Statistical Analysis Plan: I6T-MC-AMAM v2

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

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Title Page

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

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Version history

This Statistical Analysis Plan (SAP) Version 1 for Study I6T-MC-AMAM Adolescent Addendum (AMAM) was based on the protocol dated 08 June 2020 and approved prior to first patient visit.

Version 2 was approved on 02 October 2023, prior to the primary outcome analysis. The following updates were made from Version 1:

1. Updated objectives and endpoints in Section 1.1 to summarize only key efficacy endpoints and removed comparisons to adults, due to the stoppage in enrollments of adolescents. The estimand was updated in accordance with those changes to the objectives and endpoints. Details on the reasoning for the stoppage in enrollment were added as well.
2. Removed references to adult participants in Study AMAM in Section 1.2 as they are no longer relevant because no comparisons are to be performed. Updated diagram of Study Schema to latest version from amendment to the Adolescent Addendum.
3. The statistical hypothesis and multiplicity adjustment subsections in Section 2 were updated to match the updated objectives and endpoints after enrollment was stopped.
4. The sample size determination explanation in Section 3 was updated to reflect the stoppage in enrollment for the adolescents.
5. The ITT population was removed and wording for the Safety population was updated to remove treatment specific language in Section 4.
6. Updated language for analysis methods and baseline definition in Sections 5.1.1. and 5.1.2 to align with changes to SAP from Study AMAM.
7. Removed references to study intervention for adult participants in Section 5.1.4.
8. Updated ICE descriptions, missing data imputation language details for NRI, and added mBOCF method details to Section 5.1.5 to align with changes to SAP from Study AMAM.
9. Updated primary endpoint details in Section 5.3.1
10. Updated analytical approach wording for the primary analysis in Section 5.3.2 and secondary endpoints in Section 5.4.
11. Removed sensitivity analyses in Section 5.3.3
12. Safety analyses for just the induction period were removed in Section 5.6, safety analyses will be provided for the Study Treatment Period only.
13. Summaries of AEs leading to study treatment discontinuation, SAEs, vital signs, hepatic labs, immunogenicity, ISRs, cerebro-cardiovascular events, malignancies and suicidal ideation were updated to be listings in Section 5.6.2, 5.6.4, 5.6.6., 5.6.7.1 , 5.6.7.4, 5.6.7.5, 5.6.7.6, and 5.6.7.7.
14. Box plots removed from laboratory analyses in Section 5.6.3.
15. Health outcome and efficacy subgroup analyses were removed in Section 5.7.
16. The adolescent PK interim analysis was removed in Section 5.8.2.
17. Endpoint definitions for endpoints no longer needed were removed in Appendix 1 to align with the changes in the objectives and endpoints table.

18. Added RHI and GHAS histology endpoints and definitions of histologic response and remission in Appendix 1.
19. Updated analyses in Appendix 2 to remove endpoints not being summarized and align with changes in objective and endpoints table.
20. Updated Appendix 3 to include details of enrollment stoppage and subsequent changes to analyses.
21. Demographic information changed to be provided in listing instead of summary table in Appendix 4.
22. Updated study intervention compliance in Appendix 5 to align with Study AMAM changes.
23. Added details for what constitutes a specified change to concomitant CD medications in Appendix 9.
24. Added Appendix 10 with details of study visit/week definitions to align with Study AMAM.
25. Updated references and made minor editorial changes to improve clarity and consistency but did not change meaning throughout the document.

1 Introduction

1.1 Objectives and Endpoints

The addendum will compare adolescents (15 to <18 years of age) receiving mirikizumab to adults on placebo in individuals with moderately to severely active Crohn's disease (CD).

After enrolling 6 adolescent participants, adolescent enrollment in the Study AMAM addendum was stopped due to slow enrollment and instead enroll pediatric participants in a separate, stand-alone study. Due to the limited number of enrolled participants, there is limited utility in comparisons to adult participants treated with mirikizumab or placebo from Study AMAM. Thus, no comparisons will be performed unless otherwise specified. Instead, descriptive summaries and listings will be provided for specified efficacy endpoints and safety endpoints as described below.

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

- Population: modified intent-to-treat (mITT), defined in Section 4
- Strategies for intercurrent events (ICE) handling are specified below:
    - For binary endpoints, unless otherwise specified, a composite strategy is used where ICEs are included in the endpoint definition. Successful response only if:
        - response criteria from endpoint table met, and
        - no study intervention discontinuation prior to time point of interest, and
        - do not meet any of the specified changes in the concomitant CD medication prior to time point of interest (defined in Appendix 9)
    - For continuous endpoints, a hybrid strategy is used. For ICEs of study intervention discontinuation and specified changes in the concomitant CD medication, the composite strategy will be used such that measurements after the ICEs will return to baseline.

Population-level summary: The proportion of patients achieving the endpoint will be used for binary endpoints and the mean change from baseline will be presented for continuous endpoints.

Objectives	Endpoints
Co-Primary	
• To summarize: ○ clinical response at Week 12 and endoscopic response at Week 52 and ○ clinical response at Week 12 and clinical remission by CCI [redacted] at Week 52	The coprimary endpoints of: • The proportion of patients achieving clinical response CCI [redacted] at Week 12 and endoscopic response at Week 52 • The proportion of patients achieving clinical response CCI [redacted] at Week 12 and clinical remission CCI [redacted] at Week 52

Objectives	Endpoints
Secondary	
• To summarize endoscopic response	• Proportion of patients achieving endoscopic response at Week 12 • Proportion of patients achieving endoscopic response at Week 52
• To summarize clinical response at Week 12	• Proportion of patients achieving clinical response CCI at Week 12
• To summarize endoscopic remission	• Proportion of patients achieving endoscopic remission (Simple Endoscopic Score for Crohn's Disease [SES-CD]) ≤4 at Week 12 • Proportion of patients achieving endoscopic remission SES-CD ≤4 at Week 52
• To summarize clinical remission CCI	• Proportion of patients achieving clinical remission CCI at Week 12 • Proportion of patients achieving clinical remission CCI at Week 52
• To summarize change from baseline in Urgency Numeric Rating Scale (NRS)	• Mean change from baseline at Week 12 and Week 52 for Urgency NRS
• To summarize the proportion of participants with emergency room (ER) visits for CD, hospitalizations for CD, and to undergo surgery for CD over the course of the study	• Proportion of patients who had Crohn's related emergency room visits • Proportion of patients who had Crohn's related hospitalizations • Proportion of patients who had Crohn's related surgeries
• Evaluate the safety and tolerability of mirikizumab treatment	• Safety and tolerability data evaluation including but not limited to adverse events, infections, injection-site reactions, clinical chemistry, haematology, and immunogenicity

Objectives	Endpoints
• To summarize CCI [redacted]	• Proportion of patients in CCI [redacted]

1.2 Study Design

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

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

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

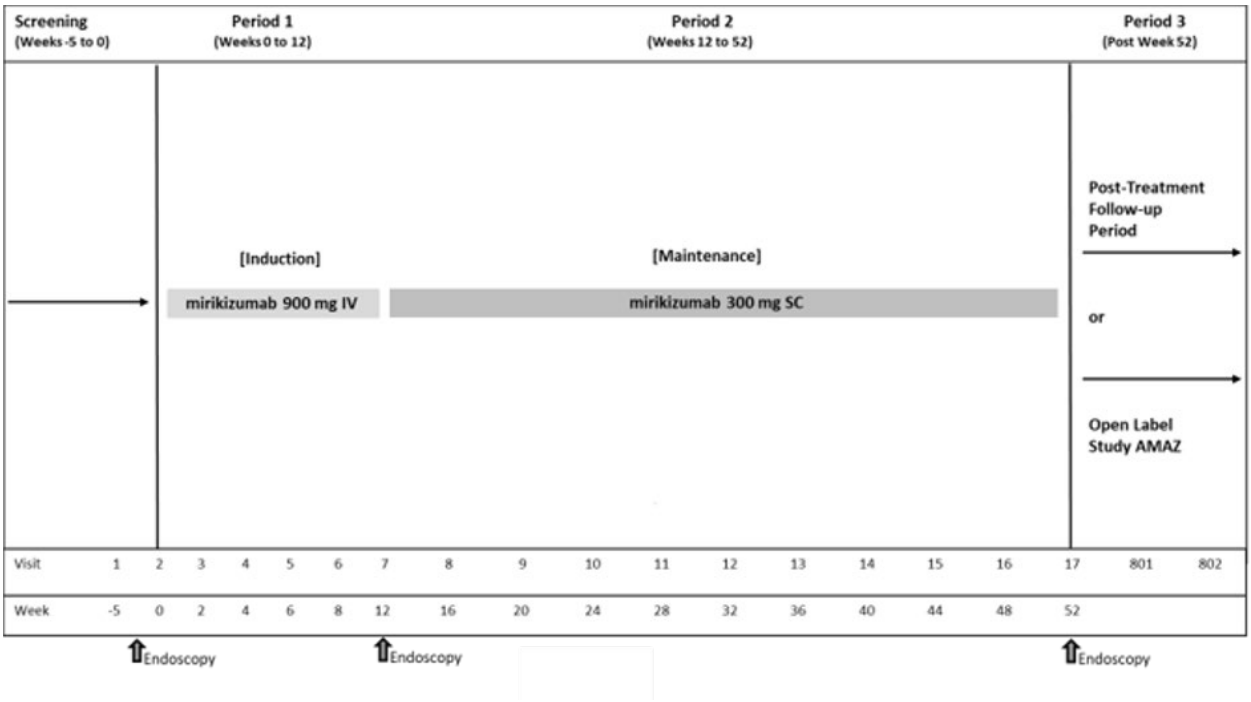
Adolescents who complete Study AMAM Adolescent Addendum through Visit 17 will be given the option to enroll in study (I6T-MC-AMAZ [AMAZ]) if they are eligible. Participants who do not meet enrollment criteria for Study AMAZ or who do not choose to participate in Study AMAZ will return for 2 post-treatment follow-up visits in Study AMAM (V801 and V802).

Study intervention may be permanently discontinued or temporarily withheld during the study (see Sections 7.1.1 and 7.1.2 of the AMAM Adolescent Addendum). 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 achieve clinical response and who are currently on corticosteroids will initiate corticosteroid tapering at or after Week 12, as described in the protocol (see Section 6.5.3 of the AMAM Adolescent Addendum).

No efficacy interim analyses are planned. A Data Monitoring Committee (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. Additional details can be found in the DMC Charter.

Primary analyses will be performed at database lock after all adolescents and all adult participants have completed Week 52 (Visit 17) assessments or ETV. Final analyses will be performed at database lock after Last Participant Last Visit.



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

Figure AMAM.1.1 Study schema.

2 Statistical Hypothesis

The primary efficacy objective is to summarize the proportion of participants who achieve the co-primary endpoints, as described in Section 1.1.

2.1 Multiplicity Adjustment

Only descriptive summaries of select efficacy endpoints will be provided due to the early stoppage of enrollment of adolescent participants in Study AMAM. Thus, no multiplicity adjustment is required.

3 Sample Size Determination

Approximately [redacted] participants were planned to be screened to achieve at least [redacted] participants assigned to study intervention and receive study intervention. After 6 participants were enrolled, the sponsor elected to stop enrollment of adolescents in Study AMAM and enroll pediatric participants in a separate, stand-alone study. The 6 enrolled participants were allowed to continue treatment and finish the study. Enrolled patients had the opportunity to continue to the long-term extension Study AMAZ if deemed eligible after completing Study AMAM.

All patients enrolled are assigned to mirikizumab.

4 Analysis Sets

For purposes of analysis, the following analysis sets are defined in Table AMAM.4.1.

Table AMAM.4.1. Populations for Analysis

Population	Description
Screening Population	**Definition:** All participants who signed informed consent. **Purpose:** Used for disposition analysis.
Modified Intent-to-Treat (mITT) Population	**Definition:** All patients from the ITT population who take at least 1 dose of study intervention, even if the participant does not take the assigned study intervention, does not receive the correct study intervention, or otherwise does not follow the protocol. **Purpose:** Used for efficacy related analysis.
Safety Population	**Definition:** Same as mITT Population. **Purpose:** Safety analyses will be conducted on this population.

5 Statistical Analyses

5.1 General Considerations

Statistical analysis of this study will be the responsibility of 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.

Unless otherwise specified, efficacy analyses will be conducted on the mITT population, and safety analyses will be conducted on the safety population as described in Section 4.

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

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

Additional exploratory analyses of the data may be conducted as deemed appropriate. Some of these additional supplementary analyses may be prespecified in a separate document.

5.1.1 Analysis Methods

For assessments of categorical endpoints, proportions of participants achieving the endpoint will be provided. For assessments of continuous endpoints, descriptive statistics will be provided for each specified visit, including mean and mean change from baseline. Where appropriate corresponding 95% CIs using the Wilson method (Wilson 1927) will be provided at each applicable visit.

5.1.2 Definition of Baseline

Visit 2 (Week 0) is the baseline treatment assignment visit. The centrally read baseline Simple Endoscopic Score for Crohn's Disease (SES-CD) score from the screening endoscopy is considered the baseline for endoscopic response and endoscopic remission endpoints. Daily diary entries obtained prior to the first dose of study intervention are also considered as baseline for diary-related endpoints. The baseline score for daily diary entries will be calculated by averaging the most recent 7 days (possibly nonconsecutive) in the 12 days prior to the day of the first dose of study intervention, after removing the day(s) of the endoscopy prep, the day of endoscopy procedure, and the 2 days following the endoscopy procedure. If less than 4 days of data are available, the baseline score will be set to missing. For other efficacy assessments, baseline is defined as the last nonmissing assessment recorded on or prior to the date of the first dose of study intervention (Period 1 start date), unless otherwise specified.

Baseline for safety analysis is described in Section 5.6.

Change from baseline will be calculated as the visit value of interest minus the baseline value. If a baseline values 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

Table AMAM.5.1 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 Table AMAM.5.1 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.

Table AMAM.5.1. Study Period Definitions

Study Period	Interval Start Definition	Interval End Definition
Screening	Informed consent date	Prior to the start of Period 1.
Period 1	At the date/time[a] of first dose of study intervention. For participants who are assigned treatment but not dosed, Period 1 starts on the date of treatment assignment.	Prior to the start of Period 2. For participants who discontinue before or on the Week 12 visit, Period 1 ends at the latest date of 1) study intervention discontinued date or 2) last study intervention visit date.
Period 2	At the Week 12 dosing date/time[a]. If the participant is unable to be dosed at the Week 12 visit, the Period 2 starts at the Week 12 Visit. If the participant misses the Week 12 visit, the Period 2 starts at Day 91.	After the Week 52 visit date. For participants who discontinue prior to Week 52, Period 2 ends at the latest date of 1) study intervention disposition date or 2) last study intervention visit date.
Study Treatment Period	Same as Period 1 interval start	The latest of the following dates: (1) the end of the Period 1, (2) the end of the Period 2.

Follow-up Period	All participants who had Visit 801 or Visit 802 are considered to have entered the Follow-up Period. The latest of Period 1or Period 2 interval end date.	The last date of the last study visit and study disposition date.

[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

Table AMAM.5.2 provides the study intervention groups to be displayed for each analysis population and analysis period.

Table AMAM.5.2. Study Intervention Groups

Analysis Population	Analysis Period	Study intervention Groups:
mITT	Study Treatment Period	• 900 miri IV Q4W / 300 miri SC Q4W (adolescent miri)
Safety Population	Study Treatment Period	• 900 miri IV Q4W / 300 miri SC Q4W (adolescent miri)

Abbreviation: IV = intravenous; miri = mirikizumab; mITT = modified intent-to-treat; SC = subcutaneous.

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 co-primary endpoints and secondary endpoints which may lead to missing endpoint data based on the estimand of interest:

1. Discontinuation of study intervention prior to time point of interest. Note: participants who take prohibited medications are required to discontinue the study treatment.
2. Specified changes in concomitant CD medications (Appendix 9) prior to time point of interest.

Participants may also have sporadically missing data due to reasons other than ICEs (e.g., failure to fill out a diary or attend an office visit).
The missing data methods described below will be used to handle missing data.

Non-Responder Imputation: As described in Section 1.1, the composite strategy will be used to handle binary endpoints; patients who discontinue study treatment or have specified changes in concomitant CD medications are categorized as treatment failures. As such, these patients are not considered missing from the perspective of the estimand of interest. 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 nonresponder imputation (NRI).

Modified Baseline Observation Carried Forward (mBOCF): As a primary analysis for continuous variables, the analysis of covariance (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 and specified changes in the concomitant CD medication, 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 all participants with sporadically missing observations prior to any ICEs, the last non-missing observation before the sporadically missing data will be carried forward to the corresponding visit.

5.2 Participant Dispositions

Screen failures and reason for screen failure will be summarized. The number of participants assigned and receiving treatment (that is, participants in the mITT population) will be summarized. Frequency counts and percentages of all participants who are assigned treatment and complete the study intervention, who complete study, who discontinue the study intervention early, and who discontinue the study early will be presented overall. Reasons for early discontinuation of the study intervention and the study will be summarized.

All participants who are assigned treatment (i.e., the mITT population) and discontinued from study intervention or study during any period from the study will be listed, and the timing of discontinuing the study will be reported. If known, a reason for their discontinuation will be provided.

5.3 Primary Endpoint(s) Analysis

5.3.1 Definition of Endpoint(s)

The co-primary endpoints are comprised of 2 separate endpoints:

- the proportion of participants achieving clinical response at Week 12 CCI and endoscopic response at Week 52, and
- the proportion of participants achieving clinical response at Week 12 CCI and clinical remission CCI at Week 52.

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

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

5.3.2 Main Analytical Approach

As specified for the primary estimand in Section 1.1, a composite strategy is proposed for other intercurrent events including discontinuing study intervention or having specified changes on concomitant CD medications prior to the time point of interest. The NRI methodology described in Section 5.1.5 will be applied when any of these events occur. This methodology also assumes that missing observations at Week 52 not related to any ICEs will be treated as study intervention failures if the endpoint cannot be evaluated at Week 52.

Primary analyses will consist of descriptive summaries of the efficacy endpoints listed in Section 1.1. Additional details are described in Section 6.2 (Appendix 2). Note that the details of each analysis will follow the general principles described in Section 5.1.1.

5.3.3 Sensitivity Analysis

No sensitivity analyses will be performed.

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 Endpoints.

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

5.4.1.2 Main Analytical Approach

The main analytical approach for key secondary endpoints tested at Week 52 will be done similar to the co-primary endpoints and is described in Section 5.3.2.

Additional details for secondary endpoints are described in Appendix 2.

5.5 Tertiary/Exploratory Endpoint(s) Analysis

Not applicable.

5.6 Safety Analyses

The planned analysis of safety data will be performed with an intent to maintain consistency with compound level standard safety analyses. These standards are based on internal standards which were informed by Clinical Data Interchange Standards Consortium (CDISC) standards, regulatory guidance (for example, FDA Clinical Review Template), and cross-industry standardization efforts (for example, Pharmaceutical Users Software Exchange [PhUSE] white papers from the Standard Analyses and Code Sharing Working Group provided in the PhUSE Computational Science Deliverables Catalog [WWW]).

In general, safety evaluations will be based on the Safety Population. The analysis treatment period of interest will be the Study Treatment Period described in Section 5.1.3.

Unless otherwise stated, safety data collected during the follow-up periods for patients that do not enroll in the long-term extension Study AMAZ will be listed.

5.6.1 Extent of Exposure

Duration of exposure to study intervention will be summarized for the safety analysis population in the Study Treatment Period. Exposure will be calculated as (Date of end date in the Interval – Date of start date in the Interval + 1 day). Total patient-years of exposure will be reported including all adolescents in the safety analysis population.

Descriptive statistics will be provided for participants-weeks of exposure and the frequency of participants falling into different exposure ranges will be summarized.

- ≥0, ≥4 weeks, ≥8 weeks, ≥12 weeks, ≥16 weeks, ≥24 weeks, ≥32 weeks, ≥40 weeks, ≥48 weeks.

- >0 to <4 weeks, ≥4 weeks to <8 weeks, ≥8 weeks to <12 weeks, ≥12 weeks to 16 weeks, …, ≥48 weeks

Additional exposure ranges may be considered if necessary.

Reasons for not taking study intervention and reasons for not taking the planned amount of study intervention will be reviewed.

5.6.2 Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after baseline. The Medical Dictionary for Regulatory Activities (MedDRA) Lowest level Term (LLT) will be used in the treatment-emergent computation. The maximum severity for each LLT during the baseline period will be used as baseline. For events with a missing severity during the baseline period, it will be treated as "mild" in severity for determining treatment-emergence. Events with a missing severity during the postbaseline period will be treated as "severe" and treatment-emergence will be determined by comparing to baseline severity. For events occurring on the day of first taking study medication, the start times of the study treatment and adverse event (AE) will be used to determine whether the event was pre- versus post-treatment. If the start time for the AE is missing, it will be assumed to have started in the postbaseline period.

The summary analyses will be presented for the safety population corresponding to the Study Treatment period alone and with the follow-up period as described in Table AMAM.5.3. Summary tables include the number and percentage of participants reporting an event. For events that are sex-specific (as defined by MedDRA), the number of participants at risk will include only participants from the given sex.

Table AMAM.5.3. Analysis of AEs

Analysis
Overview of AEs
Summary of TEAE PTs by decreasing frequency
Summary of TEAE PTs by decreasing frequency within SOC
Summary of TEAE PTs by maximum severity by decreasing frequency
Listing of AEs leading to study treatment discontinuation
Listing of SAEs
Listing of Deaths

Abbreviations: AE = adverse event; PT = Preferred Term; SAE = serious adverse event; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

For the Safety Population, the baseline period and postbaseline will be defined as follows:

- the baseline period is the Screening Period.
- the postbaseline period will be a) the Study Treatment Period alone, and b) the Study Treatment combined with the Follow-up Period.

5.6.2.1 Deaths, Other Serious Adverse Events, and other Notable Adverse Events

A listing of SAEs will be provided. A listing of all deaths from screening to end of study participation will be provided for all entered participants.

Additionally, a listing of participants who permanently discontinued from study treatment due to an AE (including AEs that led to death) during the treatment period will be provided.

5.6.3 Clinical Laboratory Evaluations

As described fully in compound level safety standards and in the laboratory-related PhUSE white papers (PhUSE 2013, 2015), the clinical laboratory evaluations will be summarized with the following displays for the Safety Population during the Study Treatment period only as described in Table AMAM.5.4.

Table AMAM.5.4. Clinical Laboratory Analyses

Analysis
Treatment-emergent abnormal high lab values (that is, participants shifting from a normal/low maximum baseline value to a high maximum postbaseline value) or low lab values (that is, participants shifting from normal/high minimum baseline value to a low minimum postbaseline value)
Scatter plot of maximum (minimum) postbaseline value versus maximum (minimum) baseline value
Shift tables showing the number of participants who shift from each category of maximum (minimum) baseline observation to each category of maximum (minimum) postbaseline observation. Here, categories may be low, normal, or high with cut-offs defined in the compound level safety standards.
Listing of abnormal findings

For these displays, the postbaseline periods will include the Study Treatment Period alone. Postbaseline measurement of continuous analysis (for example, boxplots) will include only scheduled measurements, while postbaseline categorical analysis (for example, shifts) will include both scheduled and unscheduled measurements.

Measurements are defined to be in the baseline periods as follows:

- Safety Population:
    - For analyses of continuous measurements: the last scheduled or unscheduled non-missing measurement recorded during the Screening Period.
    - For analyses of categorical measurements: all scheduled or unscheduled non-missing measurements recorded during the Screening Period.

For any lab given on the day of first taking study medication at the start of the postbaseline period, the start time of the study intervention will be used to determine whether the lab was pre- versus postbaseline. If time for the lab is missing, it will be assumed to be in the baseline period (that is, we assume the protocol defined order of procedures was followed).

5.6.4 Vital Signs and other Physical Findings

Vital signs (including weight, height, weight velocity, and z-scores for weight and height) will be provided via listings. A listing of abnormal vital signs will also be provided. For vital signs, the low and high limits are based on a combination of a specified value and a change or percentage change as shown in Table AMAM.5.5.

Table AMAM.5.5. Categorical Criteria for Abnormal Treatment-Emergent Blood Pressure and Pulse Measurement for Adolescents

Age (years)		Systolic BP (mm HG)	Diastolic BP (mm HG)	Pulse/HR (bpm)
≥13 and <18	Low	≤90 and DFB ≥20	≤50 and DFB≥10	≤50 and DFB ≥15
	High[a]	≥129 and IFB ≥20	≥86 and IFB ≥10	>120 and IFB ≥15

Abbreviations: BP = blood pressure; DFB = decrease from baseline; HR = heart rate; IFB = increase from baseline.

[a] The high limit values in this table correspond to the 95th percentile for the age group under the 2017 ACC/AHA Task Force on Clinical Practice Guidelines revised criteria for hypertension. Values higher than the 95th percentile are consistent with Stage 1 or Stage 2 hypertension. Under some circumstances it may be appropriate to conduct analyses considering only the change from baseline reference limit.

Sources: Flynn et al. 2017; Whelton et al. 2017.

5.6.5 Electrocardiograms

Electrocardiograms (ECGs) will be read locally. Complete ECG data will not be part of the clinical database. Any clinically significant findings from ECGs that result in a diagnosis and that occur after the participant receives the first dose of study drug will be reported as an AE via electronic case report form (eCRF).

5.6.6 Immunogenicity

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 ADAs are induced or boosted by exposure to study drug (i.e., when at least 1 postbaseline ADA sample has a 4-fold increase in titers 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 ADAs were present at baseline).

Compound level safety standards will be followed in the analyses of immunogenicity. Listings of immunogenicity assessments will be provided.

5.6.7 Special Safety Topics

This section includes areas of interest whether due to observed safety findings, potential findings based on drug class, or safety topics anticipated to be requested by a regulatory agency for any reason. In general, potential adverse events of special interest (AESI) relevant to these special safety topics will be identified by one or more Standardized MedDRA Query(ies) (SMQs), by a Lilly defined MedDRA Preferred Term (PT) listing based upon the review of the most current version of MedDRA, or by treatment-emergent relevant laboratory changes, as described below. Additional special safety topics may be added as warranted.

Unless otherwise specified, a listing of the AESIs will be provided during the Study Treatment Period.

Full details of the search terms and rules for deriving AESIs in each of the sections below are described in the compound level safety standards along with information about the types of summaries and listings to be provided.

5.6.7.1 Hepatic Safety

Analyses for laboratory analyte measurements are described in Section 5.6.3. This section describes additional analyses for the topic.

Hepatic labs include alanine aminotransferase (ALT) and aspartate transaminase (AST), total bilirubin (TBL) and serum alkaline phosphatase (ALP). When criteria are met for hepatic evaluations, investigators will complete a follow-up Hepatic Safety eCRF.

Analyses will include:

- Alanine aminotransferase and AST: a listing of participants with a measurement greater than or equal to 3 times (3 ×) the Covance age-adjusted upper limit of normal (ULN) during the treatment period.
- Total bilirubin and ALP: a listing of participants with a measurement greater than or equal to 2 times (2 ×) the performing lab ULN during the treatment period.
- Plots of maximum postbaseline ALT versus maximum postbaseline TBL (entire safety population), maximum postbaseline AST versus maximum postbaseline TBL, maximum postbaseline ALP versus maximum postbaseline TBL.
- A listing of the information collected on the Hepatic-Safety eCRF.

5.6.7.2 Infections, including opportunistic infections and serious infections

Infections will be defined using the PTs from the MedDRA Infections and Infestations System Organ Class (SOC). Treatment-emergent infections will be analyzed for: all infections (by maximum severity), serious infections and opportunistic infections (OI). The MedDRA terms used to identify infections considered to be OI in participants with immune mediated inflammatory conditions treated with immunomodulatory drugs are based on Winthrop and colleagues (2015) and are listed in the compound level safety standards. The list contains narrow (more specific) and broad (less specific) PTs with respect to these prospectively defined opportunistic infections. Analyses will include:

- Infections/Serious Infections: treatment-emergent (TE) Infections by PT.
- Opportunistic Infections: TE OI by narrow terms and broad terms separately.

5.6.7.3 Hypersensitivity Reactions

Hypersensitivity reactions is used as an overarching term to describe events that are systemic or localized reactions that likely have an allergic/hypersensitivity etiology. Participants will be evaluated by the investigator for signs and symptoms suggestive of hypersensitivity, and investigators will complete a follow-up eCRF designed to record additional information.

Potential hypersensitivity reactions will be determined using the following SMQs: anaphylactic reaction (SMQ 20000021), hypersensitivity (SMQ 20000214), and angioedema (SMQ 20000024). Potential hypersensitivity will be categorized as Immediate (i.e., occurring within 24 hours from end of the study drug administration) and non-immediate (i.e., occurring after the day of study drug administration but prior to subsequent drug administration), based on the timing of the reaction.

Analyses will include:

- For Immediate Hypersensitivity: (1) combined narrow/algorithmic search (i.e., any narrow term from any one of the SMQs, or anaphylaxis algorithm), (2) narrow search (i.e., any narrow term) by SMQ, (3) broad search (i.e., any narrow or broad term) by SMQ, and (4) TEAEs occurring on the day of study drug administration by PT not in any of the 3 SMQs.
- For Non-Immediate Hypersensitivity: (1) combined narrow search (i.e., any narrow term from any one of the SMQs), (2) narrow search (i.e., any narrow term) by SMQ, and (3) broad search (i.e., any narrow or broad term) by SMQ.

5.6.7.4 Infusion/Injection Site Reactions

Infusion or injection site reactions are AEs localized to the immediate site of the administration of a drug. The evaluation of study drug related injection-site reactions (ISRs) will be through the unsolicited reporting of ISR TEAEs and through the use of an Infusion or Injection Site Reaction Follow-up Form completed by the investigator for each ISR reported.

Injection site reactions will be defined using the following MedDRA High-Level Terms (HLT):

- Injection site reaction, excluding certain PTs (e.g., those PTs related to joint), and
- Infusion site reaction, excluding certain PTs (e.g., those PTs related to joint).

Analyses will include a listing of all injection and infusion site reactions.

5.6.7.5 Cerebro-Cardiovascular Events

The cerebro-cardiovascular events reported in the study will be adjudicated by an independent, external adjudication committee (AC). All confirmed events after adjudication will be used for the analysis of cerebro-cardiovascular events.

Analyses will include:

- by-participant listing for all participants having a TEAE of cerebro-cardiovascular or venous thromboembolic event (confirmed event, no event, or insufficient documentation for event determination) at any time.

5.6.7.6 Malignancies

Malignancies will be defined using PTs from the Malignant tumors SMQ.

Analyses will include:

- by-participant listing for all participants having a TEAE of malignancy at any time

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5.7 Other Analyses

Crohn's related ER visits, hospitalizations, and Crohn's related surgeries will be provided using by-participant listings for the Study Treatment period, and if applicable, the Study Treatment period plus Follow-up Period.

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.

No member of the DMC may have contact with study sites. A statistical analysis center (SAC) is external to the mirikizumab team and may be Lilly employees or from third-party organization designated by Lilly. No member of the SAC will have contact with study sites. Access to the unblinding safety data will be limited to the DMC and the SAC or their designees. The study team will not have access to the unblinded data. 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. Study AMAM 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.

5.8.2 Week 52 Database Lock

A primary database lock for the addendum is planned after the primary database lock for adult participants and all adolescent participants complete the Week 52 visit or the ETV. The analysis based on data from the primary database lock will be conducted by the sponsor or a designee and no multiplicity adjustment will be implemented. The final database lock will occur after all patients complete the study, including safety follow-up.

The primary objective of the study will be completed at this database lock. This is the final analysis for the efficacy endpoints. A limited number of Lilly employees or their designees not in direct contact with the clinical sites may be provided access to the data from this database lock.

6 Supporting Documentation

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

Measure	Description	Variable	Derivation / Comment / Endpoints	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 grand total is obtained as the sum of all endoscopic scores across all bowel segments. The endoscopic scores for each bowel segment are called subscores. Total scores range from 0 to 56, with higher scores indicating more severe disease.	SES-CD total score Change from baseline in SES-CD total score	SES-CD total score is calculated as average of total scores from all readers. Change from baseline in SES-CD total score = SES-CD total score – baseline SES-CD total score	Missing if endoscopy was not done for baseline or endpoint or if 2 or more endoscopies were deemed 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 for baseline or endpoint or if 2 or more endoscopies were deemed unreadable
		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

Measure	Description	Variable	Derivation / Comment / Endpoints	Definition of missing
CDAI	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]). 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 electronic 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 response by PRO	Clinical response by PRO is defined as at least a 30% decrease in 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
		CDAI total score Change from baseline in CDAI total score	CDAI total score is based on the CDAI questionnaire in Appendix 7. It also utilizes the standard weights table in that section. Change form baseline in CDAI score is defined as CDAI score – baseline CDAI score.	Missing if CDAI total score is missing at endpoint. 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.
		Clinical remission by CDAI	Clinical remission by CDAI is defined as a CDAI total score <150.	Missing if CDAI total score is missing at endpoint.

Measure	Description	Variable	Derivation / Comment / Endpoints	Definition of missing
		Clinical response by CDAI	Clinical response by CDAI is defined as a decrease from baseline in the CDAI total score ≥ 100 or a CDAI total score <150. Description of CDAI total score is provided above. If CDAI score – baseline CDAI score ≤ -100 or if CDAI total score <150, then clinical response by CDAI is achieved.	Missing if CDAI total score is missing at either baseline or endpoint.
		AP average Change from baseline in 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 endpoint
		SF average Change from baseline in 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 endpoint
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Measure	Description	Variable	Derivation / Comment / Endpoints	Definition of missing
Urgency NRS	The Urgency NRS is a single patient-reported item that measures the severity for the urgency (sudden or immediate need) to have a bowel movement in the past 24 hours using an 11-point NRS ranging from 0 (no urgency) to 10 (worst possible urgency).	Urgency NRS Score Change from baseline in urgency NRS score	Urgency NRS score is calculated by averaging data from all available daily electronic diary entries of Urgency NRS from the most recent 7 days as described for AP and SF average scores. Endpoint: • Change from baseline in urgency NRS score at each scheduled visit	Missing if fewer than 4 available measurements in the relevant 7 days
Growth	Observed height velocity by gender	Height Velocity	Observed height velocity by gender will be calculated at baseline, Week 12, Week 24, and Week 52 according to the following formula: • (Present Height [cm] – Previous Height [cm]/Interval Between Measurements (months) × 12	Missing if either present or previous height is missing.
	Height Z-score and percentile by sex and age will be calculated using the CDC growth data shown at: https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm This approach uses a Box-Cox transformation to calculate the height z-score and percentile of the normal distribution for the corresponding age and sex.	Height z-score change from baseline	Observed height z-score will be calculated at Week 12, Week 24, and Week 52 according to the following formula: • (Observed Height [cm]-Mean Height for age and gender [cm])/(Standard Deviation of the Mean)	Missing if height at visit is missing.

Measure	Description	Variable	Derivation / Comment / Endpoints	Definition of missing
	Weight Z-score and percentile by sex and age will be calculated using the CDC growth data shown at: https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm This approach uses a Box-Cox transformation to calculate the weight z-score and percentile of the normal distribution for the corresponding age and sex.	Weight z-score change from baseline	Observed weight z-score will be calculated according to the following formula: • (Observed Weight [kg]-Mean Weight for age and gender [kg])/(Standard Deviation of the Mean)	Missing if weight at visit is missing.
Medical resource utilization and health economics	Crohn's related ER visits, hospitalizations, and 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. Any participant that has a count of 1 or greater after first study intervention will be counted in the endpoints below.	
[redacted]				

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

Measure	Description	Variable	Derivation / Comment / Endpoints	Definition of missing
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Abbreviations: AP = abdominal pain; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CDC = Centers for Disease Control and Prevention; eCRF = electronic case report form; ER = emergency room; ESR = erythrocyte sedimentation rate; CCI ; PRO = patient-reported outcome; CCI SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency.

6.2 Appendix 2: Description of Analyses

Measure	Variable	Analysis Method (Section 5.1.1)	Population (Section 4)	Time Point(s)
Combined Endpoints	Clinical response CCI at Week 12 and Endoscopic Response at Week 52	Descriptive summaries	mITT	Week 52
	Clinical response CCI at Week 12 and Clinical Remission by PCDAI at Week 52	Descriptive summaries	mITT	Week 52
SES-CD	Endoscopic Response	Descriptive summaries	mITT	Week 12 Week 52
	Endoscopic remission SES-CD ≤4	Descriptive summaries	mITT	Week 12 Week 52
CCI	Clinical remission CCI	Descriptive summaries	mITT	Week 12 Week 52
	Clinical response CCI	Descriptive summaries	mITT	Week 12 Week 52
Urgency NRS	Urgency NRS score, Change from BL in Urgency NRS Score	Descriptive summaries	mITT	Each applicable visit
Medical resource utilization and health economics	Proportion of participants who had Crohn's related emergency room visits	Descriptive summaries	mITT	Week 52
	Proportion of participants who had Crohn's related hospitalizations	Descriptive summaries	mITT	Week 52
	Proportion of participants who had Crohn's related surgeries	Descriptive summaries	mITT	Week 52
CCI	CCI	Descriptive summaries	mITT	Week 12 Week 52
	CCI	Descriptive summaries	mITT	Week 12 Week 52

Abbreviations: BL = baseline; NRS = Numeric Rating Scale; mITT = modified intent-to-treat population; CCI ; SES-CD = Simple Endoscopic Score for Crohn's Disease.

6.3 Appendix 3: Changes to Protocol-Planned Analyses

As compared with the AMAM Adolescent Addendum (15.2), the SAP Version 2 content differs in several respects. The analysis and endpoints describe in the SAP will supersede the language in the protocol.

Due to the early stoppage of enrollment and small number (6) of adolescent participants enrolled, there is limited utility of any comparison to adult participants treated with mirikizumab or placebo from Study AMAM. Thus, no comparisons will be performed. Instead, descriptive summaries will be provided of select key efficacy endpoints. Listings and summaries of safety related endpoints will be provided as well. Details of these listings and summaries are provided in Section 5.

6.4 Appendix 4: Demographic and Baseline Characteristics

Demographic and baseline characteristics will be provided in a listing. Information in listing includes, but is not limited to, the following variables: age, treatment, sex, race, country, region, weight at baseline, height at baseline, and BMI at baseline.

6.5 Appendix 5: Study Intervention Compliance

Study intervention compliance with investigational product will be summarized for the mITT population. Study intervention compliance for each participant will be calculated as:

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

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 the dose is administered as derived from the Exposure eCRF page. "Overall compliance" with therapy is defined as having at least 80% treatment compliance.

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 AEs, provided as a dataset which will be converted to an XML file. Both 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.
- 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.


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6.9 Appendix 9: Specified Changes in Concomitant CD Medications (Intercurrent Event)

Corticosteroids in Period 1

1. Initiation of oral corticosteroids or oral budesonide due to worsening Crohn's disease.
2. Initiation of CCI
3. CCI
4. CCI
5. CCI due to worsening Crohn's disease.

Corticosteroids in Period 2

1. Initiation of CCI
2. CCI
3. CCI
4. CCI
5. CCI due to worsening Crohn's disease.

Immunomodulator in Period 1 and/or Period 2

1. Initiation of CCI
2. CCI
3. CCI
4. CCI

6.10 Appendix 10: Study Visit or Week Definition for Daily Diary

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

Visit Number / Week Number	Start Day	End Day
Visit 2 / Baseline	Date of First Injection -12 days	Date of First Injection – 1 day
Visit 3 / Week 2	Max (Date of First Injection, Week 2 Assessment Date – 12 days)	Week 2 Assessment Date – 1 day
Visit 4 / Week 4	Max (Week 2 Assessment Date, Week 4 Assessment Date – 12 days)	Week 4 Assessment Date – 1 day
Visit 5 / Week 6	Max (Week 4 Assessment Date, Week 6 Assessment Date – 12 days)	Week 6 Assessment Date – 1 day
Visit 6 / Week 8	Max (Week 6 Assessment Date, Week 8 Assessment Date – 12 days)	Week 8 Assessment Date – 1 day
Visit 7 / Week 12	Max (Week 8 Assessment Date, Min (Week 12 Assessment Date, Start date of Period 2) – 12 days)	Min (Week 12 Assessment Date, Start date of Period 2)– 1 day
Visit 8 / Week 16	Max (Week 12 Assessment Date (i.e. Date of First Injection of Period 2), Week 16 Assessment Date – 12 days)	Week 16 Assessment Date – 1 day
Visit 9 / Week 20	Max (Week 16 Assessment Date, Week 20 Assessment Date – 12 days)	Week 20 Assessment Date – 1 day
Visit 10 / Week 24	Max (Week 20 Assessment Date, Week 24 Assessment Date – 12 days)	Week 24 Assessment Date – 1 day
Visit 11 / Week 28	Max (Week 24 Assessment Date, Week 28 Assessment Date – 12 days)	Week 28 Assessment Date – 1 day
Visit 12 / Week 32	Max (Week 28 Assessment Date, Week 32 Assessment Date – 12 days)	Week 32 Assessment Date – 1 day
Visit 13 / Week 36	Max (Week 32 Assessment Date, Week 36 Assessment Date – 12 days)	Week 36 Assessment Date – 1 day
Visit 14 / Week 40	Max (Week 36 Assessment Date, Week 40 Assessment Date – 12 days)	Week 40 Assessment Date – 1 day
Visit 15 / Week 44	Max (Week 40 Assessment Date, Week 44 Assessment Date – 12 days)	Week 44 Assessment Date – 1 day
Visit 16 / Week 48	Max (Week 44 Assessment Date, Week 48 Assessment Date – 12 days)	Week 48 Assessment Date – 1 day
Visit 17 / Week 52	Max (Week 48 Assessment Date, Week 52 Assessment Date – 12 days)	Week 52 Assessment Date – 1 day

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