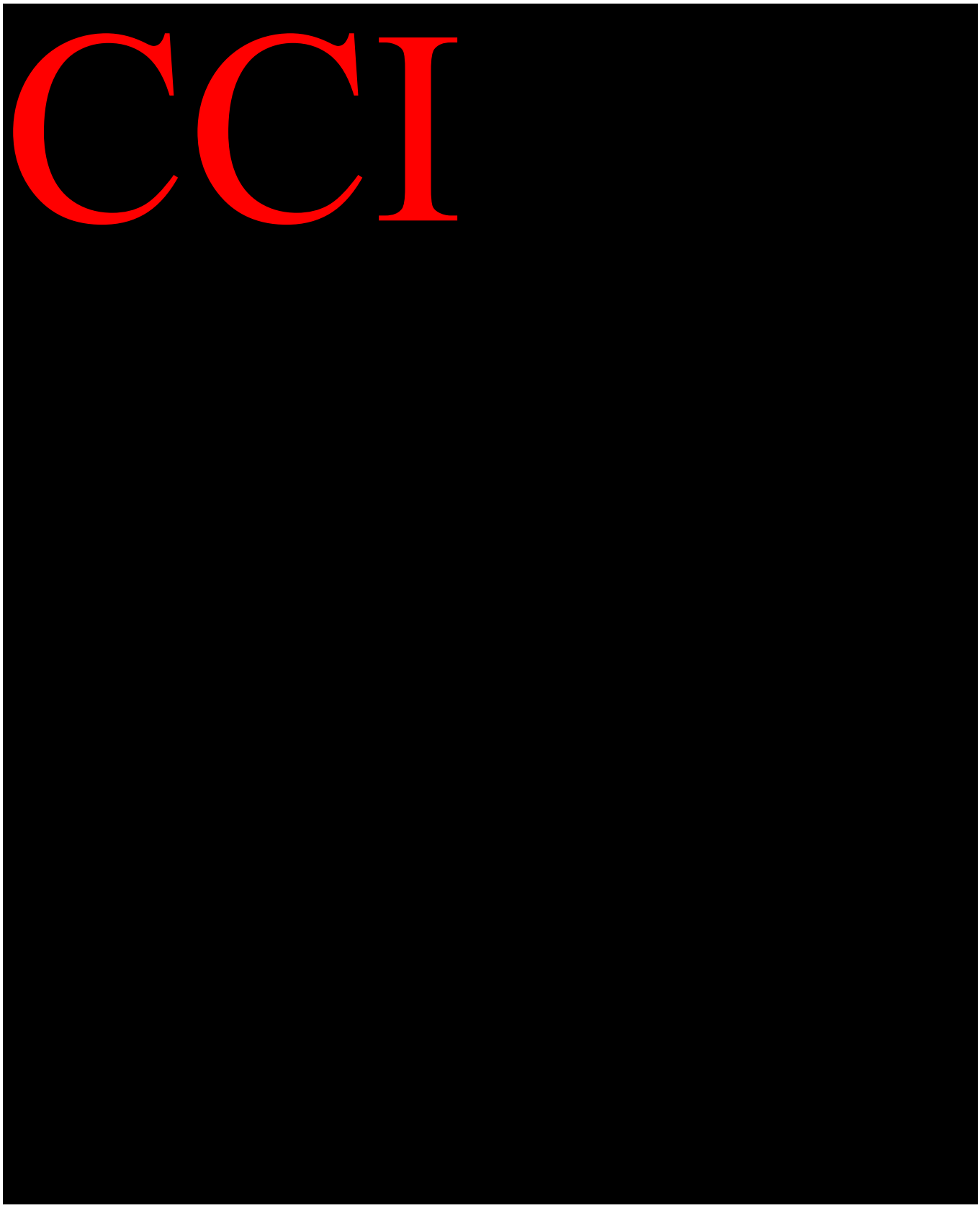
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8.2.11. Depression, Suicidal Ideation, and Behavior Risk Monitoring

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

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

These assessments are described below, and further information is provided in Section 10.9, Appendix 9.

See Section 8.3.2.1 for information about AE collection relative to collection of the CCI

See Section 7.1.2 for information regarding discontinuation of study drug for participants who have suicidal ideation or suicidal behaviors.

8.3. Adverse Events and Serious Adverse Events

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

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

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the participant to discontinue the investigational product before completing the study. The participant should be followed until the event resolves,

stabilizes with appropriate diagnostic evaluation, or is otherwise reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

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

After the informed consent form (ICF) is signed, study site personnel will record via eCRF the occurrence and nature of each participant's pre-existing conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

In addition, after the first dose of study drug, site personnel will record any change in the condition(s), including exacerbation of CD, and any new conditions as AEs. Also, if an AE occurs after signing the AMAX ICF, but prior to receiving investigational product, and is considered reasonably possibly related to an AMAX study procedure, the AE should be reported as an AE in AMAX. Any other events/diagnoses that start after signing AMAX consent but before first AMAX dosing should be recorded in the AMAX MH eCRF.

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, or
- important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an

emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

As described in Section 8.3, all AEs occurring after the participant receives the first dose of AMAX study drug are recorded as AEs in the AMAX eCRF and they will be assessed for serious criteria. The SAE reporting to the sponsor begins after the participant has signed the AMAX ICF and has received AMAX investigational product. However, if an SAE occurs after signing the AMAX 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 an AMAX study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Participants with a serious hepatic AE should have additional data collected using the hepatic eCRF packet (see Section 8.2.10).

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, for tracking purposes, any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus through the pregnancy outcome, generally no longer than 6 to 8 weeks past the estimated due date.

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 CFR 312.32, European Union Clinical Trial Regulation 536/2014 [submission of SUSARs to the EudraVigilance database], and the associated detailed guidance or national regulatory requirements in participating countries require the reporting of SUSARs. The sponsor has processes for safety reports for the identification, recording, and expedited reporting of SUSARs according to EU regulatory requirements.

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

Adverse events occurring after the participant has signed the AMAX ICF, but prior to AMAX study drug administration, will be recorded as AEs in the originating study and transcribed as pre-existing/medical history in the AMAX eCRF (except where reasonably possibly related to an AMAX study procedure, as described in Section 8.3). All AEs occurring after the participant receives the first dose of AMAX study drug are recorded as AEs in the AMAX eCRF and assessed for serious criteria. Investigators are not obligated to actively seek AEs or SAEs in participants once the participant has discontinued and/or completed the study (the participant disposition eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study and the investigator considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

8.3.2.1. AE Monitoring with a Systematic Questionnaire

Spontaneous AE collection should occur prior to the collection of the CCI [redacted]

If a suicide-related event is discovered during the CCI [redacted] but was not captured during the spontaneous AE collection, sites should not change the AE form. However, if an event is serious or leads to discontinuation, the event should be included on the AE form, and the process for reporting SAEs, if applicable, should be followed.

8.3.3. Follow-Up of AEs and SAEs

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

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE 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 all applicable regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will evaluate the reported SAEs, including confirmation of relatedness and assessment of expectedness. The sponsor will comply with applicable regulatory requirements relating to safety reporting to the regulatory authority (United States 21 CFR 312.32, European Union Clinical Trial Regulation 536/2014 [submission of SUSARs to the EudraVigilance database], and national regulatory requirements in other participating countries), IRB/IEC, and investigators in the participating regions and countries.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary. Refer to Section 8.3.1.1 for details for regulatory reporting requirements of SUSARs.

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

8.3.5. Pregnancy

- For all pregnancies occurring at any point after the start of study intervention in AMAX and until at least 16 weeks after the participant's last dose of study drug, in both female participants and female partners of male participants, details will be collected (Section 8.3.1).
- After learning of a pregnancy in the female partner of a male study participant, the investigator will attempt to obtain a consent to release information from the pregnant female partner directly as required by local guidelines.
- The guidelines in some geographies may require additional consent from pregnant female participants.

- If a pregnancy is reported, the investigator should record pregnancy information on the appropriate form and inform the sponsor within 24 hours of learning of the pregnancy. In addition, investigator should follow the procedures outlined in Section 10.3.5, Appendix 3 for SAEs (even though pregnancy is not considered an AE as described in Section 8.3.1).
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, or ectopic pregnancy) are considered SAEs.

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. CCI .

8.3.7. Adverse Events of Special Interest

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

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


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8.3.8. Complaint Handling

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a trial intervention.

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

NOTE: AEs/SAEs that are associated with a product complaint will also follow the processes outlined in Section 8.3 and Section 10.3 of the protocol.

8.3.8.1. Follow-Up of Product Complaints

- Follow-up applies to all participants, including those who discontinue study intervention.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.3.8.2. Prompt Reporting of Product Complaints to Sponsor

Product complaints will be reported to the sponsor according to the instructions in the product complaints form after the investigator determines that the event meets the protocol definition of a product complaint.

8.4. Treatment of Overdose

In the event of a suspected overdose, the investigator should

1. contact the medical monitor and sponsor immediately
2. closely monitor the participant for any AE/SAE and laboratory abnormalities (hematology, chemistry, vital signs, and oxygen saturation); supportive care should be provided as necessary, and
3. document all AEs associated with the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

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.

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

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. The results will not be provided to the investigator.

Additional Samples

CCI [redacted] In the case of systemic allergic/hypersensitivity reactions (Section 8.3.7.2), additional blood samples will be obtained, as described in the SoA (Section 1.3).

Sample Retention

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

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are listed in Section 10.2, Appendix 2.

8.9. Immunogenicity Assessments

Visits and Times

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

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

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

Sample Collection, Handling, and Use

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

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

Treatment-emergent (TE) ADAs are defined in Section 9.4.6.

Sample Retention

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

8.10. 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

No formal hypothesis testing will be conducted in this open-label trial.

9.2. Sample Size Determination

The sample size of Study AMAX will be determined by the number of participants who enroll in Study AMAX from the preceding studies (AMAM and AMAG). It is anticipated that approximately 50% to 70% of the participants from Study AMAM and Study AMAG will be enrolled. Based on this assumption, 640 to 900 participants are expected to enroll in Study AMAX.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined.

Intent-to-Treat (ITT) Population

The ITT population is defined as all participants who enter Study AMAX and receive a treatment assignment, even if the participant does not receive the correct treatment or otherwise does not follow the protocol. Participants will be analyzed according to the treatment to which they were assigned.

Modified Intent-to-Treat (mITT) Population

All participants from the ITT population who take at least 1 dose of study drug in Study AMAX.

Primary Analysis Set

All patients from the mITT population who h[redacted]

Safety Population

Same as mITT.

9.4. Statistical Analyses

9.4.1. General Considerations

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

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, such as the analysis method for the primary objective. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

The first version of the SAP will be finalized prior to First Patient Visit and it will include a more technical and detailed description of the statistical analyses described in this section. The SAP may be modified, as required, during the trial. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and secondary endpoints.

This is an open-label extension study with no randomization. ParticipantsCCI [redacted] r mirikizumab SC or to mirikizumab IV CCI [redacted] herefore, no intervention comparisons will be done. Analyses and summaries will be focused on point estimates and confidence intervals.

Efficacy summaries will be provided CCI [redacted] using the primary analysis set (as described in Section 9.3) and will be summarized by intervention group and by the intervention received in the originating study. Select efficacy summaries may also be conducted in the mITT population.

Safety summaries will be provided using the safety population (as described in Section 9.3) and will be summarized by originating study, intervention group, and the intervention received in the originating study.

Handling of missing, unused, and spurious data is addressed prospectively in the overall statistical methods described in the protocol and in the SAP, where appropriate. Adjustments to the planned analyses are described in the final CSR.

9.4.1.1. Analyses

Continuous data will be summarized in terms of mean, standard deviation, median, and minimum and maximum values; categorical data will be summarized as frequency counts and percentages.

For assessment of categorical efficacy and health outcome endpoints for participants from Study AMAM, proportions for each intervention group will be summarized by the intervention groups as defined in the SAP. The 95% confidence intervals will also be reported using the Wilson Score method (Wilson 1927, Newcombe 1998). Categorical repeated measure analyses such as the generalized linear model may be explored for selected endpoints.

For continuous endpoints with more than 1 postbaseline timepoint, the least squares mean from a restricted maximum likelihood-based mixed-effects model of repeated measures (MMRM) with the corresponding 95% confidence interval may be summarized. The MMRM model will include baseline value, visit, intervention group as defined in the SAP, and visit by intervention group interaction. Alternative versions of MMRM may be implemented as deemed appropriate. Least squares means will be reported along with the 95% confidence interval.

For continuous efficacy and health outcome variables for participants CCI [redacted], the mean response will be estimated using analysis of covariance, including baseline value and intervention group as defined in the SAP. Least squares means will be reported along with the 95% confidence intervals. Missing data imputation method for the analysis of covariance model will be specified in the SAP.

Utilizing visualization tools will also be used to summarize the data as deemed appropriate.

9.4.1.2. Definition of Baseline

Unless otherwise specified, all references to baseline for efficacy and health-outcome-related endpoints in this study refer to baseline values of the originating study (that is, the study in which the participant received their first dose for this program). Further details about baseline definitions along with any supportive analysis will be described in the SAP.

9.4.1.3. Estimand

The estimand (International Council for Harmonisation [ICH] 2017) associated with each endpoint/analysis is documented in the following places:

- The population of interest is described in the inclusion/exclusion criteria (Section 5.1 and Section 5.2) and in "Populations for Analyses" (Section 9.3)
- The endpoints are listed in Objectives and Endpoints (Section 3)
- The handling of intercurrent events is summarized in "Missing Data Imputation" (Section 9.4.1.4), and
- Population summary measures are described in "General Considerations" (Section 9.4.1)

Additional details will be provided in the SAP.

9.4.1.4. Missing Data Imputation

While every effort will be made to reduce missing data, the missing data imputation methods described below will be used to assess the efficacy endpoints when participants are permanently discontinued from study drug or otherwise have missing data.

- Nonresponder imputation (NRI): For analysis of categorical efficacy and health outcomes variables, missing data will be imputed using an NRI method. Participants will be considered a Nonresponder for the NRI analysis if they
    - do not achieve the endpoint(s) being analyzed
    - have missing data at the time point of interest that results in nonassessment of (an) endpoint(s) at the time point of interest, or
    - discontinue treatment prior to the time point of interest due to reasons other than participants switching to commercially available mirikizumab or extraordinary circumstances, e.g., inability to supply study drug to a particular region
- Mixed-model for repeated measures: For continuous variables, the analysis may include the MMRM with the missing-at-random assumption for handling missing data. This analysis takes into account both missingness of data and the correlation of the repeated measurements. Additional details will be provided in the SAP.
- Modified Baseline Observation Carried Forward with ANCOVA: For continuous variables, single imputation will be used based on carrying the baseline observation forward. Additional details will be provided in the SAP.

Additional details and sensitivity analyses, including imputed and observed data, will be specified in the SAP.

Methodology to address missing data due to participants switching to commercially available mirikizumab or extraordinary circumstances, e.g., inability to supply study drug to a particular region, will be addressed in the SAP.

9.4.1.5. Multiple Comparisons/Multiplicity

The data analyses and summaries will not include hypotheses testing, so no multiple comparisons adjustments will be considered for this open-label study.

9.4.2. Treatment Group Comparability

9.4.2.1. Participant Disposition

The number of participants in the mITT/PAS population will be summarized for each originating study by AMAX study intervention and by the intervention assigned in the originating study. Frequency counts and percentages of all participants who complete the study or who discontinue the study or treatment intervention early will be presented. Reasons for early discontinuation of the study intervention or of the study will be summarized.

9.4.2.2. Participant Characteristics

Demographic and baseline characteristics will be summarized by intervention group and by the intervention in the originating study for the mITT population and primary analysis set; no testing will be performed for baseline characteristics.

9.4.2.3. Concomitant Therapy

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

9.4.2.4. Treatment Compliance

Deviations from the prescribed dosage regimen will be described in a patient listing. Additional details will be described in the SAP.

9.4.3. Efficacy Analyses

9.4.3.1. Primary Efficacy Analyses

Primary efficacy analyses will be performed in the primary analysis set CCI [redacted]

The co-primary objective is in participants who completed treatment CCI [redacted] Study AMAM and is comprised of two separate endpoints:

- Proportion of participants achieving clinical remission by CDAI at Week 52 of AMAX
- Proportion of participants achieving endoscopic response at Week 52 of AMAX

Clinical remission by CDAI is defined as CCI [redacted] where CDAI is calculated as a weighted sum of its 8 subscores: 3 patient-reported and 5 physician-reported/laboratory items.

Endoscopic response is defined CCI [redacted] where the SES-CD Total Score will be calculated as the sum of its 5 subscores: ileum; right colon, transverse colon, left colon, and rectum. If at least 1 subscore is nonmissing, missing subscores will be imputed with a zero value when deriving the SES-CD Total Score.

The proportion of responders with associated confidence intervals will be provided following the methods specified in Section 9.4.1.1.

9.4.3.2. Secondary Efficacy Analyses

The secondary endpoints are specified in Section 3.

Secondary endpoints will be analyzed following the methods described in Section 9.4.1.1. 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.

9.4.4. Safety Analyses

Safety endpoints are better assessed in the context of combining the safety data from the originating study with the safety data from this study. All safety data from this study will be used as part of integrated summaries.

For the purposes of the CSR for Study AMAX alone, a listing and summary of SAEs and AEs leading to permanent discontinuation of study intervention will be created.

The primary safety objective of the study is to accumulate long-term safety data for inclusion in integrated assessments of mirikizumab.

Safety analyses will be performed in the safety population.

The safety data from this study will also be used as part of ongoing safety reviews.

9.4.5. Pharmacokinetic Analyses

Analyses of PK data will be limited to graphical or tabular summaries of mirikizumab concentrations. No model-based analyses of the data are planned unless deemed necessary based on unanswered questions raised in preceding studies. Exploratory evaluations of the relationships between mirikizumab exposure and efficacy and safety may be performed.

Additional analyses may be conducted if they are deemed appropriate. Data from this study may be combined with other study data, if appropriate. Further details on PK analyses will be provided in the PK analysis plan.

9.4.6. Evaluation of Immunogenicity

Immunogenicity will be evaluated cumulatively, using data both from the participant's originating study and from the present study. Baseline for ADA assessment will be the baseline ADA assessment from the originating study, and postbaseline will be time after initiation of mirikizumab.

The frequency and percentage of participants with pre-existing (baseline) ADA, ADA postbaseline, and with TE ADA to mirikizumab will be tabulated. If no ADAs are detected at baseline, TE ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution of the assay. For samples with ADAs detected at baseline, TE ADAs are defined as those with a 4-fold (2 dilutions) increase in titer compared to baseline. For participants who have TE ADAs, the distribution of maximum titers will be described.

The frequency of neutralizing antibodies will also be tabulated. The relationship between the presence of antibodies and the PK parameters and pharmacodynamic response, including safety and efficacy to mirikizumab, will be assessed as deemed appropriate.

9.4.7. Other Analyses

9.4.7.1. Health Economics

The health outcome and quality of life measures, including CCI [redacted] CCI [redacted] and IBDQ, will be analyzed using methods described for continuous data as described for efficacy measures in Section 9.4.1.1.

9.5. Interim Analyses

Since this study is open-label, any permanent data snapshot or database lock will not require unblinding. PK, immunogenicity, biomarker, and hypersensitivity values taken prior to Week 12 for AMAM originating participants are blinded in data transfer before AMAM primary endpoint database lock. Details can be found in the Blinding and Unblinding Plan.

At least 1 interim analysis is planned to be conducted CCI [redacted] Additional interim analyses may be performed as deemed appropriate or to fulfill the need of regulatory interactions or publication purposes. The final database lock will occur after the last participant has completed Study AMAX.

Additionally, a DMC consisting of members external to Lilly will be established for interim safety monitoring across all the sponsor's Phase 3 studies in participants with CD. See Section 10.1.5 for more information.

9.6. Data Monitoring Committee

For details on the DMC, refer to Section 10.1.5.

A DMC consisting of members external to Lilly will be established for interim safety monitoring across all the sponsor's Phase 3 studies in participants with CD. See Section 10.1.5 for more information.

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
  - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for
  - 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 to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity.
- Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study to the participant or his or her legally authorized representative, explain the risks and benefits of participating in the study, and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant participated in any study procedure or received the investigational intervention. The statement must include the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF(s).
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of each ICF must be provided to the participant or the participant's legally authorized representative. A copy of each ICF is kept on file.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor to protect the participant's personal data. Any participant information, such as records, datasets, or tissue samples that are transferred to the sponsor will contain the identifier only. Participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent. This is done by the site personnel through the informed consent process.
- The participant must be informed through the informed consent by the site personnel that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The sponsor has processes in place to ensure information security, data integrity, and data protection. These processes address management of data transfer, and prevention and management of unauthorized access, disclosure, dissemination, alteration or loss of information or personal data. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.
- The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. The sponsor's processes are compliant with local privacy laws and relevant legislations, including the General Data Protection Regulation.

10.1.5. Committees Structure

CCI [redacted]

DMC

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

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

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

10.1.6. 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.

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

Data

The sponsor provides access to all individual participant data collected during the trial, after anonymization, with the exception of PK data.

Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available.

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement.

Data and documents, including the study protocol, SAP, CSR, and blank or annotated 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.vivli.org.

Publications

For policies on publications, see Section 10.1.10.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important excursions from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues, and monitoring techniques are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (for example, contract research organizations).

- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement (CTA) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

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

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

Additionally, clinical outcome assessment data (participant-focused outcome instrument) will be collected by the participant and investigator site personnel via a paper source document and will be transcribed by the investigator site personnel into the EDC system. See the SoA, Section 1.3, for which instruments are administered via paper source document.

Additionally, electronic Clinical Outcome Assessment (eCOA) data (participant-focused outcome instrument) will be directly recorded by the participant and investigator site personnel into an instrument (for example, handheld smart phone or tablet). The eCOA data will serve as the source documentation and the investigator does not maintain a separate written or electronic record of these data. See the SoA, Section 1.3, for which instruments are administered via an eCOA instrument.

Data collected via the sponsor-provided data capture system(s) will be stored at third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). Prior to decommissioning, the investigator will receive 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 reports/electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

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

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF 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.
- The definition of what constitutes source data can be found in Section 10.1.7.

10.1.9. Study and Site Start and Closure

Study start

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

First act of recruitment

The first act of recruitment is the opening of the first site.

Study or site termination

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator, or
- Total number of participants enrolled earlier than expected.

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

10.1.10. Publication Policy

In accordance with the sponsor's publication policy, the results of this study will be submitted for publication by a peer-reviewed journal.

10.1.11. Investigator Information

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

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed below will be performed by the central or local laboratory (see the SoA, Section 1.3).
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Urine pregnancy testing will be local prior to dosing. If a urine pregnancy test is not available, a local serum pregnancy test is an acceptable alternative. Between visits, urine pregnancy tests are to be performed prior to monthly home dosing (see Section 8.2.7.1).

Investigators must document their review of each laboratory safety report.

Laboratory and/or analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel.

Clinical Laboratory Tests	**Comments**
Clinical Chemistry	Assayed by Lilly-designated laboratory.
Sodium	
Potassium	
Chloride	
Bicarbonate	
Total bilirubin	
Direct bilirubin	
ALP	
ALT	
AST	
GGT	
BUN	
Creatinine	
CK	
Uric acid	
Total protein	
Albumin	
Calcium	
Glucose	Random
Glucose	Fasting
Cholesterol	
Triglycerides	
Hematology	Assayed by Lilly-designated laboratory.
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs)	

Clinical Laboratory Tests	Comments
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Leukocytes (WBCs)	
Absolute neutrophil count (segmented and bands) (calculated)	
Absolute count of:	
Neutrophils, segmented	
Neutrophils, bands (if detected)	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology	
Reticulocyte count	
Lipid Panel	Assayed by Lilly-designated laboratory. Participant should not eat or drink anything except water for 12 hours before the test.
HDL-C	
LDL-C	
Urinalysis	Assayed by Lilly-designated laboratory.
Specific gravity	
pH	
Protein	
Glucose	
Ketones	
Bilirubin	
Urobilinogen	
Blood	
Nitrite	
Urine leukocyte esterase	
Microscopic examination of sediment	
Hormones (Female)	
Pregnancy test (serum)	Optional - Evaluated locally.
Pregnancy test (urine)	Evaluated locally.
FSH	Assayed by Lilly-designated laboratory. Optional, performed as needed to confirm participant's postmenopausal status.
Serology	Assayed by Lilly-designated laboratory.
TB testing:	See the protocol (Section 8.2.6) for more information about TB testing.

Clinical Laboratory Tests	Comments
QuantiFERON-TB Gold test	Assayed by Lilly-designated laboratory OR locally.
T-SPOT or TST	Evaluated locally.
HIV testing	Assayed by Lilly-designated laboratory.
HCV testing:	Assayed by Lilly-designated laboratory. Will be confirmed with an additional testing method.
HCV antibody	
Hepatitis C RNA PCR	Participants with a previous diagnosis of hepatitis C who have been treated with antiviral therapy and achieved a sustained virologic response may be eligible for inclusion in the study, provided they have no detectable HCV RNA at study entry. 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.
HBV testing:	Assayed by Lilly-designated laboratory.
HBV DNA	Performed only for participants who test positive for HBcAb.
HBcAb	
HBsAg	
PK Samples – LY3074828 concentration	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Stool Sample	
Stool culture	
Clostridium difficile testing	*C. difficile* Toxins A and B, and GDH, with reflex Toxin PCR.
Biomarkers	Assayed by Lilly-designated laboratory. Results from samples taken prior to AMAX Week 12 will not be provided to the investigative sites until AMAM database lock or later.
CCI	
Fecal calprotectin	
Immunogenicity Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Anti-LY3074828 antibodies	
Anti-LY3074828 antibodies neutralization	
Hypersensitivity Tests	Selected test should be obtained in the event of anaphylaxis, systemic allergic/hypersensitivity reactions, or severe/generalized non-systemic hypersensitivity reactions involving a single organ system (Section 6.7). Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Anti-LY antibodies (Immunogenicity)	
LY Concentrations (PK)	
Tryptase	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; HBcAb = hepatitis B core antibody; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; FSH = follicle-stimulating hormone; GDH = glutamate dehydrogenase; GGT = gamma-glutamyl transferase; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HDL-C = high-density lipoprotein-cholesterol; HIV = human immunodeficiency virus; CCI [redacted]; LDL-C = low-density lipoprotein-cholesterol; PCR = polymerase chain reaction ; PK = pharmacokinetic; RBC = red blood cell; TB = tuberculosis; TST = tuberculin skin test; WBC = white blood cell.

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

10.3.1. Definition of AE

10.3.1.1. AE Definition

- An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

  Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

10.3.1.2. Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, or vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae.

10.3.1.3. Events Not Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

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

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in Death

b. Is Life-Threatening

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

c. Requires Inpatient Hospitalization or Prolongation of Existing Hospitalization

- In general, hospitalization signifies that the participant has been admitted to the hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline of the originating study is not considered an AE.

d. Results in Persistent Disability/Incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a Congenital Anomaly/Birth Defect or Other Abnormal Pregnancy Outcome

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

f. Other Situations:

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

10.3.3. Definition of Product Complaints

See Section 8.3.8.

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

10.3.4.1. AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to sponsor or designee in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

10.3.4.2. Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

10.3.4.3. Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information for marketed products in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.3.4.4. Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor or designee, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.

10.3.5. Reporting of SAEs

Note that pregnancies (during maternal or paternal exposure to investigational product) are also reported using the SAE reporting process for tracking purposes (even though pregnancy is not considered an AE/SAE as described in Section 8.3.1). Refer to Section 8.3.4 for regulatory reporting requirements for SAEs.

10.3.5.1. SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone.
- Contacts for SAE reporting can be found in site training documents.

10.3.5.2. SAE Reporting via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

Contacts for SAE reporting can be found in site training documents.

10.4. Appendix 4: Liver Safety: Suggested Actions and Follow-Up Assessments

Hepatic Evaluation Testing

CCI [redacted]

The Lilly-designated central laboratory should complete the analysis of all selected testing except when testing is required at an increased frequency and a local laboratory must be used for feasibility for the patient (with sponsor approval) CCI [redacted], or for testing listed in the investigator-designated local laboratory table. The central laboratory will report results if a validated test or calculation is available.

Notes for the use of local labs:

- The local laboratory must be qualified in accordance with applicable local regulations.
- Site personnel should update documentation per local requirements and sponsor guidance.
- Assay results and reference ranges should be collected and documented as per sponsor guidance.

Local testing may also be performed *in addition to central testing* when necessary for immediate participant management.

Tests assayed by Lilly-designated central laboratory	
Hepatic Hematology Panel	**Hepatitis A virus (HAV) testing**
Hemoglobin	HAV total antibody
Hematocrit	HAV IgM antibody
Erythrocytes (RBCs - red blood cells)	**Hepatitis B virus (HBV) testing**
Leukocytes (WBCs - white blood cells)	Hepatitis B surface antigen (HBsAg)
Differential:	Hepatitis B surface antibody (anti-HBs)
Neutrophils, segmented	Hepatitis B core total antibody (anti-HBc)
Lymphocytes	Hepatitis B core IgM antibody
Monocytes	Hepatitis B core IgG antibody
Basophils	HBV DNA [b]
Eosinophils	**Hepatitis C virus (HCV) testing**
Platelets	HCV antibody
Cell morphology (RBC and WBC)	HCV RNA [b]
Hepatic Clinical Chemistry Panel	**Hepatitis D virus (HDV) testing**
Total bilirubin	HDV antibody
Direct bilirubin	**Hepatitis E virus (HEV) testing**
Alkaline phosphatase (ALP)	HEV IgG antibody
Alanine aminotransferase (ALT)	HEV IgM antibody
Aspartate aminotransferase (AST)	HEV RNA [b]

Gamma-glutamyl transferase (GGT)	**Anti-nuclear antibody (ANA)**
Creatine kinase (CK)	**Anti-smooth muscle antibody (ASMA)** [a]
Hepatic Coagulation Panel	**Anti-actin antibody** [c]
Prothrombin time, INR (PT-INR)	**Immunoglobulin IgA (quantitative)**
Urine Chemistry	**Immunoglobulin IgG (quantitative)**
Drug screen	**Immunoglobulin IgM (quantitative)**
Haptoglobin	**Epstein-Barr virus (EBV) testing**
	EBV antibody
Tests assayed ONLY by investigator-designated local laboratory	
Acetaminophen	**Epstein-Barr virus (EBV) testing**
Acetaminophen protein adducts	EBV DNA [b]
Alkaline phosphatase isoenzymes	**Cytomegalovirus (CMV) testing:**
Ceruloplasmin	CMV antibody
Copper	CMV DNA [b]
Ethyl alcohol (EtOH)	**Herpes simplex virus (HSV) testing:**
	HSV (Type 1 and 2) antibody
	HSV (Type 1 and 2) DNA [b]
	Liver kidney microsomal type 1 (LKM-1)
	Microbiology
Phosphatidylethanol (PEth)	Culture:
Urine Chemistry	Blood
Ethyl glucuronide (EtG)	Urine

[a] Not required if anti-actin antibody is tested.

[b] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

[c] Not required if anti-smooth muscle antibody (ASMA) is tested.

CCI [redacted]

10.5. Appendix 5: Risk Factors for Latent Tuberculosis Infection

Risk Factors for 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, IV drug use

Abbreviations: IV = intravenous; LTBI = latent tuberculosis infection.
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
IV drug use
Weight ≥10% below normal
Smoking

Abbreviations: HIV = human immunodeficiency virus; IV = intravenous; LTBI = latent tuberculosis infection; TB = tuberculosis; TNF = tumor necrosis factor.
Source: Adapted from Horsburgh and Rubin 2011.

WHO 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

Abbreviation: WHO = World Health Organization.
Source: WHO 2015.

10.6. Appendix 6: 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
TB
Non-TB 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
HBV reactivation
HCV progression
Herpes simplex (invasive disease only)
Herpes zoster (any form)
Posttransplant lymphoproliferative disorder (Epstein-Barr virus)
PML, 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*

Parasitic
Leishmaniasis (visceral only)
Strongyloidosis (hyperinfection syndrome or disseminated disease)
Microsporidiosis
Toxoplasmosis
Trypanosoma cruzi infection (Chagas' disease progression) (disseminated disease only)
Cryptosporidiosis (chronic disease only)

Abbreviations: HBV = hepatitis B virus; HCV = hepatitis C virus; JC = John Cunningham; PML = progressive multifocal leukoencephalopathy; TB = tuberculosis.
Source: Adapted from Winthrop et al. 2015.

10.7. Appendix 7: Prohibited Medications

This section outlines medications that are prohibited during both the originator studies and the AMAX study. 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
The following medications are prohibited throughout duration of study:	
Anti-TNF antibodies (for example, infliximab, adalimumab, or certolizumab pegol)	Prohibited throughout duration of study.
Anti-integrin antibodies:	
Natalizumab	Prohibited throughout duration of study.
Other anti-integrin antibodies (for example, vedolizumab)	Prohibited throughout duration of study.
Agents depleting B or T cells (for example, rituximab, alemtuzumab, or visilizumab)	Prohibited throughout duration of study.
Immunomodulatory medications, including oral cyclosporine, IV cyclosporine, tacrolimus, mycophenolate mofetil, thalidomide, or JAK inhibitors (other than topical)	Prohibited throughout duration of study.
Rectally administered 5-ASA therapies (enemas or suppositories)	Prohibited throughout duration of study.
Rectally administered corticosteroids (enemas or suppositories)	Prohibited throughout duration of study.
Corticosteroids	A course of IV corticosteroids is prohibited throughout duration of study, except for use as premedication for infusion or for short-term treatment of acute non-CD events (for example, allergic reactions). IV corticosteroids used for CD may result in discontinuation, therefore consult your medical monitor. From Week 0 to Week 12, initiation or adjustment of systemic corticosteroids for non-CD indications is prohibited unless needed due to AEs or for appropriate medical management. After Week 12, participants may transiently initiate or increase doses (that is, for <4 weeks) of corticosteroids for reasons other than loss of response to treatment for CD (for example, premedication for infusions, and stress doses of corticosteroids for surgery, asthma, and allergic reaction). Locally administered corticosteroids (for example, inhaled, intranasal, intra-articular, or topical) are allowed. Systemic corticosteroid use is allowed for adrenocortical insufficiency (Section 6.5 and 6.7.1).
Any investigational therapy (biologic or nonbiologic)	Prohibited throughout duration of study.
Interferon therapy	Prohibited unless medically necessary for short-term COVID treatment

Drug Class	Guidance for Use
Leukocyte apheresis (leukapheresis, for example, Adacolumn)	Prohibited throughout duration of study.
Anti-IL-23p19 antibodies (for example, risankizumab [BI-655066], brazikumab [MEDI-2070], guselkumab [CNTO1959], or tildrakizumab [MK-3222]) for any indication, including investigational use	Prohibited throughout duration of study.
Anti-IL 12/23p40 antibodies (for example, ustekinumab)	Prohibited throughout duration of study.
BCG vaccine	BCG vaccination prohibited throughout the duration of the study and for 12 months after discontinuation of study drug.
Live attenuated vaccines	Live attenuated vaccines are prohibited throughout the duration of the study and for 3 months after discontinuation of study drug.
Medicinal and recreational marijuana (includes CBD Oil)	Marijuana use is prohibited through the end of the long-term extension period of the study. If use is identified prior to this time, it may result in discontinuation, consult the medical monitor.

Abbreviations: 5-ASA = 5-aminosalicyclic acid; AE = adverse event; BCG = Bacillus Calmette Guerin; CBD = cannabidiol; CD = Crohn's disease; COVID = coronavirus disease; IL = interleukin; IM = intramuscular; IV = intravenous; JAK = Janus kinase; TNF = tumor necrosis factor.

10.8. Appendix 8: Permitted Medications with Dose Stabilization

Drug Class	Guidance for Use
Oral 5-ASAs (for example, mesalamine, balsalazide, or olsalazine)	Prescribed dose should remain stable for the duration of the study unless modifications are needed due to AEs or for appropriate medical management.
Oral corticosteroids (prednisone ≤30 mg/day or equivalent or budesonide 9 mg/day)	Prescribed dose should remain stable until Week 12 unless modifications are needed due to medical necessity. After Week 12, see Section 6.5.3. If doses above 30 mg/day are felt to be necessary, please consult sponsor.
Immunomodulators (for example, AZA, 6-MP, or methotrexate)	Doses should remain stable throughout study unless medication is discontinued due to a toxicity related to the medication or modifications are needed due to AEs or for appropriate medical management.
Antibiotics being used specifically for the treatment of CD (for example: rifaximin or Cipro)	Prescribed dose must remain stable for the duration of the study unless modifications are needed due to AEs or for appropriate medical management.
Antidiarrheals (for example, loperamide or diphenoxylate with atropine)	May continue during study with stable doses encouraged.
Low-dose or baby aspirin (75 mg to 162.5 mg)	Daily use for cardiovascular prophylaxis permitted.
Nonlive (killed, inactivated, or subunit) vaccines (including RNA-based)	Allowed during the study. Must be reported as concomitant medications, and the verbatim for any associated adverse events should note the relationship to vaccination. The efficacy of nonlive vaccinations with concomitant mirikizumab treatment is unknown.

Abbreviations: 5-ASA = 5-aminosalicyclic acid; 6-MP = 6-mercaptopurine; AE = adverse event; AZA = azathioprine; CD = Crohn's disease.

10.9. Appendix 9: Patient-Reported Outcome Instruments

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

Daily Diary (eDiary/Paper Diary – including 1-Day and 14-Day)	Paper Questionnaires[a]
CCI	CCI
CDAI-SF/Bristol Stool Scale (Reference to Types 6 & 7)	
CDAI-AP	IBDQ
CDAI-well-being	CCI
CCI	

Abbreviations: AP = abdominal pain; CCI ; CDAI = Crohn's Disease Activity Index; CDAI-AP = Crohn's Disease Activity Index – Abdominal Pain; CDAI-SF = Crohn's Disease Activity Index – Stool Frequency; CCI IBDQ = Inflammatory Bowel Disease Questionnaire; CCI CCI CCI SF = stool frequency; CCI

[a] Not including 1-Day or 14-Day paper diary.

CCI

The following are descriptions of additional PRO instruments for this study, using Patient eDiary and/or paper diary and paper questionnaire (listed in order of administration).

CCI

CDAI-(SF, AP: abdominal pain, 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=slightly under par, 2=poor, 3=very poor, 4=terrible).

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.

CCI

CCI

IBDQ: A 32-item patient-completed questionnaire that measures 4 aspects of patients' lives: symptoms directly related to the primary bowel disturbance, systemic symptoms, emotional function, and social function (Guyatt et al.1989; Irvine et al. 1994; Irvine et al. 1996). Responses are graded on a 7-point Likert scale in which 7 denotes "not a problem at all" and 1 denotes "a very severe problem." Scores range from 32 to 224; a higher score indicates a better quality of life. In general, patients in symptomatic remission have an IBDQ score ≥170 (Irvine 2008).

CCI


CCI


CCI

10.11. Appendix 11: Abbreviations and Definitions

Term	Definition
abuse	use for recreational purposes or to maintain an addiction or dependence
ADA	antidrug antibody
ADR	adverse drug reaction
AE	adverse event: Any untoward medical occurrence in a participant or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AP	abdominal pain
AST	aspartate aminotransferase
BCG	Bacillus Calmette Guerin
CCI	[redacted]
CBD	cannabidiol
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
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CMV	cytomegalovirus
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice, and applicable regulatory requirements.
CRF/eCRF	case report form/electronic case report form designed to record protocol-required information to be reported to the sponsor for each trial participant
CSR	clinical study report
CCI	[redacted]
CT	computed tomography
CXR	chest x-ray
D. Bil	direct bilirubin
DMC	data monitoring committee. A data monitoring committee or data monitoring board is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention and to make recommendations to the sponsor regarding the stopping of a study for efficacy, harms, or futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
ECAV	extended continued access visits

Term	Definition
ECG	electrocardiogram
eCOA	electronic Clinical Outcome Assessment
EDC	electronic data capture
CCI	[redacted]
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
CCI	[redacted]
ERCP	endoscopic retrograde cholangiopancreatography
ET	early termination
ETV	early termination visit
CCI	[redacted]
GCP	good clinical practice
GGT	gamma-glutamyltransferase
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDV	hepatitis D virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IGRA	interferon gamma release assay
IL	interleukin
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
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, marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	Institutional Review Board
ITT	intent-to-treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participants allocated to a treatment group should be followed up, assessed, and analyzed as members of that group, irrespective of their compliance to the planned course of treatment.
IV	intravenous/intravenously
LTBI	latent tuberculosis infection
mITT	modified intent-to-treat
MMRM	mixed-effects model for repeated measures
MRCP	magnetic resonance cholangiopancreatography
NOAEL	no-observed-adverse-effect level

Term	Definition
NRI	nonresponder imputation
CCI	[redacted]
participant	Equivalent to Clinical Data Interchange Standards Consortium term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control.
CCI [redacted]	[redacted]
PK	pharmacokinetic(s)
PRO	patient-reported outcome
PT	prothrombin time
CCI [redacted]	[redacted]
SAC	statistical analysis center
SAE	serious adverse event
SAP	statistical analysis plan
SDALs	study drug administration logs
CCI [redacted]	[redacted]
SC	subcutaneous/subcutaneously
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.
SERMs	selective estrogen receptor modulators
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF	stool frequency
SoA	Schedule of Activities
SUSARs	suspected unexpected serious adverse reactions
TB	tuberculosis
TBL	total bilirubin level
TE	treatment-emergent
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TNF	tumor necrosis factor
TST	tuberculin skin test
UC	ulcerative colitis
ULN	upper limit of normal
WHO	World Health Organization
WNOCBP	women not of childbearing potential
WOCBP	women of childbearing potential
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 requirements in which notification is required (for example, upon implementation and suspension of changes). All approvals and notifications must be retained in the study records.

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

Considerations for making a change

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

Informed consent

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

- participation in remote visits, as defined in Section "Remote visits" below,
- 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 and will be determined by the sponsor in accordance with applicable local regulations.

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.

Types of remote visits

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
- Review of diary compliance
- Questionnaires will be collected by verbal reporting from the participant to the site for entry on paper, and then entry into the eCRF.
- Product complaint (if applicable)
- Verification of negative pregnancy test (if applicable)
- Status/observation of self-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 may include, but are not limited to:

- Coordination of signature needed for study documents
- Concomitant medication reviews
- Tobacco/nicotine use
- AE collection
- Vital signs (T, PR, BP), weight
- Laboratory collection (including stool collections)
- Review of diary compliance
- Coordinate questionnaire administration (must be collected by site via telemedicine, see section above)
- Dosing (SC only)
- Study drug self-administration training

- Delivery of required ancillary supplies or IP product for self-administration
- Urine pregnancy test (as applicable)

The below procedures also may be performed, but may require additional qualifications and sponsor approval:

- Physical exam
- CCI
- CCI
- Clinician CDAI
- 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. In instances where an alternate 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 IP, or SC injection of IP by a trained healthcare professional.

- Alternate facilities for central or local laboratory sample collection. Where available, participants should utilize laboratory facilities affiliated with the study's central laboratory vendor.

Data capture

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.

Safety reporting

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and product complaints remain unchanged.

Return to on-site visits

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.

Local laboratory testing option

- Local laboratory testing may be conducted in lieu of central laboratory testing for safety labs including chemistry, hematology, and HBV DNA. Local laboratories may also be used for HBV serology, HCV, and HIV testing and for urinalysis. However, only central laboratory testing should be used for CCI PK, immunogenicity, hypersensitivity tests, fecal calprotectin, CCI to support endpoints. The local laboratory must be qualified in accordance with applicable local regulations. Site personnel should update documentation per local requirements and sponsor guidance. Assay results and reference ranges should be collected and documented as per sponsor guidance. Investigators must document their review of each laboratory safety result 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 locally if needed. Local laboratory collections will be used for immediate patient management and safety but will not be included in the data for analysis, except for hematocrit which may be included at key timepoints as needed to calculate CDAI if central lab results are not available. (Local labs may also be used for follow-up monitoring of hepatic lab abnormalities as described in Section 8.2.10, and in this case may be included in hepatic safety analyses.) See information related to local laboratory testing options below.

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 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, or by self-administration of SC injections after appropriate training.
    - Dosing can proceed only if central or local safety labs have been performed within 14 weeks (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 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 1 hour or longer after IV dosing, according to investigator practice or local standard of care.
- Adherence to the detailed instructions for investigational product administration, including infusion rate and SC injections, provided by the sponsor must continue to be followed. Maintain accurate records of study drug dispensing and collection.
- Site staff will document the IP package numbers that are dispensed and shipped for home administration on the Study Drug Administration Log.
    - Participants will complete Study Drug Administration Logs to document the doses administered and return this documentation to the site at the next on-site visit.
    - Instruct participants to retain sharps container with used IP, as well as any unused IP in order to return to the site at the next on-site visit.
- For doses intended to be performed at the office according to the SoA, the site staff will reassess the ability of the participant to receive study drug in office for the next scheduled visit before a subsequent dose will be shipped to the participant's home.
- All unused medication must be returned to Lilly or its designee unless the sponsor and sites have agreed unused medication is to be destroyed by the site, as allowed by local law.

Concomitant therapy

Steroid Tapering: During the first 12 weeks of the study, the principal investigator should use clinical judgement of the benefit/risk of tapering for each individual participant, and consider Gastrointestinal Society guidance, to determine if corticosteroid dosage adjustment is indicated for their patients during the exceptional circumstances. If the investigator believes steroid tapering is in the best interest of the study participant, dosages above 15 mg of prednisone (or equivalent) may be reduced to a dose of 15 mg CCI [redacted] following the recommended tapering regimen in the protocol, per local practice, or per Gastrointestinal Society guidance. After Week 12, see Section 6.5.3.

Use of prohibited medications in exceptional circumstances, and continuation in the study, should be discussed with your medical monitor.

Screening period guidance

To ensure safety of study participants, screening laboratory values and other eligibility assessments are valid for a maximum of CCI . In exceptional circumstances, if one or more screening laboratory assessments cannot be performed at AMAM Visit 17 (for AMAM-originating participants) or at AMAX Visit 1, if valid results had been obtained for other visits/purposes for that assessment within CCI prior to AMAX first dosing, those results can be used to confirm eligibility. This situation must be reported to the sponsor, and that assessment must be performed again as soon as it is available and could result in discontinuation if the delay raises safety concerns. The following rules will be applied for consented rollover participants prior to receiving the first dose in AMAX whose participation in the study must be paused due to exceptional circumstances:

- An extension from CCI for the maximum dosing interval between last dose in the originator trial (AMAG or AMAM) and the first dose in AMAX may be allowed (for example but not limited to, due to prolonged turnaround time for screening labs, endoscopy suite backlogs for participants originating from AMAM needing AMAM Week 52 endoscopy, and site closure and inability to dose). The total screening window may also be extended as needed, but must occur within the allowed interdosing interval.
    - 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 and document this confirmation in the source documentation.

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.

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 during visit window adjustments, 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 within the previous CCI (or within a shorter timeframe for participants with previous abnormal lab results, as medically indicated). 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 AMAX.10-1 for additional details.

Visits 1 through 3

- Extending the visit window to the beginning of the next visit window will be allowed. If the patient visit exceeds the extended window, the visit must occur at the earliest opportunity.
- Timeframes for future participant visits must be adjusted to bring the participant back into compliance with the protocol defined visit windows, while keeping all doses at least CCI apart.
- Sites should remind AMAM-originating participants to continue to record all daily eDiary data through Visit 4.

Visit 4 through end of trial

- Beginning with Visit 4, at which self-administration may begin, the visit window may extend to the beginning of the next *dosing* window. If the participant visit exceeds the extended window, the visit must occur at the earliest opportunity.
- Timeframes for future participant visits and self-administration of dosing, where applicable, must be adjusted to bring the participant back into compliance with the protocol defined visit windows, while keeping all doses at least CCI apart.

Throughout trial

- A urine pregnancy test (if applicable) must be obtained prior to each IP administration.
- If a 14-Day paper diary is in use and the subsequent visit is delayed, the participant should continue to record the daily data, even beyond 14 days, until the next visit occurs (guidance will be provided for ensuring sufficient forms are available).
- Note: Per protocol, participants who miss CCI must be considered for ET.

Endoscopies

- For CCI, the window for the CCI If the CCI cannot be performed within the extended window, the CCI should be performed as soon as possible.
- For CCI, if the AMAX Week 52 CCI endoscopy cannot be performed within the extended V9 window, the site should still perform all other assessments and may continue with dosing. The Week 52 endoscopy should be performed as soon as possible. At the time of the endoscopy, an unscheduled fecal-calprotectin stool sample should be collected.
- If the CCI endoscopy cannot be performed within the extended CCI window, the site should still perform all other assessments. The CCI should be performed as soon as possible. At the time of the endoscopy, an unscheduled fecal-calprotectin stool sample should be collected.

- The overall length of exposure will not be extended for this trial.

Posttreatment Follow-Up Visits 801 and 802

- Visit 801: Visit window may be extended up to 2 weeks earlier or less than 12 weeks from the last visit (LV) or ETV (LV/ETV + 2 weeks to <12 weeks).
- Visit 802: Visit window may be extended up to 4 weeks earlier (provided Visit 802 is at least 4 weeks from Visit 801) or 8 weeks later than the protocol visit date (LV/ETV + 8 weeks to 24 weeks). 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, visits, 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 "Adjustments to visit windows" above for further details. There must be a minimum of CCI between study drug doses.

Table AMAX.10-1 Extended Visit Windows for Exceptional Circumstances

Study Visit/ Dose[a]	Study Week	Protocol Specified Day	Protocol Specified Visit Tolerance Interval	Mitigation Extension of Visit Interval Tolerance	Mitigation Study Day Range	Notes
V1	CCI	CCI	Total interval from last dose in the originating study to first dose in AMAX is no more than CCI	Total interval from last dose in the originating study to first dose in AMAX is no more than CCI	CCI	V1 is a split visit. V1 dosing is defined as Day 1. Most other V1 activities may be erformed in prior days and must be ompleted prior to dosing.
V2			±7 days	-7 to +20 days		
V3			±7 days	-7 to +20 days		When AMAG-originating participants are rovided the 14-Day paper diaries to omplete prior to their next visit, additional opies should be provided in case the visit may need to move out. In that situation, the articipant should continue to record the daily ata, even beyond 14 days, until the actual ext visit occurs.
V4 Phone			At least 15 days prior to actual next visit date	At least 15 days prior to actual next visit date		Phone reminder must occur at least 15 days rior to intended next visit to ensure ollection of 14-Day diary data.
V4 Office			±7 days	-7 to +20 days		
CCI			±7 days	-7 to +20 days		
V5			±7 days	-7 to +20 days		
CCI			±7 days	-7 to +20 days		
V6			±7 days	-7 to +20 days		
CCI			±7 days	-7 to +20 days		
V7			±7 days	-7 to +20 days		
CCI			±7 days	-7 to +20 days		

Study Visit/ Dose[a]	Study Week	Protocol Specified Day	Protocol Specified Visit Tolerance Interval	Mitigation Extension of Visit Interval Tolerance	Mitigation Study Day Range	Notes
V8	CCI		±7 days	-7 to +20 days	CCI	When participants are provided the 14-Day paper diaries to complete prior to their next visit, additional copies should be provided in case the visit may need to move out. In that situation, the participant should continue to record the daily data, even beyond 14 days, until the actual next visit occurs.
CCI			±7 days	-7 to +20 days		
V9 Phone			At least 15 days prior to actual next visit date	At least 15 days prior to actual next visit date		Phone reminder must occur at least 15 days prior to intended next visit to ensure collection of 14-Day diary data.
V9 Office			±7 days	-7 to +20 days		CCI
CCI			±7 days	-7 to +20 days		
V10 Office			±7 days	-7 to +20 days		
CCI			±7 days	-7 to +20 days		
V11 Office			±7 days	-7 to +20 days		When participants are provided the 14-Day paper diaries to complete prior to their next visit, additional copies should be provided in case the visit may need to move out. In that situation, the participant should continue to record the daily data, even beyond 14 days, until the actual next visit occurs.
CCI			±7 days	-7 to +20 days		

Study Visit/ Dose[a]	Study Week	Protocol Specified Day	Protocol Specified Visit Tolerance Interval	Mitigation Extension of Visit Interval Tolerance	Mitigation Study Day Range	Notes
V12 Phone	CCI		At least 15 days prior to actual next visit date	At least 15 days prior to actual next visit date	CCI	Phone reminder must occur at least 15 days prior to intended next visit to ensure collection of 14-Day diary data.
V12 Office			±7 days	-7 to +20 days		
CCI			±7 days	-7 to +20 days		
CCI			±7 days	-7 to +20 days		
V13 Office			±7 days	-7 to +20 days		When participants are provided the 14-Day paper diaries to complete prior to their next visit, additional copies should be provided in case the visit may need to move out. In that situation, the participant should continue to record the daily data, even beyond 14 days, until the actual next visit occurs.
CCI			±7 days	-7 to +20 days		
CCI			±7 days	-7 to +20 days		
V14 Phone			At least 15 days prior to actual next visit date	At least 15 days prior to actual next visit date		Phone reminder must occur at least 15 days prior to intended next visit to ensure collection of 14-Day diary data.
V14 Office			±7 days	-7 to +20 days		
CCI			±7 days	-7 to +20 days		
CCI			±7 days	-7 to +20 days		
V15 Office			±7 days	-7 to +20 days		When participants are provided the 14-Day paper diaries to complete prior to their next visit, additional copies should be provided in case the visit may need to move out. In that situation, the participant should continue to record the daily data, even beyond 14 days, until the actual next visit occurs.
CCI			±7 days	-7 to +20 days		
CCI			±7 days	-7 to +20 days		

Study Visit/ Dose[a]	Study Week	Protocol Specified Day	Protocol Specified Visit Tolerance Interval	Mitigation Extension of Visit Interval Tolerance	Mitigation Study Day Range	Notes
V16 Phone	CCI		At least 15 days prior to actual next visit date	At least 15 days prior to actual next visit date	CCI	Phone reminder must occur at least 15 days prior to intended next visit to ensure collection of 14-Day diary data.
V16 Office			±7 days	-7 to +20 days		
CCI			±7 days	-7 to +20 days		
CCI			±7 days	-7 to +20 days		
V17 Office			±7 days	-7 to +20 days		
CCI			±7 days	-7 to +20 days		
CCI			±7 days	-7 to +20 days		
V18 Office			±7 days	-7 to +20 days		When participants are provided the 14-Day paper diaries to complete prior to their next visit, additional copies should be provided in case the visit may need to move out. In that situation, the participant should continue to record the daily data, even beyond 14 days, until the actual next visit occurs.
CCI			±7 days	-7 to +20 days		
V19 Phone			At least 15 days prior to actual next visit date	At least 15 days prior to actual next visit date		Phone reminder must occur at least 15 days prior to intended next visit to ensure collection of 14-Day diary data.
V19 Office			±7 days	-7 to +20 days		If the Week 156 endoscopy cannot be performed within the extended V19 window, the site should still perform all other assessments. The Week 156 endoscopy should be performed as soon as possible. At the time of the endoscopy, an unscheduled fecal-calprotectin stool sample should be collected.
V801			±10 days	LV/ETV + 2 weeks to <12 weeks		
V802				LV/ETV + 8 weeks to 24 weeks		V802 must occur at least 4 weeks after V801.

Study Visit/ Dose[a]	Study Week	Protocol Specified Day	Protocol Specified Visit Tolerance Interval	Mitigation Extension of Visit Interval Tolerance	Mitigation Study Day Range	Notes
CCI						

Abbreviations: CCI ; ETV = early termination visit; LV = last visit; V = Visit.

a If a visit occurs after the extended visit window, the visit should be conducted at the earliest possible timepoint. Future participant visits must be adjusted to bring the participant back into compliance with the protocol defined visit windows. Doses must occur at least CCI apart. See "Adjustments to Visit Windows" above for further details.

10.13. Appendix 13: Optional Continued Access Period

10.13.1. Overview

This appendix will provide optional continued access to open-label mirikizumab for eligible patients following the completion of the long-term extension period of AMAX.

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

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


CCI


CCI

10.13.3. Schedule of Activities for Continued Access Period

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

All visits

Office visits will generally occur every CCI . Self-administration of mirikizumab CCI is required, regardless if the dosing is onsite or remote (refer to Section 10.13.7 for more detail). All other visit activities should be completed prior to self-administration of mirikizumab, unless otherwise stated below.

Continued Access Treatment (Visit 501 to last dosing visit)

Visit 501 activities should occur on the same day as Visit 19 of the long-term extension period if possible. It is recommended that the Visit 19 endoscopy be performed first, on a prior date within the Visit 19 window, followed by a combined Visit 19/ Visit 501 office visit on a later day also within the Visit 19 window.

If this is not possible, the Visit 19 endoscopy can be performed on the same day as the Visit 19 office visit, with Visit 501 being performed on a later date within window. Ensure all Visit 19 activities are completed prior to starting Visit 501 activities and dosing.

If Visit 19 and Visit 501 do not occur on same day, Visit 501 activities may need to be repeated, as detailed in the continued access period SoA.

If Visit 19 and Visit 501 occur more than 2 weeks apart, the following laboratory tests must be repeated: hematology, clinical chemistry, and HBV DNA.

Extended continued access visits (ECAV)

After Visit 502 (CCI), ECAV continue until criteria for the final visit occurs (outlined in Section 10.13.8).

Onsite ECAV Visits occur every CCI

Visit numbers will be registered sequentially after Visit 502. This table provides an example of the ECAV visit structure that will continue until the final visit.

Visit Number	Visit ID	Weeks from AMAX Visit 1
502	502	CCI
ECAV	503	
ECAV	504	
ECAV	505, 506, 507…	ECAV will continue until criteria for final visit occurs

Discontinuation (DC) visit

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

Continued Access Period follow-up (4 weeks)

Visit 901

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

V901 may be performed onsite when onsite activities are required or at investigator's discretion.

Unscheduled visits

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

Procedures	AMAX Continued Access Period Schedule of Activities[a]					
Visit Number	**501**	**502**	**ECAV**	**DC**	**UV**	**V901**
Visit Type	**Office**	**Office**	**Office**	**Office**	**Office**	**Phone**
Week Relative to Study Drug Start[b]	CCI					
Visit Tolerance Interval (VTI) in days						
All Participants (X); Optional (Opt) (See footnotes for additional key details)						
Confirmation of Informed consent	X					
Inclusion and exclusion criteria	X					
Concomitant medications	X[c]	X	X	X	X	X
Tobacco/Nicotine use			X[d]			
AEs[e] (See Section 8.3)	X[c]	X	X	X	X	X
Physical Evaluation						
Vital signs (T, PR, BP) (See Section 8.2.1)	X[c]	X	X	X	X	
Weight	X[c]	X	X	X	X	
Physical examination[f] (See Section 8.2.2)	X[c]	X	X	X	X	
TB Risk Assessment Monitoring[g]	X[c]	X	X	X		
Participant Education						
Self-administration retraining	Opt[h]				Opt[h]	
Laboratory Tests						
Chemistry	X[i]	X	X	Opt	Opt	
Hematology	X[i]	X	X	Opt	Opt	
Urine pregnancy (local)[j] (See Section 8.2.7.1)	X[c]	X	X	X		X
HBV DNA monitoring[k]	X[i]	X	X	X		
Hypersensitivity kit (tryptase, PK, and immunogenicity)	X[l]					
On-Site Questionnaires (Paper)						
QIDS-SR16			X[m]	X	Opt	
CCI						

Procedures	AMAX Continued Access Period Schedule of Activities[a]					
Visit Number	501	502	ECAV	DC	UV	V901
Visit Type	Office	Office	Office	Office	Office	Phone
Week Relative to Study Drug Start[b]	CCI					
Visit Tolerance Interval (VTI) in days						
CCI						

CCI

CXR = chest x-ray; DC = discontinue; ECAV = extended continued access visits, FSH = follicle-stimulating hormone; HBcAb = hepatitis B core antibody; HBV = hepatitis B virus; IGRA = interferon gamma release assay; IP = investigational product; IWRS = Interactive Web Response Systems; PK = pharmacokinetic; PR = pulse rate; CCI); SoA = schedule of activities; T = temperature; TB = tuberculosis; TST = tuberculin skin test; UV = unscheduled visit; V = visit.

a Please see detailed instructions provided by the sponsor for calculation of visit dates. Additional AMAX SoA procedures may be performed during Continued Access at other timepoints at the investigator's discretion (for example HBV DNA monitoring, urine pregnancy tests, TB Risk Assessment Monitoring, or others). Please contact your monitor for questions.

b All activities should be completed prior to any study drug administration unless otherwise stated. ECAV visits will occur every CCI until patient meets discontinuation criteria.

c If visits 501 and V19 do not occur on the same day, these activities must be repeated

d Tobacco/Nicotine use data will be collected yearly.

e For AESIs, additional data are collected (See Section 8.3.7).

f Includes a symptom-directed evaluation as well as examination of eyes, heart, lungs, abdomen, and visual examination of the skin (Section 8.2.2).

g Throughout the study, participants will be assessed for risk factors for TB (Section 10.5, Appendix 5). If the participant has a risk factor(s) or any TB-related signs or symptoms identified as part of the discussions of AEs or as part of the standard physical exam, 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 or other factors that the investigator feels warrant testing and imaging, an IGRA or TST and CXR should be performed (Table AMAX.1-3 Unscheduled assessments). A CT scan can be performed as an alternative to the CXR based on regional standard of practice (Section 8.2.6).

h Complete at the investigator's discretion. See Section 10.13.7.

i If there are not results available from safety laboratory collections within CCI of Visit 501, these laboratory tests must be repeated and results reviewed prior to dosing.

j To be performed only on women of child-bearing potential. Done locally and prior to dosing (Section 8.2.7.1). Between visits, urine pregnancy tests are to be performed prior to monthly at-home dosing. Optional FSH may be performed as needed to confirm postmenopausal status in female participants. See Section 5.1

k Perform only if participant had ongoing monitoring for HBV DNA during the long-term extension period of Study AMAX, or for participants in the Continued Access period who were found to be HBcAb+ and meet the requirements to continue in the study as described in Section 8.2.8. Such participants will undergo monitoring of HBV DNA at specified intervals. Any participant not meeting the requirements to continue in the study at any time must be discontinued from the study and receive appropriate follow-up medical care (Section 8.2.8).

l In the event of a systemic allergic/hypersensitivity event, blood samples will be collected for PK, ADA, CCI at the following time points: as close as possible to: (1) the onset of the systemic allergic/hypersensitivity event, (2) the resolution of the systemic allergic/hypersensitivity event, CCI

m CCI to be administered every 6 months during continued access period.

n Visit procedures and assessments must be completed prior to dosing.

o Dispense study drug at each office visit CCI Changes cannot be made to dispensing and planned office visit schedules without prior sponsor approval (and potentially changes to safety lab testing schedule). Continue to dispense ancillary supplies at each visit as needed. Note that any used or unused study drug may be returned as an optional unscheduled activity at subsequent visits (see Table AMAX.1-3).

p Site to complete and dispense *Patient Study Drug Administration Log*. Provide syringes for next dosing, inform participant of dosing date for self-injection, and provide ancillary supplies to participant.

q Participant to return the *Patient Study Drug Administration Log* at the next visit.

10.13.4. Study Drug Self Administration Between Office Visits for Continued Access Period

Procedures						
Name of Visit Interval at which Study Drug Administration Occurs[a]	501a	501b	502a	502b	ECAVa	ECAVb
Week Relative to Study Drug Start	CCI					
Days Relative to Study Drug Start and Visit Interval Tolerance (Days)						
CCI						

a This table shows administration intervals between office visits. Please complete the *Patient Study Drug Administration Log*. If the participant is a woman of childbearing potential, a urine pregnancy test must be performed before dosing. Phone visits can be performed if needed to provide additional support/guidance.

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10.13.5. Overall Design

Transition of participants from the AMAX long-term extension period to optional Continued Access period

A participant will

- complete AMAX Visit 19 activities, including the Visit 19 study endoscopy with biopsies, and
- complete the Continued Access section of the main AMAX study consent form and Visit 501 activities of the Continued Access Period.
    - If a potentially eligible participant does not meet all inclusion and exclusion criteria at Visit 501, that participant should enter the posttreatment follow-up period of the main study protocol and complete Visits 801 and 802 as indicated in Section 1.3.
    - If a potentially eligible participant meets all inclusion and exclusion criteria at Visit 501, that participant should continue visits and procedures according to the SoA in Section 10.13.3

10.13.6. Study Population

The inclusion and exclusion criteria in this section are specific to this optional Continued Access Appendix, in addition to the inclusion and exclusion criteria listed in Section 5.

10.13.6.1. Inclusion Criteria

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

Informed consent

32. Have given signed informed consent to take part in the Continued Access Period prior to any procedures specific to Continued Access Period being completed.

Participant and disease characteristics

33. Have completed the AMAX long-term extension period, including
    - Visit 19 activities, including the CCI [redacted] with biopsies without early termination of mirikizumab in main AMAX study, and
    - in the opinion of the investigator, would continue to derive benefit from treatment with mirikizumab.
34. Have the ability to complete Visit 501, including the first dose of mirikizumab of the Continued Access Period, on the same day as Visit 19, or within approximately CCI [redacted] after Visit 19.
    - It is strongly recommended that no more than CCI [redacted] occur between the last dose in the long-term extension period CCI [redacted] and the Visit 501 dosing of the Continued Access Period. Participants requiring a longer duration for entry into the Continued Access

Period, but not to exceed approximately CCI , must be discussed on an individual basis with the medical monitor.

35. Are willing and able to complete the SoA for the Continued Access Period, including self-administration of mirikizumab (by participant or caregiver). Also, in the opinion of the investigator, are able to reliably perform remote, self-administration procedures, and related required documentation.

10.13.6.2. Exclusion Criteria

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

Gastrointestinal exclusion criteria

36. Had a reported AE or SAE in the long-term extension period prior to Visit 501 that would disqualify them from treatment with mirikizumab according to originator study and/or long-term extension criteria.
37. Had permanently discontinued study drug in the long-term extension period or had a temporary interruption of study drug in the long-term extension period such that, in the opinion of the investigator or sponsor, restarting of mirikizumab would pose an unacceptable risk for the participant in Study AMAX.
38. Meet any of the exclusion criteria from the AMAX long-term extension during the long-term extension period prior to Visit 501 (see Section 5.2)
39. Are likely to require surgery for the treatment of worsening CD during the Continued Access Period.

Other exclusion criteria

40. Have been diagnosed with a condition, underwent a surgical procedure, received prohibited treatment, or experienced a laboratory abnormality that met criteria for permanent discontinuation from mirikizumab treatment prior to Visit 501 of the Continued Access Period. See Section 7.1.
41. Currently meet temporary discontinuation of study intervention criteria (see Section 7.1). Note: Once resolution of the condition or appropriate treatment is met, the participant may be eligible for the Continued Access Period if the maximum roll-over period to enter the Continued Access Period has not been exceeded.
42. Have initiated a new prohibited medication (see Section 10.7) prior to Visit 501 of the Continued Access Period.
43. Have an underlying disease, or surgical, physical, or medical condition that, in the opinion of the investigator, would potentially affect participant safety within the Continued Access Period.
44. Are pregnant or planning pregnancy (females only) while enrolled in the continued access period, or within 16 weeks after receiving the last dose SC dose of mirikizumab.
45. Have enrolled or plan to enroll 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.

46. Are unsuitable for inclusion in the Continued Access Period in the opinion of the investigator or sponsor for any reason that may compromise the subject's safety or confound the safety data interpretation.

10.13.7. Study Intervention

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

Administration of mirikizumab should always be done after completion of all other visit activities, as specified in SoA (Section 10.13.3).

If self-administration is not possible, the study site staff may administer the dose at the study site and provide source documentation for the reason. If self-administration is not possible for repeated visits, study site should contact the medical monitor. Also note that the caregiver or participant may be allowed to administer limited injections at the study site, if needed.

Reporting requirements

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

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

Treatment compliance

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

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

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

10.13.8. Discontinuation of Study Intervention and Participant Discontinuation from the Continued Access Period

In addition to the study intervention discontinuation requirements in Section 7.1, the following also apply to the Continued Access Period:

- a safety concern assessed by investigator as being related to study intervention, that should result in drug discontinuation
- loss of response as assessed by the investigator

- CCI [redacted]
- investigator's assessment that another clinical trial is appropriate for the participant
- CCI [redacted]
- mirikizumab is locally commercially available and reimbursable (this includes patient access programs when and where available)
- once a participant stops the Continued Access Period, they would not be eligible to resume, and
- CCI [redacted]

Following discontinuation from mirikizumab during the Continued Access Period, the participant should complete both the discontinuation visit and Visit 901, as indicated in the Continued Access Period SoA (Section 10.13.3).

10.13.9. Safety Assessments

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

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

See Sections, 8.2, 8.3, and 10.3 for more details.

10.13.10. Concomitant Medication/Therapy

10.13.10.1. Permitted Concomitant Medications/Therapies during Continued Access

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

Drug Class (examples)	Comments
Oral corticosteroids (including oral budesonide or beclomethasone) for treatment of CD • prednisone ≤30 mg/day or equivalent • budesonide ≤9 mg/day, or • beclomethasone dipropionate ≤5 mg/day (gastro-resistant prolonged-release tablet)	Short courses of corticosteroids, including budesonide, are permitted with tapering to begin as soon as clinically feasible, with a goal of discontinuing within 3 months. Participants who require increasing doses and repeated courses or are intolerant to tapering of corticosteroids should be considered for treatment discontinuation and termination from the Continued Access Period

Drug Class (examples)	Comments
Corticosteroids for non-CD indications	Permitted as follows: • continued use to treat adrenal insufficiency • locally administered use, e.g., inhaled, intranasal, intra-articular, and topical • single doses (oral or IV) corticosteroids as premedication for miri self-administered injection • limited use for acute conditions per investigator discretion, and • possible use for chronic conditions must be discussed with medical monitor
Rectally administered corticosteroids (enemas or suppositories)	Permitted with the goal of tapering as soon as clinically feasible or discontinuing within 3 months.
Immunomodulators for CD (oral AZA, 6-MP, or methotrexate)	Permitted
Antibiotics being used specifically for the treatment of CD (for example: rifaximin or Cipro)	Permitted
Oral 5-ASAs (mesalamine, balsalazide, olsalazine) and sulfasalazine for CD	Permitted
Rectally administered 5-ASAs (enemas or suppositories)	Permitted
Topical JAK inhibitors and topical calcineurin inhibitors	Permitted
Antidiarrheals (loperamide, diphenoxylate with atropine)	Permitted
Low-dose or baby aspirin (75 to 162.5 mg)	Daily use for cardiovascular prophylaxis permitted
Non-live vaccines (killed, inactivated, subunit, or RNA-based)	Permitted
Complementary alternative medicine for CD and non-CD indications (dietary/herbal supplements, vitamins, probiotics)	Permitted

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

10.13.10.2.Prohibited Concomitant Medications/Therapies during Continued Access

This section outlines medications that, if initiated, require treatment and study discontinuation (Section 10.13.8) during the AMAX Continued Access Period, if applicable. If there are any questions on medications, please contact the medical monitor.

Drug Class (examples)	**Continued Access Period Comments and Guidelines**
IV corticosteroids for CD	Course of IV corticosteroids prohibited
Systemic corticosteroids for non-CD indication, oral or IV Allowed exceptions: See Section 10.13.10.1	Prohibited
Immunomodulatory medications, oral or IV: Cyclosporine, mycophenolate mofetil, thalidomide, tacrolimus Other immunomodulatory medications should be discussed with medical monitor prior to use	Prohibited
Agents depleting B or T cells (alemtuzumab, rituximab, visilizumab)	Prohibited
Interferon therapy	Prohibited unless medically necessary for short term COVID treatment
Leukocyte apheresis, leukapheresis (Adacolumn)	Prohibited
Bacillus Calmette-Guerin (BCG) vaccination	Use prohibited during study and ≤12M after last dose of mirikizumab
Live or attenuated vaccines (for measles, mumps, rubella, or varicella)	Use prohibited during study and ≤3M after last dose of mirikizumab

Abbreviations: CD = Crohn's disease; COVID = coronavirus disease; IV = intravenous; M = month.

10.13.10.3. Alternative Treatment after Discontinuation of Mirikizumab in the Continued Access Period

When investigator or sponsor assess, based on current evidence, that an alternative treatment is an acceptable option and is available locally, the participant should be discontinued from the Continued Access Period.

Examples of alternative treatment for CD after discontinuation are described in this table.

Drug Class (examples)	Continued Access Period Comments and Guidelines
Anti-TNF antibodies (adalimumab, golimumab, infliximab)	May use after discontinuation of mirikizumab
Anti-IL-12/23p40 antibodies (ustekinumab)	
Anti-IL-23p19 antibodies (risankizumab, brazikumab, guselkumab, tildrakizumab)	
Anti-integrin antibodies (vedolizumab)	
JAK inhibitors, oral (tofacitinib, upadacitinib)	
Small-molecule S1P receptor modulator (ozanimod)	
Any investigational therapy, biologic or non-biologic	

Abbreviations: CD = Crohn's disease; IL= interleukin; JAK = Janus kinase; S1P = Sphingosine-1-phosphate; TNF = tumor necrosis factor.

10.14. Appendix 14: Optional CCI [redacted] Substudy

10.14.1. Overview

This substudy is optional for participants who are active in the main study. This substudy is being conducted on a subset of participants to assess CCI [redacted] for self-administration by participants or caregivers.

The CCI [redacted] that is used to deliver mirikizumab. The ePFS represents an eventual commercial presentation of the combination product, which is CCI [redacted]

Informed consent will be obtained from participants and caregivers participating in the optional CCI self-administration substudy.

This appendix must be followed for all participants in the optional CCI substudy, in addition to all procedures required by Protocol AMAX or any subsequent amendments to that protocol, as applicable.

10.14.2. Inclusion Criteria

CCI [redacted]) Self-Administration Eligibility

Participation in this CCI self-administration substudy is voluntary.

Participants are eligible to perform self-administration of investigational product using the CCI if they are appropriately trained and they meet the following criteria:

47. Participants must have given the written informed consent for the optional CCI self-administration substudy that has been approved by the ethical review board governing the site prior to CCI self-administration training.
48. Participants must have successfully completed (according to the investigator) at least 1 visit with training on CCI self-administration prior to performing independent self-administration of CCI

Note that participants are not required to train on CCI prefilled syringe (PFS) prior to CCI self-administration training, nor are participants required to train on ePFS prior to self-administration training for CCI PFS.

10.14.3. Study Intervention

The study intervention used in the main AMAX study is mirikizumab administered by IV or SC injection.

Subcutaneous injection for this substudy will be administered with CCI [redacted]

The doses and routes of administration reflect the multipart study design (Section 4.1).

Each dose will consist of CCI [redacted]

For the purpose of the participant's convenience, the independent CCI self-administration by the participant or caregiver (non-site staff) may be performed at home or at the study site, simulating home use.

Injection location

Possible injection sites are identified in the instructions provided by the sponsor for the investigational product. The injection site may be rotated to another area for subsequent doses. Note that in the case a study drug injection is performed in an arm, it is not to be given in the same arm from which participant blood samples, including pharmacokinetic samples, are drawn at relevant visits.

Study Drug Administration Logs

Study Drug Administration Logs will be dispensed to each participant for recording pertinent data about each injection. Details of the use of these logs are provided in Section 6.1.1.

Packaging and Labeling

Clinical trial materials will be labeled for the study and 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 GMP.

CCI

The CCI will provide a single injection of mirikizumab.

- The CCI is manufactured to deliver CCI
- The CCI is manufactured to deliver CCI

The CCI will be supplied with the appropriate quantity specific to the planned dispensing schedule. Investigational product will be provided with study-specific labels.

10.14.3.1. Participant Training and Administration

General guidance

Detailed instructions for investigational product administration will be provided by the sponsor, and the investigational product will be administered at the site by clinical staff for the first administration of Training Visit 1. At this visit, site staff will train participants on self-injection with CCI and will provide them with a log to track their doses at home.

All administrations for the following three visits will be done by the participant or caregiver.

Participant training

The participant (and/or caregiver) will begin training on the use of the CCI at a regularly scheduled office visit, once the CCI and the CCI become available.

At the training session, site personnel will train the participant and/or caregiver to perform the injections using the CCI and will administer the first injection. The participant and/or caregiver will then administer the second injection of the dose using an CCI while the site personnel provide oversight and instruction.

Additional training may occur at any time during the substudy, as needed.

Reporting requirements

Site staff must complete the *Patient Study Drug Administration Training Log* during each Training Visit, including any telemedicine visits for remote retraining (see CCI dosing table below for documentation required by site).

Remote training

If retraining needs to be performed and is conducted remotely, telemedicine visits with the participant must be conducted during the administration of the dose in order to provide additional guidance, if needed, and to confirm dosing completion.

CCI

During each CCI dosing, the participant/caregiver must complete an CCI form for each set of injections that they administer (at the training visit, the CCI responses should only refer to the injection that is given by the participant/caregiver). The participant will need to report product complaints, any user error or use issues, issues with the instructions for use, label deficiencies, etc. to the Investigator.

Independent self-administration period

During the CCI independent self-administration period, participants/caregivers will perform the next CCI with the CCI .

The *Patient Study Drug Administration Log* must be completed by participants during each self-administration. See table below for documentation required by participant.

CCI

	CCI Dosing 1[a,b,c,d]	CCI Dosing 2[e]	CCI Dosing 3[e]	CCI Dosing 4[e,f]
Type of Visit	Training	Independent Self-Administration	Independent Self-Administration	Independent Self-Administration
Home or Office	Office	Office or Home	Office or Home	Office or Home
Investigational Product[g]	Mirikizumab CCI CCI	Mirikizumab CCI CCI	Mirikizumab CCI CCI	Mirikizumab CCI
First CCI Injection Administered[b]	HCP	Participant and/ or Caregiver	Participant and/ or Caregiver	Participant and/ or caregiver
Second CCI Injection Administered[b]	Participant and/or Caregiver	Participant and/ or Caregiver	Participant and/or Caregiver	Participant and/or Caregiver
Documentation Required by Participant	CCI	and PATIENT STUDY DRUG ADMINISTRATION LOG	and PATIENT STUDY DRUG ADMINISTRATION LOG	and PATIENT STUDY DRUG ADMINISTRATION LOG
Documentation Required by Site	PATIENT STUDY DRUG ADMINISTRATION TRAINING LOG[h]	N/A	N/A	N/A

Abbreviations: CCI ; HCP = health care provider; PFS = prefilled syringe; CCI SDATL = Study Drug Administration Training Log.

a CCI training must start on a regularly scheduled office visit and must begin no earlier than V4 and no later than V16. CCI substudy will not be allowed to start at V11. If CCI training starts at Visits 12-16, participants who were not previously trained on PFS self-administration will be required to come onsite for the next PFS dosings after they complete the CCI dosings, in order to receive PFS training or to have PFS dosings administered by site staff. Please see additional details provided separately by the sponsor for scenarios based on beginning CCI training at each of the allowed visits.

b If the investigator, participant, or caregiver judges at any time during the CCI period that self-administration cannot be performed independently, the participant will no longer participate in the CCI self-administration substudy. If the investigator judges that the participant or caregiver is able to successfully self-administer the PFS, the participant may continue use of PFS self-administration independently.

c CCI informed consent must be obtained before any CCI Visit 1 Procedures.

d Site to complete training with participant using the *Patient Study Drug Administration Training Log*. ePFS training may begin once the CCI and the CCI forms become available. CCI training will be completed after the participant meets eligibility criteria.

[e] At any time after the training visit, the participant or caregiver may be retrained on how to self-administer investigational product, if needed. If the retraining is performed remotely, a telemedicine visit must be conducted.

[f] After the participant completes 3 independent self-administration occurrences with CCI the participant will return to using the CCI, either by self-administration with the required prior training or administered by the HCP if the participant or caregiver is unable.

[g] CCI injections CCI can be administered in any order.

[h] If subsequent Training Visits are required, site personnel to complete the SDATL at those visits.

Returning to use of CCI PFS

After the participant/caregiver completes the third independent self-administration dosing with the CCI the participant will return to using the CCI l PFS.

The participant may continue the use of PFS self-administration independently if the investigator judges that the participant is able to perform this successfully and PFS training is completed.

If the participant/caregiver was previously trained on self-administration with the PFS, the site staff may perform re-training as needed. If the participant/caregiver has not been trained on using the PFS, they should be offered training.

If the participant is unable/unwilling to self-administer with PFS, the sponsor may approve a general exception for self-administration for a participant depending on circumstances (See Section 5.1, Criterion #4).

10.14.4. Discontinuation of Study Intervention and Participant Discontinuation from the Substudy

If the investigator or the participant/caregiver judges that CCI training is unsuccessful or the self-administration dosings cannot be performed independently, the participant will no longer participate in the CCI self-administration substudy

10.14.5. Secondary Efficacy Assessments

10.14.5.1. PROs

All Participants from AMAG and AMAM

The CCI will be collected for each set of CCI injections performed by a participant/caregiver for both training and independent administrations.

CCI

10.14.6. Complaint Handling

See Section 8.3.8.

10.14.7. Analyses

Analyses presented for this substudy will be descriptive, including frequency counts and percentages, and use the modified intent-to-treat population in participants who have enrolled in the CCI substudy.

CCI

In participants who have completed CCI training, analyses of successful administration with an CCI may be presented by administration attempt.

10.15. Appendix 15: Country-specific Requirements

This appendix is applicable for sites in EU-member states and Turkey.

Note: Deletions to the main protocol sections are identified by ~~strikethrough format~~ and additions by underlined text.

10.15.1. Hungary, Latvia, and Romania

This section describes protocol changes applicable for participants in study sites in Hungary, Latvia, and Romania

This table describes the changes and provides a rationale for the changes

Protocol Section Number and Name	Description of the Change	Brief Rationale
5.1 Inclusion Criteria	Updated inclusion criterion [6]	To align with contraceptive use for all sites in Hungary, Latvia, and Romania

The revised text in the following sections show the changes applicable for participants at study sites in Hungary, Latvia, and Romania.

5.1 Inclusion Criteria

[6] Contraception: Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male Participants:

~~No male contraception is required except in compliance with specific local government study requirements.~~ Agree to use a reliable method of birth control during the study and for at least 16 weeks following the last dose of the study drug.

b. Female Participants:

Women **of childbearing potential** (WOCBP, defined as all adult females unless they are WNOCBP as defined below) may participate if they meet the following criteria**:**

A. must test negative for pregnancy prior to initiation of treatment as indicated by a negative urine pregnancy test at Visit 1/Week 0 of this study

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 a combination of 2 ~~effective~~ methods of contraception ~~or 1 highly effective method of contraception~~ for the entirety of the study, where at least 1 method must be highly effective and the other method is effective or highly effective. ~~Abstinence or e~~Contraception must continue for **16 weeks** following completion of study drug administration ~~for **16 weeks.**~~

i. Effective methods of contraception may include barrier methods such as male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges (which usually are made with spermicide). The barrier method must include use of a spermicide to be counted as one effective method.

ii. Highly effective (<1% failure rate) methods of contraception (at least one of which must be used) include
- female sterilization
- combination oral contraceptive pill
- progestin-only contraceptive pill (mini-pill)
- implanted contraceptives
- injectable contraceptives
- contraceptive patch (only women <198 pounds or 90 kg)
- vasectomy (if only sexual partner)
- fallopian tube implants (if confirmed by hysterosalpingogram)
- combined contraceptive vaginal ring, or
- intrauterine devices

iii. Ineffective forms of contraception, whether used alone or in any combination, include
- spermicide alone
- periodic abstinence
- fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal)
- withdrawal
- postcoital douche or
- lactational amenorrhea

Women **not of childbearing potential** (WNOCBP) may participate and include those who are:

A. infertile due to surgical sterilization (total hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, bilateral oophorectomy, or tubal ligation)[a], have a congenital anomaly such as Müllerian agenesis

OR

B. postmenopausal[b] – defined as either:

i. a woman at least 40 years of age with an intact uterus, not on hormone therapy, who has had either:
- cessation of menses for at least 1 year, without an alternative medical cause
- at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone level >40 mIU/mL

ii. a woman 55 years or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea, or

iii. a woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

[a] Note that if it has been less than 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, she will be required to use contraception until she has reached 6 weeks since the procedure.

[b] For the purpose of defining the length of time of amenorrhea to determine postmenopausal status, only count time in which the woman was not taking medications such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, SERMs, or chemotherapy that could induce transient amenorrhea.

10.15.2. Netherlands and Turkey

This section describes protocol changes applicable for adult participants in study sites in Netherlands and Turkey

This table describes the changes and provides a rationale for the changes

Protocol Section Number and Name	Description of the Change	Brief Rationale
7.2. Participant Discontinuation/Withdrawal from the Study	Added information about inadvertently enrolled participants	To remove inadvertently enrolled participants from the study

The revised text in the following sections show the changes applicable for adult participants at study sites in Netherlands and Turkey.

7.2 Participant Discontinuation/Withdrawal from the Study

<u>If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled into AMAX, the participant must be withdrawn from the study in order to comply with local regulations.</u>

10.15.3. Czech Republic

This section describes protocol changes applicable for adult participants in study sites in the Czech Republic.

This table describes the changes and provides a rationale for the changes

Protocol Section Number and Name	Description of the Change	Brief Rationale
1.3 Schedule of Activities	Updated tuberculosis risk assessment and yearly screening for active and latent TB in participants	Updated in accordance with regulatory requirements in the Czech Republic
5.1 Inclusion Criteria	Updated inclusion criteria [6] b	Revised in accordance with regulatory requirements in the Czech Republic
8.2.4 Chest Radiography	Added Czech Republic-specific details for chest radiography	Updated in accordance with regulatory requirements in the Czech Republic
8.2.6 Tuberculosis Testing	Added Czech Republic-specific details for tuberculosis testing and removed general instructions for initial screening test	Updated in accordance with regulatory requirements in the Czech Republic

The revised text in the following sections show the changes applicable for adult participants at study sites in the Czech Republic.

1.3 Schedule of Activities (SoA)

1.3.1 Visit 1 through Visit 9 CCI

Table AMAX.1 1. Schedule of Activities - Visit 1 through Visit 9 (CCI

Procedures	Schedule of Activities[a]											
Visit Number	V1[b]		V2	V3	V4		V5	V6	V7	V8	V9	
Visit Type	Office – Screening/ V1[a]	Office - Dosing/V1[b]	Office	Office	Phone	Office	Office	Office	Office	Office	Phone	Office
Week Relative to Study Drug Start[c]	CCI											
Day with Visit Tolerance Interval (VTI)												
All Participants (X); AMAM Rollover Participants Only (M); AMAG Rollover Participants Only (G); Optional (Opt) (See footnotes for additional key details)												
TB Risk Assessment Monitoring[i]	~~X~~[af]	X[ah]	X			X	X	X	X	X		~~X~~
Yearly screening for active and latent TB in participants in the Czech Republic*	X											X

Abbreviations: AEs = adverse events; CT = computed tomography; CXR = chest x-ray; CCI ; IGRA = interferon gamma release assay; NA = Not applicable; PK = pharmacokinetic; TB = tuberculosis; TST = tuberculin skin test; V = Visit

* Participants from the Czech Republic will be screened for active and latent TB infection annually, including at Visits 1 and 9. This will include the assessment of medical history, AEs, and clinical risk, physical examination, and a TB test as described Tuberculosis Testing section (Section 8.2.6 of main protocol and Section 8.2.6 of this appendix). Participants who had a TST must return 48 to 72 hours after placement to have their test results read by a pulmonologist. A chest X-ray may be performed if clinically indicated. A CT scan may be performed as an alternative based on regional standard of practice

a Please see detailed instructions provided by the sponsor for calculation of visit dates. Also, note that unscheduled assessments can be performed during scheduled visits, see Table AMAX.1-3 for details.

b V1 is a split visit, occurring on at least 2 office visits on different dates. Screening procedures are to be performed at the first part of V1, called Screening/V1a, in order to have results available to confirm eligibility prior to dosing. For AMAM-originating participants, it is recommended that V1a screening procedures be on the same date as AMAM V17. V1 dosing is performed at the Dosing/V1b visit. For both AMAM and AMAG-originating participants, the timing for AMAX V1a and V1b must allow for first AMAX dosing (V1b) within no more than CCI from the last dosing in the originating study. It is required that all screening assessments, including laboratory test results are reviewed to confirm eligibility from both the final visit of the originating study as well as AMAX V1a, as applicable, prior to dosing at V1b. For participants originating from AMAM, CCI [redacted]. Note that some assessments may be required at both V1a and V1b. Refer to footnotes for details. To accommodate potential lab delays and/or needs for retesting, please plan for at least 10 business days to obtain lab results after initial samples are received at the laboratory, and up to 5 business days for endoscopy results after receipt of video.

c All activities should be completed prior to any study drug administration unless otherwise stated.

d See footnote b for definitions of the V1 Screening visit (V1a) and the V1 Dosing visit (V1b). V1 dosing (V1b) is defined as Day 1. All V1 screening activities need to be performed prior to dosing, including all assessment retesting (if needed), with results available prior to dosing such that the total interval from last dose in the originating study to first dose in AMAX is no more than CCI. Please see detailed instructions provided by the sponsor for calculation of subsequent visit dates.

i ~~At V1 and t~~ Throughout the study, participants will be assessed for risk factors for TB (Section 10.5, Appendix 5). If the participant has a risk factor(s) or any TB-related signs or symptoms identified as part of the discussions of preexisting conditions or AEs, or as part of the standard physical exam, 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 or other factors that the investigator feels requires testing and imaging, an IGRA or TST and a CXR should be performed (Table AMAX.1-3 Unscheduled assessments). A CT scan can be performed as an alternative to the CXR, based on regional standard of practice (Section 8.2.6).

~~af Collect/assess at AMAX V1a if not performed at the last visit of the originator study.~~

ah If more than 14 weeks will have elapsed between last collection/assessment and the first AMAX dosing, additional procedures must be performed again prior to the V1b dosing. See sponsor guidance regarding sample collection kits or data entry for items that need to be collected again at V1b. Investigator medical judgment should be used regarding whether the repeat lab results should be available and reviewed prior to dosing (review prior to dosing not needed for PK, immunogenicity, CCI, or fecal calprotectin).

1.3.2 Visit 10 through Visit 19 CCI

Table AMAX.1 2. Schedule of Activities - Visit 10 through Visit 19 CCI

Procedures	Schedule of Activities[a]													
Visit Number	**V10**	**V11**	**V12**		**V13**	**V14**		**V15**	**V16**		**V17**	**V18**	**V19**	
Visit Type	**Office**	**Office**	**Phone**	**Office**	**Office**	**Phone**	**Office**	**Office**	**Phone**	**Office**	**Office**	**Office**	**Phone**	**Office**
Week Relative to Study Drug Start[b]	CCI													
Day with Visit Tolerance Interval (VTI)														
All Participants (X); AMAM Rollover Participants Only (M); AMAG Rollover Participants Only (G); Optional (Opt) (See footnotes for additional key details)														
TB Risk Assessment Monitoring[f]	X	X		X	X		~~X~~	X		X	X	X		~~X~~
Yearly screening for active and latent TB in participants in the Czech Republic*							X							X

Abbreviations: AEs = adverse events; CT = computed tomography; CXR = chest x-ray; IGRA = interferon gamma release assay; TB = tuberculosis; TST = tuberculin skin test; V = visit.

* Participants from the Czech Republic will be screened for active and latent TB infection annually, including at Visits 14 and 19. This will include assessment of medical history, AEs and clinical risk, physical examination, and a TB test as described in Tuberculosis Testing section (Section 8.2.6 of main protocol and Section 8.2.6 of this appendix). Participants who had a TST must return 48 to 72 hours after placement to have their test results read by a pulmonologist. A chest X-ray may be performed if clinically indicated. A CT scan may be performed as an alternative based on regional standard of practice.

a Please see detailed instructions provided by the sponsor for calculation of visit dates. Also, note that unscheduled assessments can be performed during scheduled visits, see Table AMAX.1-3 for details. Please refer to Section 10.13.3 for the optional continued access period details. Participants from the Czech Republic will continue to be screened for active and latent TB infection annually during continued access if they participate.

b All activities should be completed prior to any study drug administration unless otherwise stated.

c Site to remind participant to complete 14-Day diary and/or bowel prep, as appropriate. Phone reminder must occur at least 15 days prior to actual next visit date to ensure the participant begins the collection of diary data in time.

f Throughout the study, participants will be assessed for risk factors for TB (Section 10.5, Appendix 5). If the participant has a risk factor(s) or any TB-related signs or symptoms identified as part of the discussions of AEs or as part of the standard physical exam, 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 or other factors that the investigator feels warrant testing and imaging, an IGRA or TST and CXR should be performed (Table AMAX.1-3 Unscheduled assessments). A CT scan can be performed as an alternative to the CXR based on regional standard of practice (Section 8.2.6).

5.1 Inclusion Criteria

[6] b. Female Participants:

Women of **childbearing potential** (WOCBP, defined as all adult females unless they are WNOCBP as defined below) may participate if they meet the following criteria:

A. must test negative for pregnancy prior to initiation of treatment as indicated by a negative urine pregnancy test ~~at Visit 1/Week 0 of this study~~ 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 a combination of 2 ~~effective~~ methods of contraception ~~or 1 highly effective method of contraception~~ for the entirety of the study, where at least 1 method must be highly effective and the other method is effective or highly effective. Abstinence or contraception must continue following completion of study drug administration for **16 weeks**.

i. Effective methods of contraception may include barrier methods such as male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges (which usually are made with spermicide). The barrier method must include use of a spermicide to be counted as one effective method.

ii. At least one highly effective method of contraception must be used. A highly effective method of contraception is defined as one with a Pearl index <1 (which is used to measure the reliability of birth control methods), such as male or female sterilization, hormonal birth control like the Pill (with the exception of Mini Pill), 3-month injection, hormone implantation, hormone loop, vaginal ring, or transdermal patch. ~~Highly effective (<1% failure rate) methods of contraception include~~

- ~~female sterilization~~
- ~~combination oral contraceptive pill~~
- ~~progestin-only contraceptive pill (mini-pill)~~
- ~~implanted contraceptives~~
- ~~injectable contraceptives~~
- ~~contraceptive patch (only women <198 pounds or 90 kg)~~
- ~~vasectomy (if only sexual partner)~~
- ~~fallopian tube implants (if confirmed by hysterosalpingogram)~~
- ~~combined contraceptive vaginal ring, or~~
- ~~intrauterine devices.~~

iii. Ineffective forms of contraception, whether used alone or in any combination, include

- spermicide alone
- periodic abstinence
- fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal)
- withdrawal
- postcoital douche, or
- lactational amenorrhea.

Women **not of childbearing potential** (WNOCBP) may participate and include those who are:

A. infertile due to surgical sterilization (total hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, bilateral oophorectomy, or tubal ligation)[a], have a congenital anomaly such as Müllerian agenesis,

OR

B. postmenopausal[b] – defined as either:

i. a woman at least 40 years of age with an intact uterus, not on hormone therapy, who has had either
   - cessation of menses for at least 1 year, without an alternative medical cause
   - at least ~~6~~12 months of spontaneous amenorrhea with a follicle-stimulating hormone (FSH) level >40 mIU/mL

ii. a woman 55 years or older not on hormone therapy, who has had at least ~~6~~12 months of spontaneous amenorrhea, or

iii a woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

[a] Note that if it has been less than 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, she will be required to use contraception until she has reached 6 weeks since the procedure.

[b] For the purpose of defining the length of time of amenorrhea to determine postmenopausal status, only count time in which the woman was not taking medications such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, SERMs, or chemotherapy that could induce transient amenorrhea.

8.2.4 Chest Radiography

A posterior-anterior chest x-ray (CXR), interpreted and reported by a radiologist or pulmonologist, will be obtained if there are relevant TB-related physical findings or other factors that the investigator feels warrant testing and imaging, as specified in the SoA (Section 1.3), ~~and~~ Section 8.2.6 of main protocol and Section 8.2.6 in this appendix. A posterior-anterior CXR may be obtained at Visit 1 at the investigator's discretion, if clinically indicated for TB infection. A lateral chest x-ray can also be obtained if, in the opinion of the investigator, a lateral view is indicated. Patients with documentation of a CXR, read by a qualified radiologist, that is sufficient for TB evaluation according to local standard of care, performed within 3 months before initial screening, may not need to repeat CXR at screening, based on the judgement of the

investigator. In either case, the CXR film(s)/image(s) or a radiology report must be available to the investigator for review. A computed tomography (CT) scan can be performed as an alternative to the CXR based on regional standard of practice. An IGRA or TST should also be performed (Section 8.2.6 of main protocol and Section 8.2.6 in this appendix).

8.2.6. Tuberculosis Testing

Initial Screening

~~All participants will be evaluated for risk factors for LTBI at rollover from their originator studies during the AMAX Visit 1 (Section 10.5, Appendix 5). If the participant has risk factors or any TB-related signs or symptoms are identified as part of the discussions of preexisting conditions or as part of the standard physical exam, the investigator should conduct a thorough physical examination, including body temperature measurement and assessment of peripheral lymph nodes. For participants with relevant TB-related physical findings or other factors that the investigator feels warrant testing and imaging:~~

- ~~a TB test should be performed:~~
  - ~~IGRA (for example, QuantiFERON-TB Gold or TSPOT.TB), or~~
  - ~~Tuberculin skin test (TST; also called a purified protein derivative [PPD] or Mantoux test).~~

Participants from the Czech Republic will be screened for active and latent TB infection (LTBI) at Visit 1. This will include the following:

- Medical history of ongoing adverse events from originator study (Visit 1).
- Clinical assessment of risk (Section 10.5, Appendix 5).
- Physical examination as described in Section 8.2.2, and include body temperature measurement and assessment of peripheral lymph nodes.
- A test to assess immune response to mycobacterial antigens such as interferon-γ release assay (interferon gamma release assay [IGRA], for example, QuantiFERON-TB Gold or T-SPOT.TB).
- If a tuberculin skin test (TST) or purified protein derivative test is performed, the test will be at a designated location (a pulmonary outpatient clinic) and read by a pulmonologist.

  Note: 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.

  If participant has a history of positive TB test result with prophylaxis, TB testing should not be performed unless advised to do so based on local guidelines (See also section on Prior Treatment for LTBI).
- a CXR may ~~should~~ be performed if clinically indicated, as described in Section 8.2.4. A CT scan may be performed as an alternative to the CXR based on regional standard of practice.

Monitoring for TB during the study

For all participants, monitoring for TB is to be continuous throughout the study. Every 2 to 3 months as indicated in the SoA, the participants will be assessed for risk factors for TB (Section 10.5, Appendix 5). If the participant has a risk factor or any TB-related signs or symptoms identified as part of the AE discussions or standard physical exam, 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 or other factors that the investigator feels warrant testing and imaging, an IGRA OR TST and CXR should be performed. A CT scan can be performed as an alternative to the CXR, based on regional standard of practice.

Participants from the Czech Republic will also be screened for active and latent TB infection at yearly interval visits V9, V14, and V19 over the duration of the study (and throughout continued access if they participate), following all steps described above for Initial Screening, with medical assessment of all ongoing adverse events and with testing.

10.15.4. Hungary

This section describes protocol changes applicable for participants in study sites in Hungary.

This table describes the changes and provides a rationale for the changes

Protocol Section Number and Name	Description of the Change	Brief Rationale
1.1 Synopsis	Added additional information for participants in Hungary who were in the placebo group at Week 52 of AMAM and considered responders at Week 52 of AMAM	Updated in accordance the comments from the Medical Research Council, Ethics Committee for Clinical Pharmacology of Hungary
4.1 Overall Design	Added additional information for participants in Hungary who were in the placebo group at Week 52 of AMAM and considered responders at Week 52 of AMAM	Updated in accordance the comments from the Medical Research Council, Ethics Committee for Clinical Pharmacology of Hungary
7.2 Participant Discontinuation/Withdrawal from the study	Added AMAX participant discontinuation/withdrawal from study details for participants in Hungary who were in the placebo group at Week 52 of AMAM and considered responders at Week 52 of AMAM	Updated in accordance the comments from the Medical Research Council, Ethics Committee for Clinical Pharmacology of Hungary

The revised text in the following sections show the changes applicable for adult participants at study sites in Hungary.

1.1. Synopsis

Overall Design

Study AMAX is a Phase 3, multicenter, long-term extension study evaluating the efficacy and safety of mirikizumab in participants with moderately-to-severely active CD who have participated in an originator adult mirikizumab CD study, inclusive of the Phase 3 Study AMAM and the Phase 2 Study AMAG.

Participants who are CCI [redacted] for an extended period of time (up to 3 years) and then enter a 12- to 16-week posttreatment follow-up period. Participants who are CCI [redacted] fter completion of the long-term extension period, if mirikizumab is not yet locally commercially available and reimbursable, eligible participants will be provided with an option of continued access to open-label mirikizumab, followed by a 4-week follow-up period. The duration of the continued access will differ by participant and country.

Participants who meet all of the inclusion criteria and none of the exclusion criteria of AMAX, and who, in the opinion of the investigator, would receive benefit from open-label treatment with mirikizumab are eligible for enrollment into Study AMAX. It is possible that some participants enrolling from Study AMAM may have received placebo only in the originating study. These participants will receive mirikizumab for the first time in Study AMAX. After the AMAM final database lock, the sponsor will unblind the treatment assignments of Hungary participants from Study AMAM. To comply with the response from the Medical Research Council, Ethics Committee for Clinical Pharmacology of Hungary, any Hungary sites that have participants who were in the placebo intervention group at Week 52 of Study AMAM and were considered responders at Week 52 of Study AMAM will receive a notification through the investigator to discontinue the participant from Study AMAX. These participants will complete the AMAX Early Termination Visit (ETV) and enter the posttreatment Follow-up Period.

4.1. Overall Design

Study AMAX is a long-term study of adult participants completing studies AMAM or AMAG (see schema in Section 1.2).

Two intervention groups will be studied in participants with moderate-to-severe CD:

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

CCI [redacted]. After the AMAM final database lock, the sponsor will unblind the treatment assignments of Hungary participants from Study AMAM. To

comply with the response from the Medical Research Council, Ethics Committee for Clinical Pharmacology of Hungary, any Hungary sites that have participants who were in the placebo intervention group at Week 52 of Study AMAM and were considered responders at Week 52 of Study AMAM will receive a notification through the investigator to discontinue the participant from Study AMAX. These participants will complete the AMAX ETV and enter the posttreatment Follow-up Period.

CCI

Study participants will receive mirikizumab for an extended period of time (approximately 3 years or until commercial availability of mirikizumab, whichever comes first) and then enter a 12- to 16-week posttreatment follow-up period. After completion of long-term extension period, if mirikizumab is not yet locally commercially available and reimbursable, eligible participants will be provided with an option of continued access to open-label mirikizumab, and then enter a 4-week follow-up period (Section 10.13, Appendix 13). The duration of the continued access will differ by participant and country.

AMAM participants will require an endoscopy to be performed at Week 52, CCI in the AMAX study.

AMAG participants who are entering AMAX after completing CCI into AMAX. Participants who have not yet completed CCI

See Section 8.1.1.2 for details.

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)
- the investigator decides that the participant should be discontinued from the study
- all participants from originator Study AMAM CCI and enter the 12- to 16-week posttreatment follow-up period~~, or~~
- following the final database lock in Study AMAM, all participants in Hungary who were in the placebo intervention group at Week 52 of Study AMAM and who were considered responders at Week 52 of Study AMAM will be discontinued from Study AMAX

through a notification to the investigator and will complete the ETV and enter the posttreatment Follow-up Period, or

- the participant requests to be withdrawn from the study.

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

10.16. Appendix 16: Protocol Amendment History

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

Note: Due to the short time between approval of amendment [c] and amendment [d], it is expected that amendment [c] will not be implemented at sites, and they will instead move directly to amendment [d] once all requirements are met. To facilitate identifying changes from the last amendment version in use, the Summary of Changes Table includes the cumulative changes made in amendment [c] and amendment [d]. Section 10.16 includes a table of the changes made specifically to amendment [c].

Amendment [c]: 12-Jan-2023

Amendment [c] is considered to be substantial because it is likely to have a significant impact on the safety or the rights of the study participants.

Overall Rationale for Amendment [c]:

The changes include

- the addition of an optional Continued Access appendix
- the addition of an optional CCI [redacted] that may be conducted on a subset of participants to assess the CCI [redacted], and
- protocol addenda approved by EU Member States have been incorporated into appendices for the purpose of creating a consolidated protocol that will support the transition to the EU Clinical Trial Regulation.

Amendment [d]: 06-Feb-2023

The changes that are specific to amendment [d] are considered nonsubstantial and primarily impact the new Continued Access appendix incorporated in amendment [c], which has not yet been implemented.

Overall Rationale for Amendment [d]:

The changes include

- changes to the Continued Access appendix Schedule of Activities, and
- removal of the Netherlands from Appendix 10.15.1 since it was determined that this appendix is not applicable to and was not implemented in the Netherlands.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Updated word from short title to brief title, deleted acronym, added regulatory agency identified numbers, replaced disclosure statement with brief summary, and added study population and ethical considerations of benefit/risk	To align with current sponsor protocol template
Section 1.2 Schema	Updated schema with continued access period details	Updated to include continued access period details
Section 1.3.1 Visit 1 through Visit 9 CCI	Added Chemistry and Hematology labs at Visit 3	The addition of chemistry and hematology at Visit 3 (office visit) was included to continue hepatic safety monitoring CCI for the first 12 weeks of the study and to have an additional hematocrit value close to Week CCI if needed for CDAI purposes.
Section 1.3.2 Visit 10 through Visit 19 CCI	Footnote "a" was updated Footnote "r" was added Footnote "g" was updated	A cross-reference to Section 10.13.3 was added to provide more details on continued access period To note that patients moving to continued access should move directly from V19 to V501, and not perform V801 or V802 Updated for clarity in Amendment [d]
Section 1.3.3 Early Termination, CCI Unscheduled Visits/Assessments, and Follow-up Visits	Removed "G" at office visit following Endoscopy in Patient 14-Day paper diary dispensed row Footnote "a" was updated Footnote "y" was added	To clarify that 14-day diary is not dispensed on the same day as it is returned. A cross-reference to Section 10.13.3 was added to provide more details on continued access period To note that patients moving to continued access should move directly from V19 to V501, and not perform V801 or V802
Section 1.3.4 Study Drug Self-Administration	Updated table name and footnote "a"	Updated for clarity

Section 2.2.4 IL-23p19 Blockade in Crohn's Disease	Updated efficacy of IL-23p19 blockade in Crohn's disease information per recent data	Updated per recent data
Section 2.3 Benefit/Risk Assessment	Added AMAX in overall benefit/risk conclusion	Updated to include AMAX information
Section 5.2 Exclusion Criteria	Updated wording from duration of the study to duration of the long-term extension period of the study	Update to clarify that marijuana is prohibited during long-term extension of the study
Section 6.1 Study Intervention(s) Administered	Removed text and added tables that lists the interventions in the study	To align with current sponsor protocol template
Section 8.1.2.3 Inflammatory Biomarkers	Removed "from samples taken prior to Week 12 of AMAX"	To clarify that no CCI or fecal calprotectin results will be shared until after database lock
Section 9.5 Interim Analyses	Added additional information for clarification	Update for clarity
Section 10.1.1 Regulatory and Ethical Considerations	Added additional information per template	To align with current sponsor protocol template
Section 10.1.2 Financial Disclosure	Added this section per template	To align with current sponsor protocol template
Section 10.1.3 Informed Consent Process	Updated language per template	To align with current sponsor protocol template
Section 10.1.4 Data Protection	Added additional information per template	To align with current sponsor protocol template
Section 10.1.6 Dissemination of Clinical Study Data	Added additional information per template	To align with current sponsor protocol template
Section 10.1.9 Study and Site Closure	Added additional information per template	To align with current sponsor protocol template

Section 10.1.11 Investigator Information	Added the investigator information section per template	Added per template
Section 10.3.1.2 Events Meeting the AE definition	Removed lack of efficacy details	Removed as lack of efficacy is not considered as an adverse event in this study
Section 10.7 Appendix 7: prohibited Medications	Updated guidance for use for interferon therapy	Updated for clarity
Section 10.11 Appendix 11: Abbreviations and Definitions	Added abbreviations and definitions as per changes in the document	Added per updated information
Section 10.13 Appendix 13: Optional Continued Access Period	Added Optional Continued Access Period details	Added Continued Access Period in Amendment [c]. Made changes to the Overview, Schedule of Activities, and Study Intervention language for the planned Continued Access Period and removed some of the phone visits for Continued Access Period in Amendment [d]
Section 10.14 Appendix 14: CCI [redacted]	Added CCI [redacted] details	Added an optional CCI [redacted] substudy in amendment [c] that may be offered to a subset of participants to assess the CCI [redacted] Corrected the word from addendum to substudy in Section 10.14.2 in Amendment [d]
Section 10.15 Appendix 15: Country-specific requirements	Added EU countries addenda into this appendix	Protocol addenda approved by EU Member States were incorporated into appendices in amendment [c] for the purpose of creating a consolidated protocol that will support the transition to the EU Clinical Trial Regulation. The Netherlands was removed from Appendix 10.15.1 in Amendment [d] since it was determined that this appendix is not applicable to and was not implemented in the Netherlands
Throughout the protocol	Changed the CCI [redacted]	Updated to make the screening labs interval consistent through the document

Throughout the protocol	Minor editorial changes	Modified for clarity
Section 10.16 Appendix 16: Protocol Amendment History	Added Amendment (c) summary of changes table	Addition of amendment (c) details
Section 11 References	Updated reference as per the changes in protocol	Updated as per protocol changes

Amendment [c]: 12-Jan-2023

This amendment is considered to be substantial.

The amendment is considered to be substantial because it is likely to have a significant impact on the safety or the rights of the study participants.

Overall Rationale for the Amendment:

The changes in this amendment include

- the addition of a Continued Access appendix
- the addition of an optional CCI that may be conducted on a subset of participants to assess the CCI, and
- all protocol addenda approved by EU Member States, which have been incorporated into appendices for the purpose of creating a consolidated protocol that will support the transition to the EU Clinical Trial Regulation.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Updated word from short title to brief title, deleted acronym, added regulatory agency identified numbers, replaced disclosure statement with brief summary, and added study population and ethical considerations of benefit/risk	To align with the current sponsor protocol template
Section 1.2 Schema	Updated schema with Continued Access Period details	Updated to include Continued Access Period details
Section 1.3.1 Visit 1 through Visit 9 CCI	Added Chemistry and Hematology labs at Visit 3	The addition of chemistry and hematology at Visit 3 (office visit) was included to continue hepatic safety monitoring CCI for the first 12 weeks of the study and to have an additional hematocrit value close to CCI if needed for CDAI purposes
Section 1.3.2 Visit 10 through Visit 19 CCI	Footnote "a" was updated Footnote "r" was added	A cross-reference to Section 10.13.3 was added to provide more details on Continued Access Period To note that patients moving to Continued Access should move directly from V19 to V501 and not perform V801 or V802
Section 1.3.3 Early Termination, CCI Unscheduled Visits/Assessments, and Follow-up Visits	Removed "G" at office visit following Endoscopy in Patient 14-Day paper diary dispensed row Footnote "a" was updated Footnote "y" was added	To clarify that 14-day diary is not dispensed on the same day as it is returned A cross-reference to Section 10.13.3 was added to provide more details on Continued Access Period To note that patients moving to continued access should move directly from V19 to V501 and not perform V801 or V802
Section 1.3.4 Study Drug Self-Administration	Updated table name and footnote "a"	Updated for clarity

Section 2.2.4 IL-23p19 Blockade in Crohn's Disease	Updated efficacy of IL-23p19 blockade in Crohn's disease information per recent data	Updated per recent data
Section 2.3 Benefit/Risk Assessment	Added AMAX in overall benefit/risk conclusion	Updated to include AMAX information
Section 5.2 Exclusion Criteria	Updated wording from duration of the study to duration of the long-term extension period of the study	Update to clarify that marijuana is prohibited during long-term extension of the study
Section 6.1 Study Intervention(s) Administered	Removed text and added tables that lists the interventions in the study	To align with the current sponsor protocol template
Section 8.1.2.3 Inflammatory Biomarkers	Removed "from samples taken prior to Week 12 of AMAX"	To clarify that no CCI or fecal calprotectin results will be shared until after database lock
Section 9.5 Interim Analyses	Added additional information for clarification	Update for clarity
Section 10.1.1 Regulatory and Ethical Considerations	Added additional information per template	To align with the current sponsor protocol template
Section 10.1.2 Financial Disclosure	Added this section per template	To align with the current sponsor protocol template
Section 10.1.3 Informed Consent Process	Updated language per template	To align with the current sponsor protocol template
Section 10.1.4 Data Protection	Added additional information per template	To align with the current sponsor protocol template
Section 10.1.6 Dissemination of Clinical Study Data	Added additional information per template	To align with the current sponsor protocol template
Section 10.1.9 Study and Site Closure	Added additional information per template	To align with the current sponsor protocol template

Section 10.1.11 Investigator Information	Added the investigator information section per template	Added per template
Section 10.3.1.2 Events Meeting the AE definition	Removed lack of efficacy details	Removed as lack of efficacy is not considered as an adverse event in this study
Section 10.7 Appendix 7: prohibited Medications	Updated guidance for use for infection therapy	Updated for clarity
Section 10.11 Appendix 11: Abbreviations and Definitions	Added abbreviations and definitions as per changes in the document	Added per updated information
Section 10.13 Appendix 13: Optional Continued Access Period	Added Optional Continued Access Period details	Added Continued Access Period details
Section 10.14 Appendix 14: CCI [redacted]	Added CCI [redacted] details	Addition of an optional CCI [redacted] substudy that may be offered to a subset of participants to assess the CCI [redacted]
Section 10.15 Appendix 15: Country-specific requirements	Added all EU countries addenda into this appendix	All protocol addenda approved by EU Member States have been incorporated into appendices for the purpose of creating a consolidated protocol that will support the transition to the EU Clinical Trial Regulation
Throughout the protocol	Changed the CCI [redacted]	Updated to make the screening labs interval consistent through the document
Throughout the protocol	Minor editorial changes	Modified for clarity
Section 10.16 Appendix 16: Protocol Amendment History	Added Amendment (b) summary of changes table	Addition of amendment (b) details
Section 11 References	Updated reference as per the changes in protocol	Updated as per protocol changes

Amendment [b]: 03-Aug-2022

This amendment is considered to be substantial.

The amendment is considered to be substantial because it is likely to have a significant impact on the

- safety or the rights of the study participants, and
- reliability and robustness of the data generated in the clinical study.

Overall Rationale for the Amendment:

The primary rationale for this amendment is to revise the objectives and endpoints for the study in alignment with changes made to the originator AMAM study. Revisions based on new standard safety language are also being incorporated.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis and Section 3 Objectives and Endpoints	Updated objectives and endpoints	To align with changes to AMAM protocol to place more emphasis on clinical outcomes
Section 1.2 Schema	Added "Frequency" row	To clarify the time between visits
Section 1.3.1 Schedule of Activities - Visit 1 through Visit 9 CCI [redacted]	Added additional column for V1 Office - Dosing and defined V1 screening as V1[a] and V1 Dosing as V1[b]	To clarify that V1 has procedures both on screening and dosing dates
	Removed "Data from Originator Study (R)" and added "See footnotes for additional key details"	To co-locate the details regarding when each procedure is required in the footnotes
	Added CCI [redacted] in footnote t to the 14-Day and 1-Day paper diaries for all patients	To collect CCI [redacted] data in addition to the data collected from AMAM-originating patients in the first 12 weeks by the eDiary
	Added footnote ah, which requires that if more than CCI [redacted] have elapsed at the time of rollover to AMAX between the last procedures in AMAM and the first dosing in AMAX, additional procedures must be performed prior to the first AMAX dosing at V1b	To ensure information at the time of first AMAX dosing is sufficiently current

Section # and Name	Description of Change	Brief Rationale
	Updated reference to footnotes throughout table.	For clarification
	Updated footnotes b, d, f, j, l, q, u, v, w, and z. Added footnotes ae, af, and ag.	For clarification and to provide additional information.
Section 1.3.2 Schedule of Activities - Visit 10 through Visit 19 [redacted]	Removed "Data from Originator Study (R)" and added "See footnotes for additional key details"	To co-locate the details regarding when each procedure is required in the footnotes
	Added chemistry and hematology at additional office visits	To monitor safety labs at approximately [redacted] intervals through the [redacted] of this long-term extension study
	Added [redacted] in footnote l to the 14-Day and 1-Day paper diaries for all patients	To collect [redacted] data in addition to the data collected from AMAM-originating patients in the first [redacted] by the eDiary
Section 1.3.3 Schedule of Activities - Early Termination, [redacted], Unscheduled Visits/Assessments, and Follow-up Visits	Removed "Data from Originator Study (R)" and added "See footnotes for additional key details"	To co-locate the details regarding when each procedure is required in the footnotes
	Added chemistry and hematology at additional office visits	To monitor safety labs at approximately [redacted] intervals through the [redacted] of this long-term extension study
	Removed "complement, cytokine panel" from Hypersensitivity kit row	These tests no longer need to be considered as part of the hypersensitivity assessment, based on updated sponsor guidelines
	Added [redacted] in footnote v to the 14-Day and 1-Day paper diaries for all patients	To collect [redacted] data in addition to the data collected from AMAM-originating patients in the first [redacted] by the eDiary
Section 2.2.5 Preclinical and Clinical Studies of Mirikizumab	Updated information added	To align with updated Investigator's Brochure and Risk Profile and disclosures

Section # and Name	Description of Change	Brief Rationale
Section 2.3 Benefit/Risk Assessment	Updated information added	To align with updated Investigator's Brochure and Risk Profile and disclosures
Section 4.2 Scientific Rationale for Study Design	Updated primary objectives and endpoint information	To align with Section 1.1 and Section 3
Section 5 Study Population	Added information explaining V1 split visit	For clarification
Section 5.1 Inclusion Criteria	Inclusion criteria [2] and [3]: Updated "preferred" to "recommended" and added additional information about situations where participants may not be able to complete all assessments within the recommended visit window	For clarification
	Inclusion criterion [5]: Removed "an established" Updated "elevated bilirubin levels" to "elevated serum total bilirubin levels"	To allow for enrollment of participants who are diagnosed with Gilbert's syndrome during screening For clarification
	Inclusion criterion [6]: Updated contraception guidance for female participants	To align with current standard safety language
Section 5.2 Exclusion Criteria	Exclusion criterion [22]: Removed adenoma without dysplasia, added colonic adenomatous polyp, and revised criteria to include size, dysplasia grade, and being in a non-colitic area	To reflect most recent data
	Exclusion criterion [23]: Removed colonic dysplasia, added adenomatous polyp, and revised criteria to include size, dysplasia grade, presence of any serrated	To reflect most recent data

Section # and Name	Description of Change	Brief Rationale
	lesion, and being in a non-colitic area	
	Exclusion criterion [27]: Updated to include "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"	To align with parent study AMAM.
Section 5.3 Lifestyle Considerations	Removed instruction for participants not to donate sperm during the study or for 16 weeks following study participation	This is not necessary for mirikizumab.
	Updated instruction for participants not to donate blood or blood products during the study or for 16 weeks following study "drug administration" instead of study "participation"	For clarification and to align with eligibility criteria
Section 5.4 Screen Failures	Updated definition of screen failures to specify participants who are not enrolled due to failing one or more eligibility criteria	For clarification
	Updated instructions for participants who do not "meet eligibility criteria" to not "subsequently enroll"	For clarification
Section 6.1 Study Intervention(s) Administered	Preparation and Administration: Added instructions for participants who choose self-administration of syringes, at Visit 4 the site personnel will administer the first injection and the participant will administer the second injection	For clarification

Section # and Name	Description of Change	Brief Rationale
	Updated instructions for recording the timing of injections from "taken to confirm the full dose was achieved within the given time range" to "administered"	For clarification
	Investigator Responsibilities: Added bullet point about ensuring that participants are dosed with the correct combination of prefilled syringes	To emphasize that there are two different sizes of syringes
Section 6.1.1 Study Drug Administration Log	Updated information about Study Drug Administration Training Log	For clarification
Section 6.5.1 Permitted Therapy	Added information about modifications needed due to medical necessity	For clarification
Section 6.5.3 Corticosteroid Taper	Added instruction for participants who have not begun corticosteroid tapering at Week 12 or those who start corticosteroids after Week 12	For clarification
Section 6.7 Management of Hypersensitivity, Infusion-Related Events, Infusion Site Reactions, and Injection Site Reactions	"Injection Site Reactions or Infusion Site Reactions": Changed "angioedema" to "edema"	For accuracy
Section 7.1.1 Liver Chemistry Stopping Criteria	This section has been added to replace the section for Hepatic Event or Liver Test Abnormality. The rest of Section 7.1 has been renumbered to reflect this change	To align with the current protocol template

Section # and Name	Description of Change	Brief Rationale
Section 7.1.2 Permanent Discontinuation	This section has been renumbered. Removed intestinal dysplasia and added any colonic adenomatous polyp, dysplasia in GI tract, or presence of any serrated lesion in safety considerations	To reflect most recent data
	Updates made throughout section	To align with current standard safety language
	Updated treatment noncompliance bullet point in "Other Reasons"	For clarification
Section 7.1.3 Criteria for Temporary Interruption (Withholding) of Study Drug	This section has been renumbered Updated "should" to "must": "Cases that may merit temporary withholding of study drug must be discussed with the medical monitor"	To ensure this important communication occurs
Section 7.1.3 Discontinuation of Inadvertently Enrolled Participants	This section has been removed	Deleted as internal process will be followed for inadvertent enrollment
Section 8 Study Assessments and Procedures	Updated instructions for collecting new screening labs prior to dosing for samples taken more than CCI [redacted] prior to dosing	For clarification
Section 8.1.1 Primary Efficacy Assessment	Updated primary endpoint information. Added Clinical Remission and CDAI information that was previously in Section 8.1.2 The remaining sections of 8.1.2 have been renumbered.	To align with Sections 1.1 and 3
Section 8.1.2.2 PROs	Added CCI [redacted] to list of PROs collected in all	The CCI [redacted] is being added to the paper diary

Section # and Name	Description of Change	Brief Rationale
	participants from AMAG and AMAM	
Section 8.2.5 Stool Testing	*C. difficile* Toxin updated to include "(toxins A and B, and glutamate dehydrogenase, with reflex to polymerase chain reaction testing as needed)"	For clarification
CCI		
Section 8.3 Adverse Events and Serious Adverse Events	Added information, "Any other events/diagnoses that start after signing AMAX consent but before first AMAX dosing should be recorded in the AMAX MH eCRF"	For clarification
Section 8.3.1 Serious Adverse Events and Section 10.3.5. Appendix 3 Reporting of SAEs	Updated "to fulfill regulatory requirements" to "for tracking purposes" for pregnancy reporting	For clarification
	Added text, "through the pregnancy outcome, generally no longer than 6 to 8 weeks past the estimated due date" to the pregnancy reporting information	To align with current standard safety language
Section 8.3.5 Pregnancy	Updated the following language: • obtaining a consent from the female partner of a male study participant • recording pregnancy information on the appropriate form, and • clarifying that pregnancy is not considered an AE although SAE reporting procedure is used	For clarity, per current Lilly protocol template

Section # and Name	Description of Change	Brief Rationale
Section 8.5 Pharmacokinetics	Added information that results of additional samples will not be provided to the investigator.	For clarification
Section 9.3 Population for Analyses	Added primary analysis set to be the population for efficacy analyses	To maintain continuity between study AMAM and study AMAX populations used for analyses.
9.4.1 General Considerations	Revised to clarify that the SAP may be modified during the trial	While the first version of the SAP is finalized prior to FPV, revisions may be made during the study prior to final DBL
	Modified text to add the primary analysis set as the population for efficacy analysis	To maintain continuity between study AMAM and study AMAX populations used for analyses
	Added text that select efficacy summaries may also be conducted in the mITT population	To allow for conduct of other relevant analyses
Section 9.4.2.2. Participant Characteristics and Section 9.4.2.3 Concomitant Therapy	Added “and primary analysis set” to the populations being summarized	To align with Section 9.3
Section 9.4.3 Primary Efficacy Analyses	Changed “mITT population” to “primary analysis set”	To align with Section 9.4.1
	Updated information to reflect the new co-primary objectives	To align with Sections 1.1 and 3
Section 10.2 Appendix 2: Clinical Laboratory Tests	Added “Absolute neutrophil count (segmented and bands) (calculated)” and “Neutrophils, bands (if detected)” to Clinical Laboratory Tests	For clarification

Section # and Name	Description of Change	Brief Rationale
	Added "Toxins A and B, and GDH, with reflex Toxin PCR" to *C. difficile* testing and removed "Confirmed by a test for C. difficile toxin gene expression"	For clarification
	Removed Cytokine panel and Complement (C3 and C4)	These tests no longer need to be considered as part of the hypersensitivity assessment, based on updated sponsor guidelines
Section 10.3.1.3 Appendix 3: Events Not Meeting the AE Definition	Updated information about planned surgeries and nonsurgical interventions not being reported as AEs unless the underlying medical condition has worsened during the course of the study	For clarification
Section 10.3.2 Appendix 3: Definition of SAE	Updated to add that other Abnormal Pregnancy Outcomes are also considered SAEs	For clarification
Section 10.3.3 Appendix 3: Definition of Product Complaint	This section has been added to reference Section 8.3.8 for the definition of product complaint The rest of Section 10.3 has been renumbered to reflect this change	To align with current template
Section 10.3.5 Appendix 3: Reporting of SAEs	Added text that pregnancies are also reported using the SAE reporting process for tracking purposes	To align with current standard safety language
Section 10.4 Appendix 4: Liver Safety: Suggested Actions and Follow-Up Assessments	This section has been updated	To align with current standard safety language
Section 10.7 Appendix 7: Prohibited Medications	Clarified that topical JAK inhibitors are allowed	For clarification

Section # and Name	Description of Change	Brief Rationale
Section 10.8 Appendix 8: Permitted Medications and Dose Stabilization	This section has been updated	For clarification
Section 10.9 Appendix 9: Patient-Reported Outcome Instruments	Removed language indicating that the CCI [redacted] is in the eDiary only Updated footnote a to add 14-Day paper diary	CCI [redacted] is being added to the paper diaries For clarification
Section 10.12 Appendix 12: Provisions for Changes in Study Conduct During Exceptional Circumstances	Added text that flexibilities outlined will be determined by the sponsor in accordance with applicable local regulations	For clarification
	Added text about remote visits data collection and reporting of AEs, SAEs, and product complaints	For clarification
	Added text that every effort should be made to enable participants to return to on-site visits as soon as reasonably possible	To ensure that study conduct returns to align with the requirements of the main protocol when possible
	Updated local laboratory testing option information. Added text that local laboratories may also be used for HBV serology, HCV and HIV testing and for urinalysis	For clarification
	Added text that site personnel should update documentation per local requirements and sponsor guidance.	To provide additional detail
	Updated text that local laboratory testing may be performed locally if needed. Removed information about logistics related to sample	For clarification

Section # and Name	Description of Change	Brief Rationale
	stability and feasibility to collect at alternate location	
	Added text that hematocrit results from local labs may be included in analyses at key timepoints as needed to calculate CDAI if central lab results are not available	To provide additional flexibility to collect key information in exceptional circumstances
	[redacted]	
	Updated screening period guidance for screening laboratory assessments	To provide additional accommodation for screening labs if needed
Section 10.13 Appendix 13: Protocol Amendment History	This section has been added	To include the revision history for the previous amendment
Throughout	Editorial corrections	Minor, therefore not described

Amendment [a]: 01-Jul-2021
This amendment is considered to be substantial because it is likely to have a significant impact on the safety or physical/mental integrity of participants and/or the scientific value of the study.

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.

Secondary updates for this amendment include the revision of the Schedule of Activities office visits changing from every CCI [redacted]) in the study. As this is a long-term extension study, the participants should benefit from having fewer office visits and allowing for participants to self-administer at home during CCI [redacted] of the study while still monitoring participant health and long-term safety data.

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

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	• Updated to match revisions in Section 3. • Revised text to clarify CCI [redacted]	• To improve clarity and completeness. • Clarification
1.2 Schema	• Updated schema.	• To incorporate change in visit schedule from every CCI [redacted]
1.3 Schedule of Activities	• Reformatted SoA, created footnotes from Notes column of previous version, and split into separate subsections containing tables by year(s) (Table AMAX.1-1, Table AMAX.1-2, and Table AMAX.1-3). Table AMAX.1-4 placed in its own subsection. • Throughout SoA:	• Simplification

Section # and Name	Description of Change	Brief Rationale
	○ Added footnotes asking that sites see detailed instructions provided by the sponsor for calculation of visit dates.	• Clarification
	○ Added "monitoring" to HBV DNA test.	• Clarification
	○ Included footnotes adding "14-Day" to Take Home Patient Diary (Paper) dispensed.	• Clarification
	○ Added footnotes specifying "24-hour recall" for Patient 1-Day paper diary.	• Clarification
	○ Corrected phone visit days and tolerance intervals.	• Clarification
	○ Added footnotes specifying that a CT scan may be performed in lieu of a CXR.	• To allow flexibility to align with local practice for TB evaluation
	○ Clarified that the routine PK samples will be collected predose.	• Clarification
	○ Changed visits from every CCI [redacted] CCI	• To reduce participant burden
	○ Patient Study Drug Administration Training Log made optional as an unscheduled assessment.	• Investigators may train the participant at any visit at their discretion.
	○ Noted that unscheduled assessments may be performed at the discretion of the investigator during a scheduled visit (UASV).	• Clarification
	• Table AMAX.1-1.:	

Section # and Name	Description of Change	Brief Rationale
	○ TB testing (an IGRA or TST) and a CXR will only be performed at screening based on physical findings and other factors that the investigator feels warrant testing and imaging. Clarified the schedule and requirements for TB monitoring throughout study. Also, see Footnote i.	• Clarification and alignment with current recommendations for long-term extension studies
	○ Added collection of CCI on-site questionnaires at Visit 1 Day 1 (for participants originating from AMAM only)	• Clarification
	○ 	• 
		• To shorten and simplify SoA
		• To allow more time to obtain necessary screening results
		• Clarification

	○ Created footnotes from Notes column of previous version of SoA. Changes/additions to previous text as follows: ▪ Footnote b: Revised text to note that up to CCI is now allowed between last dose in originator study and first dose in AMAX. Emphasized that all screening results must be reviewed prior to dosing and must be from samples from within CCI prior to the Visit 1 dose. ▪ Footnote d: Revised text to clarify that Visit 1 dosing is defined as Day 1. ▪ Footnote l: Revised text to clarify requirements for HBV screening. ▪ Footnote m: Revised text to clarify when HBV DNA monitoring shall occur. ▪ Footnote o: Added text to clarify timing for collection of stool sample associated with endoscopies and office visits. ▪ Footnote s: Added timing details for providing, completing, and returning 14-Day paper diary for the CCI . ▪ Footnote x: Added recommendations and requirements regarding the order for performing procedures at visits associated with endoscopies. ▪ Footnote ab: Added text clarifying that study drug self-administration training may occur at	• Clarification • Clarification • Clarification • Clarification • Clarification • Clarification • Clarification and alignment with current recommendations for long-term extension studies • To shorten and simplify SoA • Clarification

	alternate/additional visits if necessary. • Table AMAX.1-2.: o Clarified the schedule and requirements for TB monitoring throughout study. Also, see Footnote f. Adjusted timing of procedures as needed to accommodate new visit schedule after V12. o Created footnotes from Notes column of previous version of SoA. Changes/additions to previous text as follows: ▪ Footnote h: Clarified text regarding HBcAb+ and HBV DNA monitoring. ▪ Footnote j: Provided additional detail regarding stool sample collection. ▪ Footnote k: Timepoints added for providing, returning, and completing patient 14-Day paper diary. ▪ Footnote m: Added recommendations and requirements regarding the order for performing procedures at visits associated with endoscopies. • Table AMAX.1-3.: o Added unscheduled assessments during a scheduled visit (UASV). o Split out the components of the CCI [redacted] in the table and provided additional details regarding lab collection and performance of procedures. o Added 10-day window for Visit 801.	• Clarification • Clarification • Clarification • To allow for additional optional data collection for UASV • Clarification • To rectify previous omission • Clarification and alignment with current recommendations for long-term extension studies • To increase visibility regarding labs that may be needed on an unscheduled basis • To shorten and simplify SoA • Clarification

Section # and Name	Description of Change	Brief Rationale
	○ TB testing and CXR will only be performed at screening and other visits based on physical findings and other factors that the investigator feels warrant testing and imaging. Clarified the schedule and requirements for TB monitoring throughout study. Also, see footnotes h, i, and l.	• Clarification • Clarification
	○ Added Hypersensitivity kit and Hepatic kit to table.	• Clarification • Clarification
	○ Created footnotes from Notes column of previous version of SoA. Changes/additions to previous text as follows: ▪ Footnote a: Added recommendation to see sponsor instructions for calculation of visit dates. ▪ Footnote c: Added instructions for conducting unscheduled visits (997). ▪ Footnote d: Added instructions for conducting optional assessments during unscheduled visits. ▪ Footnote m: Clarification regarding HBV testing. ▪ Footnote n: Clarification regarding HBV DNA monitoring. ▪ Footnote r: Provided additional detail regarding fecal calprotectin and stool sample collection and testing.	• Clarification • Clarification • Clarification • To align with schedule change

Section # and Name	Description of Change	Brief Rationale
	▪ Footnote u: Added instructions specifying that the Patient 14-Day paper diary provided by the site at the visit prior to CCI [redacted] will be collected at next scheduled office visit (and per footnote b, should be completed in the 14 days leading up to that next scheduled office visit). ▪ Footnote w: Added recommendations and requirements regarding the order for performing procedures at visits associated with endoscopies. • Table AMAX.1-4.: o Revised visit schedule to allow [redacted]	
2.2.2. Currently Available Treatments and Unmet Need	• Modified text regarding the estimated rates of clinical remission in participants failing conventional therapy and in the biologic-failure population.	• Clarification
2.3 Benefit/Risk Assessment	• Changed CCI [redacted] in reference to other ongoing studies.	• To correct a typographical error
3. Objectives and Endpoints	• Revised text throughout to clarify whether timepoints are with respect to AMAG, AMAM, or AMAX as applicable. • Secondary Endpoints: CCI [redacted] o Effect of mirikizumab CCI [redacted] Modified Objective and Endpoint text.	• To indicate to which trial each timepoint refers • To clarify specific study conditions in the analysis

Section # and Name	Description of Change	Brief Rationale
	• Secondary Endpoints: ○ Moved secondary endpoint "To evaluate the effect of mirikizumab in achieving CCI [redacted] from Section CCI [redacted] to Section CCI [redacted]"	• To clarify specific study conditions in the analysis
4.1 Overall Design	• Modified text regarding how long study participants will receive mirikizumab.	• Clarification
4.3 Justification for Dose	• Removed "based on preliminary data at the time of this writing".	• Data are no longer preliminary
5. Study Population	• Added text to specify the study population as adult participants.	• Clarification

5.1 Inclusion Criteria	• Added text to clarify that the inclusion criteria apply to all AMAX participants regardless of their originating study unless a specific originator study (AMAM or AMAG) is specified.
	• Criterion [2]:
	  ○ Clarified regarding completion of last visit in originating trial.
	  ○ Preferred interval between final dose in AMAG and first AMAX dose changed to CCI [redacted]
	  ○ Maximum interval between final dose in AMAG and first AMAX dose changed from CCI [redacted].
	• Criterion [3]:
	  ○ Clarified regarding completion of last visit in originating trial.
		• Clarification
		• Clarification
		• Changed to allow greater flexibility to accommodate screening requirements
		• Changed to allow greater flexibility to accommodate screening requirements
		• Clarification

Section # and Name	Description of Change	Brief Rationale
	○ Preferred interval between final dose in AMAM and first AMAX dose changed to CCI [redacted] ○ Maximum interval between final dose in AMAM and first AMAX dose changed from CCI [redacted]. ○ Added note specifying adolescent participants who complete AMAM cannot enroll in AMAX, but may be eligible for the pediatric extension study. • Criterion [4]: Added note regarding additional support for IP self-administration, and option for a general exception to self-administration depending on circumstances. • Criterion [6]: ○ Period of abstinence or contraception following last dose of study drug changed to 16 weeks. ○ Definition of postmenopausal women changed to ≥ 40 years of age. Cessation of menses must have occurred without an alternative medical cause.	• Changed to allow greater flexibility for timing to accommodate screening requirements • Changed to allow greater flexibility for timing to accommodate screening requirements • Clarified extension study for adolescents • Clarification that participants will not be excluded from trial if they will not self-administer • For greater consistency across trials for participants on mirikizumab • To reflect most recent internal safety guidance
5.2 Exclusion Criteria	• Criterion [7]: Deleted • Criterion [8]: Deleted	• Redundancy with Inclusion Criteria [2] and [3] • Redundancy with Inclusion Criterion [3] • Clarification

Section # and Name	Description of Change	Brief Rationale
	• Criterion [14]: Added note that participants with a history of active TB with documentation of treatment by WHO and/or CDC criteria prior to the originator study are not excluded from the study. • Criterion [15]: Added reference to Section 8.2.6. • Criterion [16]: Modified text. • Criterion [18]: Period in which women may not enroll if planning to become pregnant changed from within 12 weeks to within 16 weeks of last dose. • Criterion [19]: Deleted • Criterion [25]: Updated text regarding delivery of parenteral nutrition. • Criterion [27]: Added new criterion on prohibited marijuana use and updated Appendix 7 (Prohibited Medications) accordingly.	• For TB prophylaxis details • Clarification regarding hypersensitivity • For greater consistency across trials for participants on mirikizumab • Participants would have been discontinued during originator trial if surgery was deemed to be an issue. • Parenteral and enteral nutrition as primary source of diet are excluded due to potential to confound efficacy assessments. • To avoid potential impact on protocol assessments as cannabinoids have shown a potential role in inflammation and mucosal permeability of the gastrointestinal tract
5.3 Lifestyle Considerations	• Modified text to include instruction to study participants regarding sperm donation.	• To be more comprehensive
5.4 Screen Failures	• Added text for participants who sign informed consent to enter Study AMAX but do not meet eligibility criteria.	• To provide clarification regarding safety follow-up for participants who screen fail in AMAX
6.1. Study Intervention(s) Administered	• Added text regarding need for resuscitation equipment, emergency medication, and safety monitoring.	• To match the AMAM protocol

Section # and Name	Description of Change	Brief Rationale
	• Added text that the sponsor may approve a general exception for self-administration for a participant, as noted in Inclusion Criterion 4.	• To clarify that participants may be exempted from self-administration in the entire study, not just for a single dose
6.5. Concomitant Therapy	• Added subsection headings under concomitant therapies and prohibited medications and renumbered subsequent sections.	• Clarification
6.5.1. Permitted Therapy	• Modified text to add that participants taking permitted CD concomitant medications are recommended to keep doses stable unless modifications are needed for appropriate medical management. • Clarified that for participants entering AMAX on corticosteroids the doses should remain stable until Week 12, and after Week 12 corticosteroid tapering will occur as described in Section 6.5.3.	• Clarification • Clarification
6.5.2. Prohibited Therapy	• Added exceptions to prohibited CD medications, IV corticosteroid, systemic corticosteroids for non-CD indications, and marijuana use. • Added exception to vaccinations allowing RNA-based vaccinations.	• To align with the AMAM protocol and to improve clarity • The introduction of RNA-based COVID-19 vaccines has made it necessary to clarify that these are permitted.
6.5.3. Corticosteroid Taper	• Clarified that for participants who enter AMAX on corticosteroids, tapering should be initiated or continued for participants who at the discretion of the investigator have achieved clinical response at Week 12, with reference to Section 10.8.	• Clarification • Clarification

Section # and Name	Description of Change	Brief Rationale
	• Clarified that oral corticosteroid dose may not be increased above the baseline dose in originator study unless due to medical necessity.	
6.7. Management of Hypersensitivity, Infusion-Related Events, Infusion Site Reactions, and Injection Site Reactions	• Hypersensitivity Events: Added a note regarding PK, immunogenicity, CCI [redacted] lab results. • Noted that same steps should be performed for nonsystemic hypersensitivity reactions as with systemic hypersensitivity reactions, except that continued trial participation may be allowed.	• Clarification that these lab results are not intended for participant management and will not be shared with investigative sites • Clarification
7.1.1. Permanent Discontinuation	• Clarified that drainage specifically of a perianal or other cutaneous abscess is an allowed surgery.	• Clarification
7.1.2. Criteria for Temporary Interruption (Withholding) of Study Drug	• Revised the text for management of participants who develop decreased absolute lymphocyte count.	• To increase clarity on participant management
7.2 Participant Discontinuation/With drawal from the Study	• Removed redundant language regarding investigator or participant decision.	• Redundant
8.1.1.2 Endoscopy	• Modified text to clarify that AMAG-originating participants who have reached the CCI [redacted] • Added paragraph regarding recommendation for endoscopies to be performed on a different day than collection of questionnaire responses and IP administration or if on the same day, regarding sequence of assessments.	• Clarifications/correction s • Clarifications/correction s

Section # and Name	Description of Change	Brief Rationale
8.1.1.3 Endoscopic Biopsies	• Revised text referencing source of details of biopsy sample collection. • Added statement on biopsy sample retention.	• Clarifications/corrections • Clarifications/corrections
8.1.2.3 PROs	• Revised terminology regarding questionnaires/diaries for greater clarity.	• Modified to match other changes in the protocol where references to 1- and 14-Day paper diaries and questionnaires are used.
8.1.2.4. Inflammatory Biomarkers	• Modified text to clarify that investigators will be blinded to CCI results and fecal calprotectin results from samples taken prior to Week 12 of AMAX until after AMAM database lock.	• To improve clarity of sample blinding and timing for unblinding
8.2.4. Chest Radiography	• Modified text to clarify when imaging is required and that a CT scan can be performed as an alternative to the CXR. Noted also that an IGRA or TST should be performed.	• Clarification
8.2.6 Tuberculosis Testing	• Reorganized section. • Added Section 'Initial screening'. • Specified that if there are relevant physical findings or other factors that the investigator feels warrant testing and imaging, either at screening or at monitoring during the trial, an IGRA OR TST and CXR should be performed.	• Reorganized so that procedures would be listed in order of occurrence for greater clarity. • Clarification • Clarification and alignment with current recommendations for long-term extension studies

Section # and Name	Description of Change	Brief Rationale
	• Added that participants with 1 indeterminate QuantiFERON-TB Gold assay plus 1 borderline T-SPOT.TB assay will be excluded. Added Section 'TB Screening Outcomes and Enrollment'. Moved Section 'Diagnosis of LTBI During the Study'.	• Clarification
8.2.8. Hepatitis B Testing	• Noted that participants who were HBcAb+ in the originator study only need HBV DNA testing, not full HBV screening, and will require continued HBV DNA monitoring. • Management of participants with detectable HBV DNA: Added language regarding consultation with medical monitor.	• Clarification • Clarification that any subsequent study drug administration following HBV DNA positive result requires approval of the medical monitor
8.2.11. Depression, Suicidal Ideation, and Behavior Risk Monitoring	• Removed text regarding Self Harm Supplement Form and Self Harm "Follow-Up" Form. • Modified text on administration of CCI • Removed text that the tablet device is used to electronically capture the data for CCI	• Information currently collected via safety reporting provides sufficient information on self-harm cases. • Clarification • CCI is only on paper. No tablet is used.
8.3 Adverse Events and Serious Adverse Events	• Noted that AEs occurring after signing the AMAX ICF, but prior to dosing, if considered reasonably possibly related to an AMAX study procedure, should be reported as an AE in AMAX.	• Clarification
8.3.1. Serious Adverse Events	• Revised language to refer to Section 8.3 for details regarding general AE collection.	• Clarification

Section # and Name	Description of Change	Brief Rationale
8.3.5. Pregnancy	• Modified text on collecting details for pregnancies, including change to follow-up of pregnancies occurring until at least 16 weeks after last dose (rather than 20 weeks).	• Alignment with other time intervals related to pregnancy and contraception, as well as general clarification
9.4.1.1 Analyses	• Least squares mean from a restricted maximum likelihood-based model of MMRM substituted for estimation of mean response over time for the change from baseline in endoscopic scores for CCI [redacted] • Alternative versions of MMRM may be implemented as deemed appropriate substituted for specified statistical analyses. • For continuous efficacy and health outcome variables for participants from Study AMAM, deleted restriction of estimation using analysis of covariance in 'intervention group by intervention received in originating study interaction'.	• For all: Changes to modeling are to provide flexibility in modeling and align with the SAP
9.4.1.4 Missing Data Imputation	• Revised text to clarify that participants will be considered a Nonresponder for the NRI analysis if they have specified changes in concomitant CD medications. • Revised text: Including the MMRM with missing-at-random assumption for handling missing data in the primary analysis is optional.	• For both: To provide flexibility considering medications may change over the course of a long-term extension study
Appendix 1: 10.1.6. Data Quality Assurance	• Updated text, including noting that investigator document retention requirements are outlined in the Clinical Trial Agreement (rather than specifically 15 years).	• To provide up-to-date guidance

Section # and Name	Description of Change	Brief Rationale
Appendix 2: 10.2 Clinical Laboratory Tests	• Modified to include that QuantiFERON-TB Gold test may be done locally. • Clarified that CCI and fecal calprotectin results from samples taken prior to AMAX Week 12 will not be provided to sites until AMAM database lock or later.	• To allow flexibility for local testing in alignment with AMAM • To improve clarity
Appendix 3: 10.3.1.2 Definition of AE	• Deleted lack of efficacy from list of events meeting AE definition.	• To align with language in Section 8.3
Appendix 3: 10.3.2 Definition of SAE	• Deleted statement implying that events such as hospitalization for signs/symptoms of the disease under study or death due to progression of disease may not be SAEs.	• Clarification
Appendix 3: 10.3.4.1 SAE Reporting via an Electronic Data Collection Tool	• Noted that SAEs occurring after shutdown of the electronic data collection tool may also be reported via phone call to the medical monitor.	• Clarification
Appendix 7 10.7 Prohibited Medications	• Listed that IV corticosteroids may be used as infusion premedication or short-term treatment for acute non-CD events. • Added text to include information on IV corticosteroid used for CD that may result in discontinuation. • Added text to include information regarding initiation or adjustment of systemic corticosteroids for non-CD indications. • Added text to include information on systemic corticosteroid used for adrenal insufficiency. • Broadened language to include any anti-IL 12/23p40 antibodies.	• Incorporation of content from the body of the protocol • To allow medical discretion to prevent unnecessary discontinuation • Clarification • Clarification • To match the AMAM protocol

Section # and Name	Description of Change	Brief Rationale
	• Added text to include information on prohibited marijuana use.	• To avoid potential impact on protocol assessments as cannabinoids have shown a potential role in inflammation and mucosal permeability of the gastrointestinal tract
Appendix 8: 10.8 Permitted Medications with Dose Stabilization	• Modified dose of permitted prednisone to ≤30 mg/day. • Noted that oral corticosteroid doses for CD should be kept stable until Week 12 and should follow guidance in Section 6.5.3 thereafter. • Added text allowing RNA-based vaccines.	• To match the AMAM protocol. • Clarification. • Due to the introduction of RNA-based vaccines for COVID-19
Appendix 9: 10.9 Patient-Reported Outcome Instruments	• Removed text that the tablet device is used to electronically capture the data for CCI and other indicated PROs.	• The PROs listed are only on paper. No tablet is used.
Appendix 12: 10.12 Provisions for Changes in Study Conduct During Exceptional Circumstances	• Added appendix.	• Provides for temporary changes to procedures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.
Throughout	• Minor editorial changes	• Corrections/clarifications

Abbreviations: AE = adverse event; AMAG = I6T-MC-AMAG protocol; CCI [redacted]; AMAM = I6T-MC-AMAM protocol; AMAX = I6T-MC-AMAX protocol; CD = Crohn's disease; CDC = Centers for Disease Control and Prevention; COVID-19 = Coronavirus Disease 2019; CS = corticosteroid; CCI [redacted]; CT = computed tomography; CXR = chest x-ray; DNA = deoxyribonucleic acid; HBcAb = hepatitis B core antibody; HBV =hepatitis B virus; CCI [redacted]; ICF = informed consent form; IGRA = interferon gamma release assay; IL = interleukin; IP = investigative product; IV = intravenous; LTBI = latent tuberculosis infection; MMRM = mixed-effects model for repeated measures; mRNA = messenger ribonucleic acid; NRI = nonresponder imputation; CCI [redacted]; PK = pharmacokinetics; PRO = patient-reported outcome; CCI [redacted]; RNA = ribonucleic acid; SAE = serious adverse event; SAP = Statistical Analysis Plan; SC = subcutaneous; SoA = Schedule of Activities; TB = tuberculosis; TST = tuberculin skin test; UASV = unscheduled assessments during a scheduled visit, WHO = World Health Organization.

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