Statisical Analysis Plan I6T-MC-AMAX (3)

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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Title Page

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Version history

This Statistical Analysis Plan (SAP) for Study I6T-MC-AMAX (AMAX) is based on the protocol amendment (e) dated 10 September 2024.

SAP Version	Approval Date	Change	Rationale
3		Section 1.1, Section 5.1.5 and throughout: Estimand language updated by adding language about commercial availability and extraordinary circumstances.	To clarify and to account for commercial availability of the drug and extraordinary circumstances
		Section 1.1 and Section 5.3.1: Updated Endpoints	To align with protocol updates
		Section 1.2 and throughout: References to continued access period added throughout	To align with protocol updates
		Section 1.2: Clarified ET visits and study design	Clarification
		Section 4: Updated the populations to add PAS and describe subpopulations. Updated throughout that the PAS population is the primary efficacy population.	Align with updated protocol and clarify how subpopulations would be created without using concomitant medication intercurrent events in CCI .
		Section 5.1.1 Removed geographic region from any analysis models.	Align with updated protocol.
		Section 5.1.5: Modified non-responder imputation and modified baseline observation carried forward added.	New analysis to match updated estimands.
		Section 5.2.2: Clarified that baseline for safety analysis will be the start of Study AMAX.	Clarification.

		Section 5.1.4: Throughout the document AMAG patients will not be included in analysis models.	To focus on the primary population of interest.
		Section 5.1.4: Treatment arms to be used have changed to include treatment sequence in AMAM.	Based on the study design and the goal to understand what happens to patients depending on their treatment in CCI .
		Section 5.4.1.2: Emphasized ANCOVA as the primary method for continuous endpoints.	Using simpler method as the primary method.
		Section 5.8.3: Added information about handling early interim analysis including PAS population definition.	To avoid bias in the situation that not all patients could have completed the time point of interest.
		Appendix 1: Added details on endoscopy and CDAI data.	To avoid missing endoscopy and CCI endpoints.
		Appendix 1: Defined alternate endoscopic remission and related analysis.	To accommodate an updated understanding of how endoscopic remission should be defined.
		Appendix 1: Clarified that Corticosteroid free remission by CDAI and Corticosteroid Endoscopic Remission will be analyzed separately	Clarification.
		Appendix 1: Added CCI ≤2 analysis	Based on analysis done in study AMAM.
		Appendix 1: Added Histology Details	Based on analysis done in study AMAM
		Appendix 1: Added CCI and PGRS description.	To provide information about an endpoint in the protocol.

		Added Appendix 9 to define windows for Daily Diary calculations and handling the different types of dairy data described throughout..	Provide additional details not previously provided.
2	February 19, 2024	Section 5.7.3 Reinduction Analysis Added section	Added new analyses for re-induced subpopulations
		Section 5.8.2 Analysis of the Primary Endpoint Added tiered database lock as an option	Allow for additional data from different sources to be transferred at a later date after the initial transfer
1	March 23, 2020	Not Applicable	Original version approved prior to first patient visit

1 Introduction

This SAP includes the analysis plan for efficacy, safety, biomarkers, and immunogenicity data.

Additional exploratory endpoints may be documented in supplemental SAPs.

The table, figure, and listing (TFL) specifications are contained in a separate document.

1.1 Objectives and Endpoints

Estimands for the co-primary and secondary endpoints are defined as follows:

- Population: Primary Analysis Set (PAS) and specified sub-population (Section 4)
- Intercurrent-event strategies (IES):
    - For binary endpoints, a hybrid estimand strategy is used. For ICEs of study treatment discontinuation for reasons other than commercial availability and extraordinary circumstances including study treatment supply issues and site termination, the composite strategy will be used where participants with these ICEs are classified as non-responders subsequent to discontinuation. To handle the ICE of study treatment discontinuation due to commercial availability and extraordinary circumstances including study treatment supply issues and site termination, the hypothetical scenario where these patients remained on study treatment is envisaged as the target of estimation (see details on imputation in Section 5.1.5).
    - For continuous endpoints a hybrid estimand strategy is used. For ICEs of study intervention discontinuation for reasons other than commercial availability and extraordinary circumstances including study treatment supply issues and site termination, the composite strategy will be used such that measurements after the ICEs will return to baseline. To handle the ICE of study treatment discontinuation due to commercial availability and extraordinary circumstances including study treatment supply issues and site termination, a hypothetical scenario is envisaged in which these patients remained for the rest of the study and measurements after this ICE will be imputed (see details imputation in Section 5.1.5).
- Population level summary (PLS):
    - Binary endpoints: proportions
    - Continuous endpoints: LS mean

Objectives and Endpoints

Objectives	Endpoints
Primary	
CCI [redacted]	
• To assess the effect of mirikizumab on clinical remission by CDAI and endoscopic response CCI [redacted][a]	• Proportion of participants achieving clinical remission by CDAI (CCI [redacted]) at Week 52 of AMAX

Objectives	Endpoints
	• 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: ○ Week 12 ○ Week 52 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 • Proportion of participants CCI in AMAX at: ○ Week 52 CCI
• To evaluate the effect of mirikizumab in CCI	The following scores over time during AMAX: CCI

Objectives	Endpoints
in participants CCI	CCI • IBDQ in AMAX at CCI , Week 52, CCI 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 CCI	• Proportion of participants achieving clinical response by PRO in AMAX at: ○ Week 52 CCI
• To assess the effect of mirikizumab CCI	• Proportion of participants achieving CCI in AMAX at: ○ Week 52 CCI
• To evaluate the effect of mirikizumab CCI	• Proportion of participants achieving CCI in AMAX at: CCI ○ Week 52 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

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Objectives	Endpoints
• 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
• To assess the effect of mirikizumab CCI	• Proportion of participants achieving CCI in AMAX at: ○ Week 52 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[b] at AMAX Week 52 CCI • Proportion of participants who achieve clinical remission by CDAI or endoscopic remission[b] CCI
AMAM participants not achieving endpoints at Week 52 of AMAM:	
• 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

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

Objectives	Endpoints
• 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]
• To assess the effect of mirikizumab in the achievement of [redacted]	• Proportion of participants achieving [redacted] in AMAX at: ○ Week 52 [redacted]
• To evaluate the effect of mirikizumab in achieving [redacted] endoscopic remission [redacted]	• Proportion of participants achieving [redacted] or endoscopic remission[b] in AMAX at: ○ Week 52 [redacted]

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

[a] The phrase "participants from AMAM who completed treatment on blinded SC mirikizumab" is intended to include only patients who were randomized to mirikizumab in AMAM and completed the trial on blinded therapy.

[b] These endpoints are intended to be analyzed separately.

1.2 Study Design

Study AMAX is a long-term study of participants completing Studies I6T-MC-AMAM (Study AMAM) and I6T-MC-AMAG (Study AMAG) (see schema below).

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

- Mirikizumab CCI .
- Mirikizumab CCI .

CCI Q4W; CCI .

CCI Q4W CCI Q4W; 900 mg is the induction dose being studied in Study AMAM.

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 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 CCI follow-up period

Study AMAM participants will require an endoscopy to be performed at Week 52, CCI visit occurs more than 16 weeks after the last endoscopy in Study AMAX.

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

Study intervention may be permanently discontinued or temporarily withheld during the study (see Sections 7.1.1 and 7.1.2 of the AMAX Protocol). Participants who permanently discontinue study drug early will undergo early termination procedures, which include an early termination visit (ETV) and post-treatment follow-up visits (V801 and V802).

No rescue medication is allowed during the study. Participants who enter Study AMAX on corticosteroids should initiate corticosteroid tapering as described in the protocol (see Section 6.5.3 of the AMAX Protocol).

An interim analysis of the co-primary endpoints may be conducted when all Study AMAM participants complete Week 52 of Study AMAX. Additional ad-hoc interim analyses may be performed as deemed appropriate or to fulfill the need of regulatory interactions or publication purposes.

A Data Monitoring Committee (DMC) consisting of members external to Lilly will be established for interim safety monitoring across all the sponsor's adult Phase 3 studies in participants with CD. Additional details can be found in the AMAX protocol (see Section 10.1.5) and in the DMC Charter.

The final database lock will occur after the last participant has completed Study AMAX.


CCI


CCI
Q4W = every 4 weeks;
CCI

2 Statistical Hypotheses

This is an open-label extension study with no randomization. Participants from Study AMAM are assigned to either mirikizumab SC or mirikizumab IV followed by SC based on their endoscopy response status at Week 52 in Study AMAM. Participants from Study AMAG are assigned to mirikizumab SC. Therefore, no intervention comparisons or formal hypothesis testing will be done. Analyses and summaries will be focused on point estimates and confidence intervals.

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3 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 (Study AMAM and Study AMAG). It is anticipated that approximately 50% to 70% of the eligible participants will be enrolled from Study AMAM and Study AMAG. Based on this assumption, 640 to 900 participants are expected to enter Study AMAX.

4 Analysis Sets

For purposes of analysis, the analysis sets are defined in the table below.

Population	Description
Modified Intent-to-Treat (mITT) Population[1]	**Definition:** All enrolled participants who take at least 1 dose of study intervention, even if the participant does not receive the correct study intervention, or otherwise does not follow the protocol. Participants will be analyzed according to the assigned treatment arms described in Section 5.1.4. **Purpose:** Used for sensitivity analyses of efficacy, health outcomes and quality of life measures.
Primary Analysis Set (PAS) Population[1]	**Definition:** All patients from the mITT population who CCI [redacted]. **Purpose:** Used for primary analyses of efficacy, health outcomes and quality of life measures.
Safety Population[1]	**Definition:** Same as mITT Population. **Purpose:** Safety analysis will be conducted on this population.
Sub-Populations[1,2] **of PAS (or mITT or Safety)**	**Definition:** All participants in the PAS (or mITT or Safety) population who meet the criteria for the endpoints being examined (an example, the study primary endpoint, the endoscopic response at Week 52 in AMAX, a subset population will be the endoscopic responders at Week 52 of the originating study). Participants will be analyzed according to the assigned treatment arms described in Section 5.1.4. **Purpose:** Used for efficacy, health outcomes, quality of life measures and may be used for safety analysis.

[1] For early interim analysis where not all participants could have completed the time point of interest, participants who enrolled in AMAX after a specified date will be excluded from the analysis to ensure that all patients in the analysis could have completed the time point of interest.

[2] When defining the subpopulation of interest, concomitant medication related intercurrent events in AMAM will not be considered. For example, a patient who violated specified concomitant medication rules would be considered as an endoscopic non-responder in AMAM due to the intercurrent event, but could still considered a responder in AMAX due to directly looking at the endoscopic data.

5 Statistical Analyses

5.1 General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (hereafter, Lilly) or its designee.

Not all displays and analyses described in this SAP will necessarily be included in the clinical study report (CSR). Not all displays will necessarily be created as a "static" display. Some displays may be incorporated as interactive display tools such as Spotfire instead of or in addition to a static display. Any display described in this SAP and not provided in the CSR would be available upon request.

Any change to the data analysis methods described in the protocol will require a protocol amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol and the justification for making the change will be described in the CSR.

Additional exploratory and or sensitivity analyses of the data may be conducted as deemed appropriate. Some of these additional supplementary analyses may be prespecified in a separate supplemental SAP.

5.1.1 Analysis Methods

Unless otherwise specified, efficacy analyses will be conducted on PAS population, and safety analyses will be conducted on the safety populations as described in Section 4. Summaries will be presented by intervention group in Study AMAX and by the intervention received in the originating study.

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

For assessments of the co-primary endpoints and other binary efficacy and health outcomes endpoints, the following will be provided unless otherwise specified:

- unadjusted proportions along with the 2-sided 95% confidence intervals using the Wilson Score method (Wilson 1927; Newcombe 1998).

The primary method for binary endpoints will utilize the Wilson Score method. Additional missing data imputation methods for binary endpoints are specified in Section 5.1.5.

For continuous endpoints with more than one post baseline 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, intervention group (Section 5.1.4), visit, and visit by intervention group interaction. Alternative versions of MMRM may be implemented as deemed appropriate. The covariance structure to model the within-participant errors will be unstructured. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous

Toeplitz covariance structure followed by the heterogeneous autoregressive covariance structure will be used. The Newton-Raphson with ridging optimization technique will be used to aid with convergence. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. If the listed methods result in a lack of convergence, analysis may be limited to data through Week 52 of Study AMAX. Following, the model may be updated to remove the visit by intervention received in Study AMAM interaction. If the model fails to converge after the interaction term has been removed, MMRM may not be used for analysis. Unless otherwise specified the MMRM analysis will be performed only for patients originating from AMAM.

For variables that are not collected at each postbaseline visit, data may exist at visits where the variable was not scheduled to be collected. In these situations, data from the early discontinuation visit that do not correspond to the planned collection schedule will be excluded from the MMRM analysis (Andersen and Millen 2013). As the MMRM method accounts for missing data under the missing at random assumption, no other missing data techniques will be used with the MMRM model.

For all change from baseline measures of continuous efficacy, health outcomes, and quality of life endpoints, the least squares mean and the corresponding 95% confidence interval from analysis of covariance (ANCOVA) will be summarized. The ANCOVA model will include baseline value, and intervention group (see Section 5.1.4) in the model. Additional continuous endpoints that are not change from baseline will be presented as summaries. Unless otherwise specified the ANCOVA analysis will be performed only for patients originating from CCI .

Missing data imputation method for the ANCOVA model and summaries are specified in Section 5.1.5.

All analyses of safety data will be presented as summaries.

5.1.2 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 the mirikizumab Crohn's Disease development program). Unless otherwise specified, all references to baseline for safety analyses refer to baseline values of Study AMAX.

Change from baseline will be calculated as the visit value of interest minus the baseline value. If a baseline value or the value at the visit is missing for a particular variable, then the change from baseline is defined as missing.

5.1.3 Definition of Study Period Time Interval

The table below displays a list of study periods along with the definition of which participants will be considered to have entered the study period and when the individuals start and end the study period. The table shows both a date and a time.

To calculate the length of any time interval or time period in this study the following formula will be used:

$$Length\ of\ interval\ (days) = End\ Date - Interval\ Start\ Date + 1$$

To convert any time length from days to years, the following formula will be used:

$$Length\ of\ interval\ (years) = Length\ of\ interval\ (days)/365.25$$

To convert any time length from days to weeks, the following formula will be used:

$$Length\ of\ interval\ (weeks) = Length\ of\ interval\ (days)/7$$

Only for the purpose of calculating the length of study period time intervals, the words "prior to" in the table below should be understood to mean "the day before" while the words "after" should be understood to mean "the day after." For the purpose of determining whether a date/time lies within an interval these words are intended to convey whether the start or end of the period is inclusive of the specified date.

Study Period	Interval Start Definition	Interval End Definition
Induction Period (CCI [redacted])	At the date/time[a] of first dose of study intervention in Study AMAX. For participants who are assigned but not dosed, Induction Period starts on the date of study intervention assignment.	Prior to the start of Long-Term Extension Period. For participants who discontinue before or CCI [redacted] visit, Induction Period ends at the latest date of study intervention discontinued date or last study intervention visit date.
Long-Term Extension Period (CCI [redacted])	At the Week 12 dosing date/time[a] in Study AMAX. If the participant is unable to be dosed at the Week 12 visit, the Long-Term Extension Period starts at the Week 12 Visit. If the participant misses the Week 12 visit, the Long-Term Extension Period starts at Day 92.	After the CCI [redacted] visit date. For participants who discontinue prior to CCI [redacted], Long-Term Extension Period ends at the latest date of study intervention disposition date or last study intervention visit date.
Follow-up Period	All participants who had Visit 801 or Visit 802 are considered to have entered the Follow-up Period. The latest of Induction Period or Long-Term Extension Period interval end date.	The last date of the last study visit and study disposition date.
Complete Study Period (CCI [redacted])	At the date/time[a] of first dose of study intervention. For participants who are assigned but not dosed, Complete Study Period starts on the date of study intervention assignment.	After the CCI [redacted] visit date. For participants who discontinue prior to CCI [redacted], Complete Study Period ends at the latest date of study intervention disposition date or last study intervention visit date.

Complete Study Period + Continued Access Period	At the date/time[a] of first dose of study intervention. For participants who are assigned but not dosed, Complete Study Period starts on the date of study intervention assignment.	The last date of the last study visit within Continued Access Period.

[a] Missing dose time will be imputed as the earliest time that is consistent with available data about dose time. For example, suppose the minutes are missing but hour is present. In this case, we would impute the minutes to be 0.

5.1.4 Definition of Study Intervention by Study Period

The table below provides the study intervention groups to be displayed for each analysis population and analysis period.

Analysis Population	**Analysis Period**	**Study Intervention Groups:**
PAS/mITT/Safety population	Induction Period/Complete Study Period/ Continued Access Period	• AMAM miri/miri/ SC • AMAM miri/miri/ IV • AMAM PBO/miri/ SC • AMAM PBO/miri/ IV • AMAM uste/uste/ SC • AMAM uste/uste/ IV • AMAM PBO/PBO/ SC • AMAM PBO/PBO/ IV • All AMAM/ SC [a] • All AMAM/ IV [a] • All AMAM [a] • All AMAG/ SC [a] • Total [a]
PAS/mITT subset populations	Complete Study Period	PAS/mITT sub-population – Endoscopic Responder in the originating study: • AMAM miri/miri/ SC (co-primary analysis) • AMAM PBO/miri/ SC • AMAM uste/uste / SC • AMAM PBO/PBO/ SC • All AMAM SC [a] • Total [a] PAS/mITT sub-population – Endoscopic Nonresponder in the originating study: • AMAM miri/miri / IV • AMAM PBO/miri/ IV • AMAM uste/uste / IV • AMAM PBO/PBO/ IV • All AMAM IV [a] • Total [a]

Analysis Population	Analysis Period	Study Intervention Groups:
		Other sub-population analysis: • AMAM miri/miri/ SC • AMAM miri/miri/ IV • AMAM PBO/miri/ SC • AMAM PBO/miri/ IV • AMAM uste/uste/ SC • AMAM uste/uste/ IV • AMAM PBO/PBO/ SC • AMAM PBO/PBO/ IV • All AMAM/ SC [a] • All AMAM/ IV [a] • All AMAM [a] • All AMAG/ SC [a] • Total [a]

Abbreviations: AMAG = Study I6T-MC-AMAG; AMAM = Study I6T-MC-AMAM; IV = intravenous; miri = mirikizumab; PBO = placebo; SC = subcutaneous; uste = ustekinumab; Q4W = every 4 weeks.

[a] Unless otherwise specified, these treatment arms are not included in the modeling to estimate treatment effect for MMRM and ANCOVA analysis. Also these treatment arms may be excluded from some tables or figures to simplify the output.

For endpoints utilizing the PAS/mITT subset populations, not all intervention groupings listed above may be shown.

5.1.5 Missing Data Imputation

Intercurrent events (FDA 2017) are events which occur after the study intervention initiation and make it impossible to measure a variable or influence how it should be interpreted. Section 1.1 includes intercurrent events for the primary and secondary endpoints. The missing data methods described below may be used to address the intercurrent event strategies proposed for this study.

Non-Responder Imputation

A hybrid estimand strategy will be used to handle binary endpoints:

- Patients who discontinue study treatment due to reasons other than commercial availability and extraordinary circumstances including study treatment supply issues and the site termination, are categorized as treatment failures after discontinuation. As such, these patients are not considered missing from the perspective of the estimand of interest.
- The hypothetical strategy will be used to handle the ICE of study treatment discontinuation due to commercial availability and extraordinary circumstances including study treatment supply issues and the site termination. Participants with the ICE will be excluded from analysis for timepoints of interest after the ICE. The assumption behind this approach is that measurements after this ICE are missing completely at random and thus the estimation can be implemented using observed values.

A small number of patients who completed study treatment up to the time point of interest but are sporadically missing the binary endpoint data will still require imputation. These patients will be imputed using NRI.

Modified Baseline Observation Carried Forward (mBOCF)

As a primary analysis for continuous variables, the ANCOVA with mBOCF approach will be used for handling missing data. For continuous endpoints a hybrid estimand strategy is used:

- For ICEs of study intervention discontinuation due to reasons other than commercial availability and extraordinary circumstances including study treatment supply issues and the site termination, the composite strategy will be used such that measurements after the ICEs will return to baseline. As such, these patients are not considered missing from the perspective of the estimand of interest.
- For the additional ICE where participants discontinue due to commercial availability and extraordinary circumstances including study treatment supply issues and the site termination, a hypothetical scenario is envisaged in which these patients remained for the rest of the study, leading to a missing data problem. Participants with the ICE will be excluded from analysis for timepoints of interest after the ICE. The assumption behind this approach is that measurements after this ICE are missing completely at random and thus the estimation can be implemented using observed values.

For all participants with sporadically missing observations prior to any ICEs, the last non-missing observation before the sporadically missing data will be carried forward.

Mixed-effects Model for Repeated Measures (MMRM)

As a sensitivity analysis for continuous variables with multiple postbaseline measurements in a study period, the MMRM approach will be used 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.

For continuous endpoints, a hybrid estimand strategy is used:

- For ICEs of study intervention discontinuation due to reasons other than commercial availability and extraordinary circumstances including study treatment supply issues and the site termination, the composite strategy will be used such that measurements after the ICEs will return to baseline. As such, these patients are not considered missing from the perspective of the estimand of interest.
- For the additional ICE where participants discontinue due to commercial availability and extraordinary circumstances including study treatment supply issues and the site termination, a hypothetical scenario is envisaged in which these patients remained for the rest of the study, leading to a missing data problem. Assuming measurements after this ICE can be considered as missing at random, the MMRM approach can be used to handle the missing data.

The MMRM approach will also be used to handle sporadic missingness.

Modified Nonresponder Imputation (mNRI)

For the co-primary endpoints and selected secondary endpoints, missing data will be imputed using hybrid multiple imputation as a sensitivity analysis. Missing data for reasons of treatment discontinuation due to commercial availability and extraordinary circumstances including study treatment supply issues and the site termination will be imputed by multiple imputation (MI), while missing data due to treatment discontinuation for reasons other than commercial availability and extraordinary circumstances including study treatment supply issues and the site termination will be categorized as non-responders. Sporadically missing data (i.e., when a patient was still in the treatment period but data was not collected) will be imputed by MI.

As Observed Analysis

For some endpoints, patients who are missing the endpoint data for a specific visit for any reason including intercurrent events will be excluded from the analysis for that visit. Simple descriptive summaries will be presented.

5.2 Participant Dispositions

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

5.3 Primary Endpoint(s) Analysis

5.3.1 Definition of Endpoint(s)

The co-primary endpoints are

- the proportion of participants achieving endoscopic response at Week 52 of Study AMAX CCI [redacted] who completed treatment on CCI [redacted]
- the proportion of participants achieving clinical remission by CDAI at Week 52 of Study AMAX CCI [redacted] who completed treatment on CCI [redacted]

Endoscopies performed up to a maximum of 14 days after the Week 52 visit date of Study AMAX, but before any additional dosing, will be used for the analysis of Week 52.

Descriptions and derivations of these endpoints are shown in Appendix 1 in Section 6.1. As described in Section 5.1.4, the proportions will be reported by the sequence of treatments in AMAM and AMAX.

5.3.2 Main Analytical Approach

Section 1.1 describes the primary estimand that will be used to assess the primary objective of this study.

All analyses presented will be descriptive using the PAS population and the methods described in Section 5.1.1 and Section 5.1.5. Specifically, the NRI method will be used based on a hybrid strategy for the intercurrent event of discontinuing treatment due to different reasons prior to time point of interest. Confidence intervals using the Wilson Score method will be presented. Additional details are described in Appendix 2 in Section 6.2.

5.3.3 Supplemental Analysis

In addition to the NRI imputation method, an analysis in the PAS population using mNRI and observed case will also be presented as further analyses (see Section 5.1.5) for binary endpoints. The co-primary endpoints will also be analyzed in the mITT population. Additional details are described in Appendix 2 in Section 6.2.

5.4 Secondary Endpoint(s) Analysis

5.4.1 Secondary Endpoint(s)

5.4.1.1 Definition of Endpoint(s)

Secondary endpoints are listed in Section 1.1 under Secondary.

Descriptions and derivations of these endpoints are shown in Appendix 1 in Section 6.1.

5.4.1.2 Main Analytical Approach

Section 1.1 describes the proposed estimands to assess secondary objectives of this study.

The main analytical approach for binary secondary endpoints may be done similarly as for the primary endpoints and is described in Section 5.3.2. The main analytical approach for continuous secondary endpoints from Study AMAM participants will utilize ANCOVA as described in Section 5.1.1. Details are described in Appendix 2 in Section 6.2.

5.4.1.3 Sensitivity Analysis

Refer to Section 5.3.3 for details regarding the methods used for sensitivity analyses that may be used for binary secondary endpoints. Additional details are described in Appendix 2 Section 6.2.

For continuous endpoints, MMRM will be used as sensitivity analysis (see Section 5.1.5).

5.5 Tertiary/Exploratory Endpoint(s) Analysis

Exploratory endpoints are listed in Section 1.1 under Tertiary/Exploratory.

Descriptions and derivations of exploratory endpoints as well as additional endpoints not specified in the protocol are shown in Appendix 1 in Section 6.1.

Additional endpoints and analyses not described in Appendix 1 in Section 6.1 or Appendix 2 in Section 6.2 will be described in supplemental analysis plans.

5.6 Safety Analyses

In general, safety evaluations will be based on the Safety Population for the Induction Period and Complete Study Period. Select safety analysis will also be performed for the continued access period as needed.

For the purpose of Study AMAX alone, the following are planned:

- Listing of Serious Adverse Events (SAEs)
- Listing of adverse events leading to permanent discontinuation of study drug
- Summary of SAEs (with different columns for the intervention groups specified in Section 5.1.4)
- Summary of AEs leading to permanent discontinuation of study drug (with different columns for the intervention groups specified in Section 4)

The safety data from this study will also be used as part of ongoing safety reviews. The safety data from this study will also be used as part of integrated summaries in submissions/disclosures and ongoing safety review through study end.

5.6.1 Extent of Exposure

Duration of exposure to study intervention will be summarized by study intervention group for the Safety Population. For the Complete Study Period, exposure will be calculated as (Date of end date of Complete Study Period – Date of start date of the Complete Study Period + 1 day) described in Section 5.1.3. Calculations will use the Safety Population in the Complete Study Period.

Total participant-years (PY) of exposure will be reported for the Safety Population by study intervention group in Section 4. Descriptive statistics will be provided for participants-weeks of exposure and the frequency of participants falling into different exposure ranges will be summarized.

- >0; ≥12 weeks; ≥36 weeks; ≥52 weeks; ≥68 weeks; ≥84 weeks; ≥100 weeks; ≥116 weeks; ≥140 weeks;
- >0 to <12 weeks; ≥12 weeks to <36 weeks; ≥36 weeks to <52 weeks; ≥52 weeks to <68 weeks; ≥68 weeks to <84 weeks; ≥84 weeks to <100 weeks; ≥100 weeks to <116 weeks; ≥116 weeks to <140 weeks; ≥140 weeks

Additional exposure ranges may be considered, if necessary. No p-values will be reported in these tables as they are intended to describe the study populations, rather than test hypotheses about them.

5.6.2 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.

An individual sample is potentially examined multiple times in a hierarchical procedure to produce a sample anti-drug antibodies (ADA) assay result and potentially a sample neutralizing anti-drug antibodies (NAb) assay result. A participant has treatment-emergent anti-drug antibodies (TE-ADA) when ADA are induced or boosted by exposure to study drug; i.e., when at least one postbaseline ADA sample has a 4-fold increase in titer, compared to baseline (if ADA were present at baseline) or has a titer 2-fold greater than the minimum required dilution of 1:10 (if no ADA were present at baseline).

Compound level safety standards will be followed in the analyses of immunogenicity. The summary of TE ADA positive (TE ADA+), TE ADA+ by titers and TE ADA+ with neutralizing antibody (NAb) status to mirikizumab will be produced for the mITT population (including originating studies and Study AMAX).

5.7 Other Analyses

5.7.1 Health Outcomes/Quality of Life

The health outcome and quality of life measures including CCI [redacted] and Inflammatory Bowel Disease Questionnaire (IBDQ) will be analyzed using methods described for continuous data as described for efficacy measures in Section 5.4.1.2.

5.7.2 Efficacy Subgroup Analyses

Subgroup analyses may be conducted for the co-primary endpoints in the PAS sub-population (Section 4). The following groups will be considered for subgroup analyses:

- Not-Biologic-Failed Population: Participants who have not failed any biologic medication regardless of prior biologic exposure.
- Biologic-Failed Population: Participants who have failed at least one biologic medication.

Some additional subgroup analyses may be performed to meet regulatory requirements in specific countries. The analysis of additional subgroups will not require an amendment to the SAP.

5.7.3 Reinduction Analysis

Patients from Study AMAM who did not achieve endoscopic response at Week 52 in Study AMAM were reinduced using mirikizumab 900 mg IV Q4W (3 doses). We will further investigate outcomes in patients who

- were randomized to mirikizumab in the AMAM Primary Analysis Set
- showed some initial response on mirikizumab
- lost the response or did not achieve further improvement at AMAM Week 52, and

- were re-induced in Study AMAX.

Several analyses will be performed, including

- proportion of patients achieving clinical response by patient-reported outcomes (PRO) at Week 12 in Study AMAX among:
  - patients who achieved clinical response by PRO at Week 12 in Study CCI, and
  - who did not achieve clinical response by PRO at Week 52 in Study CCI.
- proportion of patients achieving clinical response by PRO at Week 12 in Study AMAX among:
  - patients who achieved clinical response by PRO any time between Week 2 and Week 24 in Study CCI, and
  - who did not achieve clinical response by PRO at Week 52 in Study CCI.
- Proportion of patients achieving clinical remission by PRO at Week 12 in Study AMAX among:
  - patients who achieved clinical response by PRO at Week 12 in Study CCI, and
  - who did not achieve clinical remission by PRO at Week 52 in Study CCI.
- Proportion of patients achieving clinical remission by PRO at Week 12 in Study AMAX among:
  - patients who achieved clinical remission by PRO any time between Week 2 and Week 24 in Study CCI, and
  - who did not achieve clinical remission by PRO at Week 52 in Study CCI.

Safety analysis may be performed for the corresponding subpopulations. The efficacy and safety analysis of additional subpopulation will not require an amendment to the SAP.

5.8 Interim Analyses

5.8.1 Data Monitoring Committee (DMC)

A DMC consisting of members external to Lilly is established for interim safety monitoring across Studies AMAM, and AMAX in participants with CD. This committee consists of 4 voting members, including a designated chairperson, 2 additional physicians with gastroenterology and/or clinical trial expertise, and a statistician. No member of the DMC may have contact with study sites. A Statistical Analysis Center (SAC) is external to the mirikizumab team that may be Lilly employees or from third-party organization designated by Lilly. No member of the SAC will have contact with study sites. Study AMAX is an open label study and safety data will be reviewed by the DMC. The DMC will advise Lilly regarding continuing participant safety; however, 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 studies.

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Study AMAX will not be stopped for positive efficacy. Study sites will receive information about interim assessment ONLY if they need to know for the safety of their participants. Details of the planned safety data analyses, the roles and responsibilities, and the data review process are included in the DMC Charter. Unblinding details are specified in a separated unblinding plan.

5.8.2 Analysis of the Primary Endpoint

One interim analysis is planned to be conducted CCI [redacted] Since Study AMAX is open-label, this analysis will be based on unblinded data.

5.8.3 Ad-hoc Interim Analysis

Additional ad-hoc interim analyses may be performed as deemed appropriate and/or to fulfill regulatory needs or for disclosure purposes. The final database lock will occur after the last participant has completed Study AMAX. A tiered database lock approach may be performed as deemed appropriate for interim analyses and the final database lock to allow additional data such as histology data to be transferred at a later date after the initial transfer. For early interim analysis where not all participants could have completed the time point of interest, participants who enrolled in AMAX after a specified date will be excluded from the analysis to ensure that all patients in the analysis could have completed the time point of interest. For the ad-hoc interim analysis in September 2024, the safety period will be 1 year of treatment.

6 Supporting Documentation

6.1 Appendix 1: Description and Derivation of Efficacy and Health Outcome Endpoints

Measure	Description	Variable	Derivation / Comment	Definition of missing
SES-CD	The SES-CD is an endoscopic scoring system for CD based on 4 endoscopic variables (presence and size of ulcers, proportion of surface covered by ulcers, proportion of surface affected by disease, and presence and severity of stenosis), which are assessed in 5 ileocolonic bowel segments (ileum; right, transverse, and left colon; and rectum). Each of the 4 endoscopic variables is scored from 0 to 3: presence and size of ulcers (none = score 0; diameter 0.1 cm to 0.5 cm = score 1; 0.5 cm to 2 cm = score 2; >2 cm = score 3); extent of ulcerated surface (none = 0; <10% = 1; 10% to 30% = 2; >30% = 3); extent of affected surface (none = 0; <50% = 1; 50% to 75% = 2; >75% = 3); and presence and type of narrowing (none = 0; single, can be passed = 1; multiple, can be passed = 2; cannot be passed = 3). The endoscopic scores for each bowel segment are called subscores.	SES-CD total score	The sum of all endoscopic scores across all bowel segments. Total scores range from 0 to 56, with higher scores indicating more severe disease. SES-CD total score is calculated as average of total scores from all readers. AMAG 3-year endoscopy: 1. Endoscopies performed up to 4 weeks prior to the intended AMAG 3y timepoint (3 years after randomization in AMAG) or up to <4 years after randomization in AMAG 2. If not available, ETV/unscheduled endoscopies performed up to 4 weeks prior to intended AMAG 3y timepoint or up to <4 years after randomization in AMAG Week 52 endoscopy (AMAM-originating patients only) 1. Endoscopies performed up to 14 days after actual visit, with no additional dosing allowed prior to endoscopy (other than potentially the V9 dosing) 2. If not available, unscheduled/ETV endoscopies performed up to 14 days before or after actual V9 office visit, with no additional dosing allowed prior to endoscopy (other than potentially the V9 dosing) Week 156 endoscopy (AMAG/AMAM-originating patients) 1.Endoscopies performed up to 14 days after actual V19 office visit	Missing if endoscopy was not done at time point or if 2 or more central readers deemed the endoscopy video unreadable

Measure	Description	Variable	Derivation / Comment	Definition of missing
			2. If not available, unscheduled/ETV endoscopies performed up to 14 days before or after actual V19 office visit	
		Change from baseline in SES-CD total score	Change from baseline in SES-CD total score = SES-CD total score – baseline SES-CD total score	Missing if endoscopy was not done at baseline or time point or if 2 or more central readers deemed the endoscopy video unreadable
		Endoscopic Response	Endoscopic response is defined as ≥50% improvement from baseline in SES-CD total score. If [100* (SES-CD total score – baseline SES-CD total score) / baseline SES-CD total score] ≤ -50, then endoscopic response is achieved.	Missing if endoscopy was not done at baseline or time point or if 2 or more central readers deemed the endoscopy video unreadable
		Alternate endoscopic remission SES-CD ≤4	Endoscopic remission SES-CD ≤ 4 is defined as SES-CD Total Score ≤4 and at least a 2-point reduction from baseline and no subscore >1 for any variable in any segment. If SES-CD total score ≤ 4, SES-CD total score – baseline SES-CD total score ≤ -2, and each SES-CD subscore ≤ 1, then endoscopic remission SES-CD ≤ 4 is achieved.	Same as for endoscopic response

Measure	Description	Variable	Derivation / Comment	Definition of missing
		Endoscopic remission SES-CD ≤4	Endoscopic remission SES-CD ≤ 4 is defined as SES-CD Total Score ≤4 and at least a 2-point reduction from baseline and no subscore >1. If SES-CD total score ≤ 4, SES-CD total score – baseline SES-CD total score ≤ -2, and each SES-CD subscore ≤ 1, then endoscopic remission SES-CD ≤ 4 is achieved.	Same as for endoscopic response
CDAI	Crohn's Disease Activity Index (CDAI) is an 8-item disease activity measure comprised of a composite of 3 patient-reported and 5 physician-reported/laboratory items (physical signs and a laboratory parameter [hematocrit]). Participant responses are summed over a 7-day period and all items are subsequently weighted, yielding a total score range of 0 to 600 points. All endpoints derived using participant responses will be calculated from daily diary data from the most recent 7 days (possibly nonconsecutive) out of the 12 days prior to the day of the visit, after removing the day(s) of the endoscopy prep, the day of endoscopy procedure, and the 2 days following the endoscopy procedure. SF captures the number of liquid or very soft stools. AP score is classified as 0=none, 1=mild, 2=moderate, 3=severe.	Clinical remission by PRO	Clinical remission by PRO is defined as a stool frequency (SF) average ≤3 and abdominal pain (AP) average ≤1 with both values no worse than baseline. For each visit, AP average and SF average will be calculated from daily diary data by averaging the most recent 7 days in the 12 days prior to the day of the visit, after removing the day(s) of the endoscopy prep, the day of endoscopy procedure, and the 2 days following the endoscopy procedure. If SF average ≤ 3, AP average ≤ 1, SF average ≤ baseline SF average and AP average ≤ baseline AP average, then clinical remission by PRO is achieved.	Missing if less than 4 days of data are available at either baseline or endpoint
		Clinical response by PRO	Clinical response by PRO is defined as at least a 30% decrease in either SF or AP, and no worse than baseline. If [100 * (SF average – baseline SF average) / baseline SF average] ≤ -30 or [100*(AP average – baseline AP average) / baseline AP average] ≤ -30, and SF average ≤ baseline SF average and AP average ≤ baseline AP average, then clinical response by PRO is achieved.	Missing if less than 4 days of data are available at either baseline or endpoint

Measure	Description	Variable	Derivation / Comment	Definition of missing
		CDAI total score	CDAI total score is based on the CDAI questionnaire in Appendix 7 in Section 6.7. It also utilizes the standard weights table in that section. 1.Patient-reported items from diary - the most recent 7 days are included (possibly nonconsecutive) out of the 4 weeks prior to corresponding visit after removing the day(s) of the endoscopy prep, the day of endoscopy procedure, and the 2 days following the endoscopy procedure. See Appendix 9. 2. Physician-reported questionnaire – from up to 4 weeks prior to actual visit 3.Hematocrit - central (or secondarily local) lab Hematocrit value associated with the Visit; if neither available, use closest result from 4 weeks prior to visit up to 12 weeks after visit except for Week 12; For Week 12/V4, 4 weeks before or after this visit. 4. Weight –weight associated with the Visit; If not available, closest to the visit in 6 months before or after the visit except for Week 12; For Week 12 use 12 weeks before or after this visit	CDAI total score will be missing if any of its components are missing. If none of the options in Section 4 of the CDAI questionnaire is checked, it will be assumed that no extra-intestinal manifestations were present.
		Change from baseline in CDAI total score	Change from baseline in CDAI score is defined as CDAI score – baseline CDAI score.	Missing if CDAI total score is missing at baseline or at time point.

Measure	Description	Variable	Derivation / Comment	Definition of missing
		Clinical response by CDAI	Clinical response by CDAI is defined as a decrease from baseline in the CDAI total score ≥ 100 and/or a CDAI total score <150.	Missing if CDAI total score is missing at baseline or at time point.
		Clinical remission by CDAI	Clinical remission by CDAI is defined as [redacted].	Missing if CDAI total score is missing at time point.
		AP average	Description of AP average is provided as part of the definition for clinical remission by PRO.	Missing if less than 4 days of data are available at time point
		Change from baseline in AP average	Change from baseline in AP average is defined as AP average – baseline AP average.	Missing if AP average is missing at baseline or at time point
		SF average	Description of SF average is provided as part of the definition for clinical remission by PRO.	Missing if less than 4 days of data are available at time point
		Change from baseline in SF average	Change from baseline in SF average is defined as SF average – baseline SF average.	Missing if SF average is missing at baseline or at time point
Corticosteroid-free endpoints	See CDAI sections above.	Corticosteroid-free clinical remission by CDAI	Achieving clinical remission by CDAI and being corticosteroid-free ≥12 weeks prior to time point of interest.	Missing if clinical remission by CDAI missing
	See SES-CD section above.	Corticosteroid-free endoscopic remission	Achieving alternate endoscopic remission SES-CD ≤ 4 and being corticosteroid-free ≥12 weeks prior to time point of interest.	Missing if endoscopic remission SES-CD ≤4 is missing

Measure	Description	Variable	Derivation / Comment	Definition of missing
[redacted]				

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Measure	Description	Variable	Derivation / Comment	Definition of missing
CCI				
IBDQ	Inflammatory Bowel Disease Questionnaire (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."	IBDQ score	IBDQ total score is calculated as the sum of all questions. Scores range from 32 to 224; a higher score indicates a better quality of life.	If more than 4 questions are missing or more than 2 questions for any subscore are missing, then IBDQ Score is missing. Otherwise, missing questions imputed as the mean of the other items in each subscore.
		Change from baseline in IBDQ score	Change from baseline in IBDQ is defined as IBDQ total score – baseline IBDQ total score.	Missing if IBDQ score is missing at time point or baseline
		Bowel symptoms subscore	Calculated as the sum of questions 1, 5, 9, 13, 17, 20, 22, 24, 26, 29.	If only one question is missing, impute as the mean of the other items in the subscore. Missing if more than one item in the subscore is missing
		Systemic symptoms subscore	Calculated as the sum of questions 2, 6, 10, 14, 18.	
		Emotional function subscore	Calculated as the sum of questions 3, 7, 11, 15, 19, 21, 23, 25, 27, 30, 31, 32.	
		Social function subscore	Calculated as the sum of questions 4, 8, 12, 16, 28.	

Measure	Description	Variable	Derivation / Comment	Definition of missing
		Change from baseline in IBDQ subscore	Change from baseline in any one of the IBDQ subscores is defined as IBDQ subscore – baseline IBDQ subscore.	Missing if IBDQ subscore is missing at time point or baseline
		IBDQ response	≥16 point improvement from baseline in IBDQ score as described by Irvine et al. (1996).	Missing if either baseline or observed value is missing.
		IBDQ remission	IBDQ score ≥170 as described by Irvine (2008).	Missing if the IBDQ score is missing
[redacted]				

Measure	Description	Variable	Derivation / Comment	Definition of missing
[redacted]				
Extraintestinal manifestations (EIMs)	EIMs will be collected in the eCRF and include a. arthritis, arthralgia; b. iritis, uveitis; c. erythema nodosum, pyoderma gangrenosum, aphthous, stomatitis.	EIMs Count	EIMs count will be derived by summing the number of EIMs.	If the question is not answered, it will be missing
		EIMs Presence	EIMs Count ≥1	Missing if EIMs Count is missing
Fistulae	Draining cutaneous and draining rectal/vaginal fistulae will be collected in the eCRF	Number of draining fistulae	Draining fistulae count will be calculated by adding the number of draining cutaneous and rectal/vaginal fistulae.	If the question is not answered, then it will be missing

Measure	Description	Variable	Derivation / Comment	Definition of missing
		Fistulae Presence	Number of draining fistulae ≥1	Missing if number of draining fistulae is missing
		Percent change from baseline in draining fistulae	The percent change reduction will be calculated by subtracting the number of draining fistulae at endpoint from the number of draining fistulae at baseline. The result is divided by the number of draining fistulae at baseline and multiplied by 100.	Missing if number of draining fistulae is missing at baseline or time point.
		At least 50% reduction in draining fistulae	Percent change from baseline in draining fistulae ≥50	Missing if number of draining fistulae is missing at baseline or time point.
Medical resource utilization and health economics	Crohn's related emergency room (ER) Visits, Hospitalizations, Surgeries related to Crohn's disease will be collected in the eCRF.	Crohn's related ER visits count, Hospitalizations count, and Crohn's related surgeries count.	For each participant the number of Crohn's related ER visits, the number of hospitalizations, and the number of Crohn's related surgeries will be calculated during the study.	
		Medical resource utilization presence	Crohn's related ER visits count, Hospitalizations count, or Crohn's related surgeries count ≥1	

Measure	Description	Variable	Derivation / Comment	Definition of missing
Biomarkers	C-reactive protein (CRP) is a biomarker of inflammation.	CRP	Lab value.	Single lab value. Missing if missing.
	Fecal calprotectin is used as a biomarker of intestinal inflammation in clinical practice.	Fecal calprotectin	Lab value.	Single lab value. Missing if missing.
RHI	The RHI (Mosli et al. 2015) is a histopathological index consisting of 4 items and each score from 0-3 (i.e., chronic inflammatory infiltrate level [x1], lamina propria neutrophils [x2], neutrophils in epithelium [x3], erosion or ulceration [x5]). The total score of each segment ranges from 0 to 33, with higher scores indicating more severe disease. If more than 1 image is available for a segment, the CR will score index components based on the worst features across the images and biopsy sections.	RHI segmental scores	The segmental score is calculated as sum of all items with multiplication factors.	Missing if samples are not collected or image is deemed unreadable.
		RHI colonic score	Sum of the RHI segmental scores of 4 colon segments. The range is from 0 to 132.	Missing if all of the 4 colon segments are missing.
		RHI total score	Sum of all 5 RHI segmental scores. The range is from 0 to 165.	Missing if all segments are missing.
GHAS	The GHAS (D'Haens et al. 1998) is a histopathological index consisting of 8 items (i.e., 1. Epithelial damage [from 0-2], 2. Architectural changes [from 0-2], 3. Infiltration of mononuclear cells in the lamina propria [from 0-2], 4. Infiltration of polymorphonuclear cells in the lamina propria [from 0-2], 5. Polymorphonuclear cells in epithelium [from 0-3], 6. Presence of erosion and/or ulcers [0, 1], 7. Presence of granuloma [0, 1], 8. Number of biopsy specimens affected [from 0-3]). Total score for each segment is in a range of 0 to 16.	GHAS segmental scores	GHAS segmental score is in a range of 0 to 16 and is calculated by adding up the scores for each histological variable.	Missing if samples are not collected or image is deemed unreadable.
		Modified GHAS segmental scores	Modified GHAS segmental score is defined as the sum of 5 selected items (i.e., items 1, 3, 4, 5, and 6).	Missing if samples are not collected or image is deemed unreadable.
		Modified GHAS colonic score	Sum of 4 colon segmental modified scores.	Missing if all colon segments are missing
		Modified GHAS total score	Sum of all segmental modified scores.	Missing if all segments are missing

Measure	Description	Variable	Derivation / Comment	Definition of missing
	If more than 1 image is available for a segment, the CR will score index components based on the worst features across the images and biopsy sections.	Active GHAS segmental scores	Active GHAS segmental score is defined as the sum of 4 selected items (i.e., items 1, 4, 5, and 6).	Missing if samples are not collected or image is deemed unreadable.
		Active GHAS colonic score	Sum of 4 colon segmental active scores.	Missing if all colon segments are missing
		Active GHAS total score	Sum of all segmental active scores.	Missing if all segments are missing
		Histological response for segments, colonic segment (4-segment colon), total intestine	Histological response is defined as: Absence of neutrophils in epithelium and necessarily absence of epithelial damage, erosions, and ulcerations. Neutrophil infiltration of lamina propria is allowed. OR Decrease from the baseline RHI or active GHAS score (reduction of 50% from baseline)	Missing if GHAS score and sum of RHI items 2, 3, and 4 are missing at baseline or time of interest.
		Histological remission for segments, colonic segment (4-segment colon), total intestine	Absence of mucosal neutrophils (in both epithelium and lamina propria) and absence of epithelial damage, erosions, and ulcers.	Missing if GHAS score and sum of RHI items 2, 3 and 4 are missing.
Composite		Clinical remission by CDAI and endoscopic response	Achieved both clinical remission by CDAI and endoscopic response.	Missing if clinical remission by CDAI or Endoscopic response is missing.

Measure	Description	Variable	Derivation / Comment	Definition of missing
CCI				

Abbreviations: AP = abdominal pain; CDAI = Crohn's Disease Activity Index; CD = Crohn's disease; eCRF = electronic case report form; CRP = C-reactive protein; EIM = extraintestinal manifestation; CCI IBD = inflammatory bowel disease; IBDQ = Inflammatory Bowel Disease Questionnaire; MCID = Minimal clinical important difference; CCI PRO = patient-reported outcomes; SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency; VAS = Visual Analog Scale; CCI .

6.2 Appendix 2: Description of Analyses

For each measure, analyses will be presented separately for each originating study and, for AMAM-originating participants will be summarized by intervention group in Study AMAX and intervention received in AMAM (see Section 5.1.4).

Measure	Variable	Analysis Method (Section 5.1.1)	Population (Section 4)	Time Point(s)
SES-CD	Endoscopic response	Descriptive analysis with NRI, mNRI and as Observed	PAS (primary) mITT (sensitivity) PAS – In participants with endoscopic response at W52 of originating study (sensitivity) PAS – In participants without endoscopic response at W52 of originating study	All visits with measurements in Complete Study Period
	Alternate Endoscopic remission SES-CD ≤ 4	Descriptive analysis with NRI, mNRI and as Observed	PAS	All visits with measurements in Complete Study Period
		Descriptive analysis with NRI, mNRI and as Observed	PAS - In participants with endoscopic remission at W52 of originating study PAS - In participants without endoscopic remission at W52 of originating study	All visits with measurements in Complete Study Period
	SES-CD total score	Descriptive analysis with mBOCF and as Observed	PAS – In participants from Study AMAM	All visits with measurements in Complete Study Period

Measure	Variable	Analysis Method (Section 5.1.1)	Population (Section 4)	Time Point(s)
	Change from baseline in SES-CD total score	Descriptive analysis with ANCOVA and as Observed	PAS – In participants from Study AMAM	All visits with measurements in Complete Study Period
CDAI	Clinical remission by PRO	Descriptive analysis with NRI	PAS – In participants with clinical remission by PRO at W52 of originating study PAS – In participants without clinical remission by PRO at W52 of originating study	All visits with measurements in Complete Study Period
		Descriptive analysis with NRI and as Observed	PAS	All visits with measurements in Complete Study Period
	Clinical response by PRO	Descriptive analysis with NRI	PAS – In participants with clinical response by PRO at W52 of originating study PAS – In participants without clinical response by PRO at W52 in originating study	All visits with measurements in Complete Study Period
		Descriptive analysis with NRI as Observed	PAS	All visits with measurements in Complete Study Period
	Clinical remission by CDAI	Descriptive analysis with NRI	PAS – In participants with clinical remission by CDAI at W52 of originating study PAS – In participants without clinical remission by CDAI at W52 of originating study	All visits with measurements in Complete Study Period
		Descriptive analysis with NRI, mNRI and as Observed	PAS	All visits with measurements in Complete Study Period

Measure	Variable	Analysis Method (Section 5.1.1)	Population (Section 4)	Time Point(s)
	Clinical response by CDAI	Descriptive analysis with NRI, mNRI and as Observed	PAS	All visits with measurements in Complete Study Period
	CDAI total score	Descriptive analysis with mBOCF and as Observed	PAS	All visits with measurements in Complete Study Period
	Change from baseline in CDAI total score	Descriptive analysis with ANCOVA and as Observed	PAS	All visits with measurements in Complete Study Period
	AP average	Descriptive analysis with mBOCF and as Observed	PAS	All visits with measurements in Complete Study Period
	Change from baseline in AP average	Descriptive analysis with ANCOVA and as Observed	PAS	All visits with measurements in Complete Study Period
	SF average	Descriptive analysis with mBOCF and as Observed	PAS	All visits with measurements in Complete Study Period
	Change from baseline in SF average	Descriptive analysis with ANCOVA and as Observed	PAS	All visits with measurements in Complete Study Period
Composite SES-CD and CDAI endpoints	Clinical remission by CDAI and endoscopic response	Descriptive analysis with NRI, mNRI, and as Observed	PAS – In participants with Clinical Remission by CDAI and Endoscopic Response at Week 52 of the Originating study	All visits with measurements in Complete Study Period

Measure	Variable	Analysis Method (Section 5.1.1)	Population (Section 4)	Time Point(s)
Corticosteroid Free	Corticosteroid free Clinical Remission by CDAI	Descriptive analysis with NRI, mNRI, and as Observed	PAS – In participants taking corticosteroids at baseline and with CS free clinical remission by CDAI at W52 of originating study PAS – In participants taking corticosteroids at baseline and who did not achieve CS free clinical remission at CDAI at W52 of originating study	All visits with measurements in Complete Study Period
	Corticosteroid free Endoscopic Remission	Descriptive analysis with NRI, mNRI, and as Observed	PAS – In participants taking corticosteroids at baseline and with CS free endoscopic remission by CDAI at W52 of originating study PAS – In participants taking corticosteroids at baseline and who did not achieve CS free endoscopic remission by CDAI at W52 of originating study	All visits with measurements in Complete Study Period

Measure	Variable	Analysis Method (Section 5.1.1)	Population (Section 4)	Time Point(s)
CCI				
IBDQ	IBDQ total score	Descriptive analysis with mBOCF and as Observed	PAS	All visits with measurements in Complete Study Period
	Change from baseline in IBDQ total score	Descriptive analysis with ANCOVA and as Observed	PAS	All visits with measurements in Complete Study Period
	IBDQ subscores (listed in Appendix 1)	Descriptive analysis with mBOCF and as Observed	PAS	All visits with measurements in Complete Study Period
	Change from baseline for each IBDQ subscore (listed in Appendix 1)	Descriptive analysis with ANCOVA and as Observed	PAS	All visits with measurements in Complete Study Period
	IBDQ response	Descriptive analysis with NRI, mNRI, and as Observed	PAS	All visits with measurements in Complete Study Period
	IBDQ remission	Descriptive analysis with NRI, mNRI, and as Observed	PAS	All visits with measurements in Complete Study Period

Measure	Variable	Analysis Method (Section 5.1.1)	Population (Section 4)	Time Point(s)
[redacted]				
EIMs	EIMs presence	Descriptive analysis with NRI	PAS – In participants from Study AMAM with EIMs at baseline	All visits with measurements in Complete Study Period
Fistulae	Fistulae presence	Descriptive analysis with NRI	PAS – In participants from Study AMAM with fistulae at baseline	All visits with measurements in Complete Study Period
	At least 50% reduction in draining fistulae	Descriptive analysis with NRI	PAS – In participants from Study AMAM with fistulae at baseline	All visits with measurements in Complete Study Period
Medical resource utilization and health economics	Crohn's related ER visits count, Hospitalizations count, and Crohn's related surgeries count.	Descriptive analysis with mBOCF and as Observed	PAS	All visits with measurements in Complete Study Period
	Medical resource utilization presence	Descriptive analysis with NRI	PAS	All visits with measurements in Complete Study Period

Measure	Variable	Analysis Method (Section 5.1.1)	Population (Section 4)	Time Point(s)
Biomarkers	CRP	Descriptive analysis with mBOCF and as Observed	PAS	All visits with measurements in Complete Study Period
	Change from BL in CRP	Descriptive analysis with ANCOVA and as Observed	PAS – In participants from Study AMAM without endoscopic response at W52 of originating study PAS – In participants from Study AMAG without endoscopic response at W52 of originating study	All visits with measurements in Complete Study Period
	Fecal calprotectin	Descriptive analysis with mBOCF and as Observed	PAS – In participants from Study AMAM without endoscopic response at W52 of originating study PAS – In participants from Study AMAG without endoscopic response at W52 of originating study	All visits with measurements in Complete Study Period

Measure	Variable	Analysis Method (Section 5.1.1)	Population (Section 4)	Time Point(s)
	Change from BL in Fecal calprotectin	Descriptive analysis with ANCOVA and as Observed	PAS PAS – In participants from Study AMAM without endoscopic response at W52 of originating study PAS – In participants from Study AMAG without endoscopic response at W52 of originating study	All visits with measurements in Complete Study Period
Histology	Histologic Response	Descriptive analysis with NRI, mNRI, and as Observed	PAS – In participants with active histologic disease at baseline	All visits with measurements in Complete Study Period
	Histologic Remission	Descriptive analysis with NRI, mNRI, and as Observed	PAS – In participants with active histologic disease at baseline	All visits with measurements in Complete Study Period
	Histologic Response and Endoscopic Response	Descriptive analysis with NRI, mNRI, and as Observed	PAS – In participants with active histologic disease at baseline	All visits with measurements in Complete Study Period
	Histologic Remission and Endoscopic Remission	Descriptive analysis with NRI, mNRI, and as Observed	PAS – In participants with active histologic disease at baseline	All visits with measurements in Complete Study Period

Abbreviations: ANCOVA = analysis of covariance; AP = abdominal pain; BL = baseline; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CRP = C-reactive protein; CS = corticosteroid; EIM = extraintestinal manifestation; CCI [redacted] IBDQ = Inflammatory Bowel Disease Questionnaire; ITT = intent-to-treat; NRI = Non-Responder Imputation; CCI [redacted] miri = mirikizumab; mITT = modified intent-to-treat population; MMRM = mixed effects model of repeated measures; PRO = patient-reported outcome; SES-CD = Simple Endoscopic Score for Crohn's Disease; CCI [redacted].

6.3 Appendix 3: Changes to Protocol-Planned Analyses

Not applicable.

6.4 Appendix 4: Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by intervention group in Study AMAX and by the intervention in the originating study for the mITT/PAS population; no testing will be performed for baseline characteristics. Summaries are to include values from the baseline of the originating studies and, for values that are expected to change over time, Visit 1 of AMAX. The summary of additional participant characteristics and subgroup analysis will not require an amendment to the SAP. For continuous measures, summary statistics will include sample size, mean, standard deviation, median, minimum, and maximum. For categorical measures, summary statistics will include sample size, frequency, and percentages.

Variable	Continuous Summary	Categorical Summary	Baseline Summary	
			Originating Studies	Study AMAX
Demographic Characteristics				
Age[a]	Yes	<65 years, ≥65 years	X	X
		<40 years, ≥40 years	X	X
Sex	No	Male, Female	X	
Age within Sex	No	Male <40 years, Male ≥40 years Female <40 years, Female ≥40 years	X	X
Ethnicity	No	Hispanic/Latino, Non-Hispanic/Non-Latino	X	
Race	No	American Indian/Alaska Native, Asian, Black/African American, Native Hawaiian or other Pacific Islander, White, or Multiple	X	
Geographic Region[b]	No	North America, Europe, Other	X	X
		By Country (listed in other documents)	X	X
		Asia, North America, Central America/South America, Europe and ROW (rest of world)	X	X

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Variable	Continuous Summary	Categorical Summary	Baseline Summary	
			Originating Studies	Study AMAX
Height (cm)	Yes	None	X	
Weight (kg)	Yes	<80 kg, ≥80 kg	X	X
		<100 kg, ≥100 kg	X	X
BMI[c]	Yes	Underweight (<18.5 kg/m2), Normal (≥18.5 and <25 kg/m2), Overweight (≥25 and <30 kg/m2), Obese (≥30 and <40 kg/m2), Extreme obese (≥40 kg/m2)	X	X
Tobacco use	No	Never, Current, Former	X	X
Prior CD Therapy				
Prior biologic exposure	No	Ever, Never	X	
Prior biologic failure[d]	No	Failed, not failed	X	
Inadequate response or loss of response to a biologic	No	Ever, Never	X	
Inadequate response to a biologic	No	Ever, Never	X	
Loss of response to a biologic	No	Ever, Never	X	
Number of prior biologics used	Yes	0, 1, 2, >2	X	
Number of failed[d] biologics	Yes	0, 1, 2, >2	X	
Prior biologic failure[d] and prior biologic exposure	No	Not exposed, Exposed but not failed, Exposed and failed at least one	X	

Variable	Continuous Summary	Categorical Summary	Baseline Summary	
			Originating Studies	Study AMAX
Baseline CD Therapies				
Baseline corticosteroid use	No	Yes, No	X	X
Baseline prednisone equivalent dose	Yes	None	X	X
Budesonide	No	Yes, No	X	X
Baseline use of methotrexate	No	Yes, No	X	X
Baseline Disease Characteristics				
Duration of CD[e]	Yes	<1 year, ≥1 to <5 years, ≥5 years	X	X
Age at Diagnosis of CD[f]	Yes	<10 year, ≥10 to <17 years, ≥17 years to <40 years, ≥40 years	X	
Baseline Disease Location	No	Ileal, Colonic, Ileal-colonic	X	
Baseline Fecal Calprotectin	Yes	≤250 µg, >250 µg/g	X	X
Baseline C-reactive Protein (CRP)	Yes	≤10 mg/L, >10 mg/L	X	X
Baseline SES-CD	Yes	SES-CD (<12, ≥12)	X	X
Baseline AP average	Yes	AP average (<2, ≥2)	X	X
Baseline SF average	Yes	SF average (<7, ≥7)	X	X
Baseline CDAI average	Yes	CDAI total score (<300, ≥300)	X	X
Baseline IBDQ Total Score and Domain Scores	Yes	None	X	X

Variable	Continuous Summary	Categorical Summary	Baseline Summary	
			Originating Studies	Study AMAX
CCI				

Abbreviations: AP = abdominal pain; BMI = body mass index; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; eCRF = electronic case report form; IBDQ = Inflammatory Bowel Disease Questionnaire; PCS = physical component summary; SF = stool frequency.

a Age in years will be calculated as length of the time interval from the imputed date of birth (July 1st in the year of birth collected in the eCRF) to the informed consent date.

b Ethnicity will only be reported for participants within the United States.

c Body Mass Index (BMI) will be calculated as: $BMI\ (kg\ /\ m^2) = Weight\ (kg)\ /(Height\ (m))^2$.

d Failure defined as reasons for prior treatment discontinuation are: loss of response, inadequate response or intolerance to medication.

e Length of the interval from the date of CD diagnosis to the date of informed consent.

f Age at diagnosis in years will be calculated as the time interval from the imputed date of birth (July 1 in the year of birth collected in the eCRF) to the date of CD diagnosis.

6.5 Appendix 5: Study Intervention Compliance

Study intervention compliance for each participant will be calculated as:

$$Treatment\ compliance\ (\%) = 100\ \times \frac{Total\ number\ of\ infusions\ administered}{Total\ number\ of\ infusions\ planned\ per\ protocol}$$

Here the planned drug administrations per protocol is based on the number of visits before the participant discontinued study drug. Each participant will be defined as having received a dose on a given date if they received at least 80% of the planned dose as derived from the Exposure eCRF page.

Study intervention compliance with investigational product will be summarized for the mITT/PAS population. Deviations from the prescribed dosage regimen will be described in a listing.

6.6 Appendix 6: Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

Summary of adverse events (AEs), provided as a dataset which will be converted to an XML file. Both serious adverse events (SAEs) and 'Other' AEs are summarized by study intervention group, by MedDRA PT.

- An AE is considered ‘Serious’ whether or not it is a TEAE.
- An AE is considered in the ‘Other’ category if it is both a TEAE and is not serious. For each SAE and ‘Other’ AE, for each term and study intervention group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, ‘Other’ AEs that occur in fewer than 5% of participants/subjects in every study intervention group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- Adverse event reporting is consistent with other document disclosures (e.g., the CSR, manuscripts, and so forth.

6.7 Appendix 7: CDAI Questionnaire

The CDAI score is calculated for each week using the algorithm below (Best et al. 1976). The standard weights can be determined using the Standard Weight table on the following page.

FOR REVIEW PURPOSES ONLY

Questionnaire obtained by: Lilly	Study ID	Subject Number	Visit/Cycle Number	Signature of Individual Completing Form
	Investigator Number	Page 1 of 1		Date Signed by Individual Completing Form

Patient reported outcomes in Crohn's disease

(a) Crohn's Disease Activity Index (CDAI)

VARIABLE	DAY 1	2	3	4	5	6	7	7 Day Total	Weighting Factor	Total
1. Number of liquid or very soft stools									x 2 =	
2. Abdominal pain 0=none, 1=mild, 2=moderate, 3=severe									x 5 =	
3. General well-being 0=generally well, 1=slightly under par, 2=poor, 3=very poor, 4=terrible									x 7 =	
4. Extra-intestinal manifestations, Current									Check all that apply	
a. Arthritis/arthralgia										
b. Iritis/uveitis										
c. Erythema nodosum, pyoderma gangrenosum,aphthous stomatitis										
d. Anal fissure, fistula, or abscess										
e. Other fistula										
f. Fever over 37.8C (100F) during past 7 days										
									Total number of checked boxes=	
									x 20 =	
5. Lomitil, Imodium, Opiates for diarrhea in the last 7 days									No = 0, Yes = 1	
									x 30 =	
6. Abdominal mass									None = 0, Questionable = 2, Definite = 5	
									x 10 =	
7. Local Haematocrit (%, rounded to whole)									If Male, 47-_____= If Female,42-_____= If negative, enter 0	
									x 6 =	
8. Body weight calculation									Percentage deviation from standard weight x 1 =	
									CDAI TOTAL=	

Standard Weight Table Based on Height and Sex

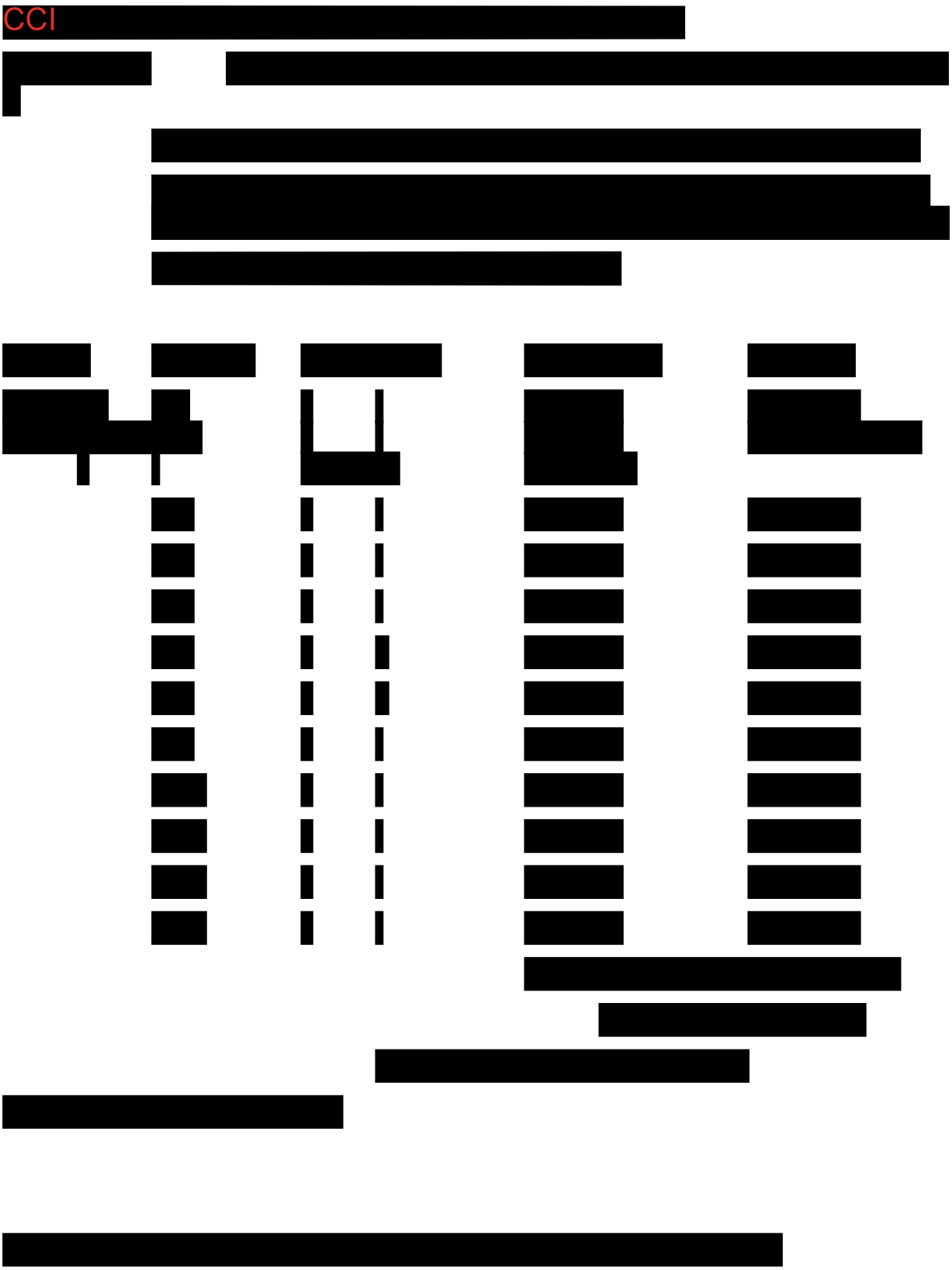
WOMEN	
Height in cm *without shoes*	Standard Weight in Kg
148	53.1
149	53.6
150	54.1
151	54.5
152	55.0
153	55.4
154	55.9
155	56.4
156	57.0
157	57.5
158	58.1
159	58.6
160	59.1
161	59.6
162	60.2
163	60.7
164	61.3
165	61.9
166	62.4
167	62.9
168	63.4
169	63.9
170	64.5
171	65.0
172	65.5
173	66.0
174	66.6
175	67.2
176	67.7
177	68.3
178	68.8
179	69.3
180	69.8
181	70.3
182	70.9
183	71.5
184	72.1
185	72.7
186	73.4

MEN	
Height in cm *without shoes*	Standard Weight in Kg
158	62.6
159	62.9
160	63.3
161	63.7
162	64.1
163	64.6
164	65.0
165	65.5
166	66.0
167	66.6
168	67.1
169	67.6
170	68.1
171	68.7
172	69.2
173	69.7
174	70.3
175	70.8
176	71.3
177	71.9
178	72.4
179	73.0
180	73.6
181	74.3
182	74.8
183	75.5
184	76.2
185	76.9
186	77.6
187	78.2
188	78.8
189	79.6
190	80.4
191	81.0
192	81.6
193	82.2
194	82.8
195	83.4
196	84.0

Modified for height without shoes from the 1983 Metropolitan Life Insurance Ideal Weights for Height tables.

CCI

CCI



6.9 Appendix 9: Study Visit or Week Definition for Daily Diary

CDAI-SF, CDAI-AP, CDAI Well-Being, CCI [redacted] and additional measures are collected using Patient Daily Diary, entries will be mapped to study week by the following:

Visit Number / Week Number	Diary Data Collection	Start Day	End Day
Baseline [1]		NA	NA
Visit 1[1]/ Week 0		NA	NA
Visit 2 / Week 4	Electronic Diary	Max (Date of First Dosing, Week 4 Assessment Date – 28 days	Week 4 Assessment Date – 1 day
Visit 3 / Week 8	Electronic Diary	Max (Week 4 Assessment Date, Week 8 Assessment Date – 28 days	Week 8 Assessment Date – 1 day
Visit 4 / Week 12	Electronic Diary	Max (Week 8 Assessment Date, Week 12 Assessment Date – 28 days	Week 12 Assessment Date – 1 day
Visit 5 / Week 20[2]	1-Day paper diary	NA	NA
Visit 6 / Week 28[2]	1-Day paper diary	NA	NA
Visit 7 / Week 36[2]	1-Day paper diary	NA	NA
Visit 8 / Week 44[2]	1-Day paper diary	NA	NA
Visit 9 / Week 52	14-Day paper diary	Max (Week 44 Assessment Date, Week 52 Assessment Date – 28 days	Week 52 Assessment Date – 1 day
Visit 10 / Week 60[2]	1-Day paper diary	NA	NA
Visit 11 / Week 68[2]	1-Day paper diary	NA	NA
Visit 12 / Week 76	14-Day paper diary	Max (Week 68 Assessment Date, Week 76 Assessment Date – 28 days	Week 76 Assessment Date – 1 day
Visit 13 / Week 88[2]	1-Day paper diary	NA	NA
Visit 14 / Week 100	14-Day paper diary	Max (Week 88 Assessment Date, Week 100 Assessment Date – 28 days	Week 100 Assessment Date – 1 day
Visit 15 / Week 112[2]	1-Day paper diary	NA	NA
Visit 16 / Week 124	14-Day paper diary	Max (Week 112 Assessment Date, Week 124 Assessment Date – 28 days	Week 124 Assessment Date – 1 day
Visit 17 / Week 136[2]	1-Day paper diary	NA	NA
Visit 18 / Week 148[2]	1-Day paper diary	NA	NA
Visit 19 / Week 156	14-Day paper diary	Max (Week 148 Assessment Date, Week 156 Assessment Date – 28 days	Week 156 Assessment Date – 1 day

[1] Baseline will be the Baseline from AMAM or AMAG. For Visit 1 the summarized value for each relevant variable will be the last available value for the patient from study AMAG or AMAM.

[2] For these visits only a single day of dairy data is collected at the office visit and will be mapped directly to an office visit in the data.

For the patient-reported items collected using the electronic diary or the 14 day patient diary, the most recent 7 days (possibly nonconsecutive) within the window described above are averaged after removing the day(s) of the endoscopy prep, the day of endoscopy procedure, and the 2 days following the endoscopy procedure. For data collected using a 1-day dairy at the office visit, the single observation may be included in a change from baseline analysis, but will not be used to calculate binary endpoints.

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