I6T-MC-AMBU Statistical Analysis Plan Version 2

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

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1. Statistical Analysis Plan: I6T-MC-AMBU: A Multicenter, Open-Label PK Study of Mirikizumab in Pediatric Patients with Moderately to Severely Active Ulcerative Colitis

Mirikizumab (LY3074828) Ulcerative Colitis

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

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Protocol I6T-MC-AMBU
Phase 2

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3. Revision History

Statistical analysis plan (SAP) Version 1 was approved prior to the first patient visit on 19 December 2019.

Statistical analysis plan Version 2 was based on protocol amendment (c) approved 22 October 2021. The following updates were made in Version 2 of the SAP before the first interim analysis by the sponsor:

- Made the following changes to secondary endpoints:
  - Added additional estimand language for clarity.
  - Updated definition of clinical remission based on protocol amendment.
  - Updated wording for age group based on protocol.
  - Updated name of histologic-endoscopic mucosal remission to match protocol amendment.
- Made the following changes to exploratory endpoints:
  - Removed CCI [redacted] as exploratory endpoints.
  - Updated wording of objectives to clarify exploratory nature of objectives/endpoints.
  - Added additional time points for summaries of Modified Mayo Score (MMS) subscores.
  - Removed Urgency numeric rating scale (NRS) and Abdominal Pain NRS as they are already in the secondary endpoint table.
- Updated Study Schema Figure AMBU.5.1 according to protocol update.
- Updated population and treatment groups in Table AMBU.6.1 and Table AMBU.6.2 according to protocol update.
- Changed analysis approach for calculating confidence intervals in Section 6.1.3.
- Added language clarifying how missing data handling for continuous endpoints as well as modifications for missing data handling as part of the interim analysis (Section 6.3).
- Fixed categorical summary definitions for Bristol stool scale and CCI [redacted] at baseline in Table AMBU.6.3.
- Made the following changes to Table AMBU.6.4:
  - Updated definitions of MMS Clinical Remission, Alternate Clinical Remission, stool frequency (SF) component of clinical remission.
  - Minor clarification of wording for Corticosteroid-free remission at Week 52
  - For histology, added definitions for CCI [redacted], Histologic Remission, and histologic-endoscopic mucosal remission.
  - For growth, added definitions for change from baseline (CFB) in height, CFB in weight, and height/weight z-scores and percentiles.
  - Removed definition of CCI [redacted]
  - Added definition of EIM subcategory.
- Made the following changes to Table AMBU.6.5:

  - Clarified missing data handling analysis methods for each endpoint variable (non-responder imputation [NRI], modified baseline observation carried forward (mBOCF), and as observed).
  - Added the following secondary endpoints to be calculated: Pediatric Ulcerative Colitis Activity Index (PUCAI) CFB, Height CFB, Weight CFB, Histologic Remission, Histologic Improvement, and Histologic-Endoscopic Mucosal Remission, 30% improvement from baseline in Abdominal Pain.
  - Clarified that Abdominal Pain will be summarized by age group.
  - Changed estradiol and testosterone level analyses to be change from baseline.
- Made the following changes to Table AMBU.6.6:
  - Removed CCI [redacted] as part of the exploratory analyses.
  - Clarified analyses that will be performed for alternate clinical remission.
  - Updated analysis method for Bristol Stool Scale.
  - Added missing data handling analysis methods for each endpoint variable (NRI, mBOCF, and as observed).
- Updated language in hepatic safety section (Section 6.13.7.1). Added an additional hepatic screening plot.
- Updated hypersensitivity analyses for immediate and nonimmediate events to be in line with adult safety analyses (Section 6.13.7.3).
- Added CDI-2 analysis to suicidal ideation/behavior and depression (Section 6.13.7.7).
- Removed language surrounding per protocol analysis.
- Updated data snapshot and interim analysis language in accordance with the protocol amendments.
- Updated which weeks will be included in CCI [redacted] diary calculations (Appendix 1).
- Fixed typos and made other minor edits.

4. Study Objectives

4.1. Primary Objective

Table AMBU.4.1. Primary Objective and Endpoints

Objectives	Endpoints
Primary	
To evaluate the pharmacokinetics (PK) of mirikizumab treatment in pediatric patients	Clearance and volume of distribution of mirikizumab

4.2. Secondary Objectives

Table AMBU.4.2 shows the protocol-defined secondary objectives and endpoints of the study. In addition, the analysis of other exploratory endpoints are described in Section 4.3 and Section 6.10.

The estimand (ICH 2019) associated with each endpoint/analysis is documented in the following places:

- The population of interest is described in the protocol inclusion/exclusion criteria and in this document in Section 6.1.1 and Table AMBU.6.4.
- The endpoint/variables may be found in Table AMBU.4.2 and Table AMBU.6.4.
- The handling of intercurrent events and missing data may be found in Section 6.3 and Table AMBU.6.4.
- Population summary measures are described in Section 6.1.3, Table AMBU.6.5, and Table AMBU.6.6.

Table AMBU.4.2. Secondary Objectives and Endpoints

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

Objectives	Endpoints
Secondary	
To evaluate the effect of treatment with mirikizumab on achieving **clinical response** at Week 12 and/or Week 52	The proportion of patients in clinical response at Week 12 The proportion of patients in clinical response at Week 52 The proportion of patients in clinical response at Week 12 who achieve clinical response at Week 52 **Clinical response** is based on the MMS and is defined as: A decrease in the MMS of ≥2 points and ≥30% decrease from baseline, and A decrease of ≥1 point in the RB subscore from baseline or a RB score of 0 or 1
To evaluate the effect of treatment with mirikizumab on achieving **corticosteroid-free remission** without surgery among patients in clinical remission at Week 52 and receiving corticosteroids at baseline	The proportion of patients who entered the study on corticosteroids and who are in MMS clinical remission at Week 52 without the use of corticosteroids **Corticosteroid-free remission** without surgery at Week 52 defined as: CCI [redacted]
To evaluate the effect of treatment with mirikizumab on **PUCAI clinical remission** at Week 12 and/or Week 52	The proportion of patients in PUCAI clinical remission at Week 12 The proportion of patients in PUCAI clinical remission at Week 52 The proportion of patients in PUCAI clinical remission at Week 12 who achieve clinical remission at Week 52 The proportion of patients in PUCAI clinical response at Week 12 who achieve clinical remission at Week 52 **PUCAI clinical remission** is defined as a PUCAI score of <10 points **PUCAI clinical response** is defined below
To evaluate the effect of treatment with mirikizumab on **PUCAI clinical response** at Week 12 and/or Week 52	The proportion of patients in PUCAI clinical response at Week 12 The proportion of patients in PUCAI clinical response at Week 52 The proportion of patients in PUCAI clinical response at Week 12 who achieve PUCAI clinical response at Week 52 **PUCAI clinical response** is defined as a reduction in baseline PUCAI score of ≥20 points
To evaluate the effect of treatment with mirikizumab on achieving **endoscopic remission** at Week 12 and/or Week 52	The proportion of patients in endoscopic remission at Week 12 The proportion of patients in endoscopic remission at Week 52 The proportion of patients in endoscopic remission at Week 12 who maintain endoscopic remission at Week 52 (durable endoscopic remission) **Endoscopic remission** is defined as: ES = 0 or 1 (excluding friability)
To evaluate the effect of treatment with mirikizumab on achieving **ES = 0** at Week 12 or Week 52	The proportion of patients with ES = 0 at Week 12 The proportion of patients with ES = 0 at Week 52
To evaluate the effect of treatment with mirikizumab on **symptomatic remission** over time	Proportion of patients in symptomatic remission at applicable study visits **Symptomatic remission** is defined as: SF = 0, or SF =1 with a ≥1-point decrease from baseline and RB = 0

Objectives	Endpoints
Secondary	
To evaluate the effect of treatment with mirikizumab on height velocity at Weeks 12, 24, and 52	Observed height velocity by gender and age group will be calculated at baseline, Week 12, Week 24, and Week 52
To evaluate the effect of treatment with mirikizumab on weight throughout the trial	Change from baseline in weight (kg) at all study visits by gender and age group
To evaluate the effect of treatment with mirikizumab on pubertal development throughout the trial in appropriate patient groups	Hormone levels and/or other related clinical measures will be evaluated
To evaluate the effect of treatment with mirikizumab on **improving patient-reported outcome endpoints** at Week 12 and Week 52	Change from baseline in 7-day average of Abdominal Pain (in past 24 hours) NRS score at Week 12 and Week 52 The proportion of patients with a NRS pain score ≥3 at baseline who achieve an improvement of ≥30% from baseline in 7-day average abdominal pain NRS score at Week 12 and Week 52 CCI [redacted]
To evaluate **histologic-endoscopic mucosal remission** following mirikizumab treatment at Week 12 or Week 52	Proportion of patients with histologic-endoscopic mucosal remission at Week 12 Proportion of patients with histologic-endoscopic mucosal remission at Week 52 **Histologic-endoscopic mucosal remission** is defined as achieving both histologic remission and endoscopic remission. **Histologic remission** is defined in Section 6.10.1.
To evaluate the development of anti-mirikizumab antibodies and their effect CCI [redacted] CCI [redacted]	Proportion of patients who have treatment-emergent anti-drug antibodies (TEADA) CCI [redacted] CCI [redacted]

Abbreviations: NRS = numeric rating scale; PK = pharmacokinetic; PUCAI = Pediatric Ulcerative Colitis Activity Index.

4.3. Exploratory Objectives

Table AMBU.4.3. Exploratory Objectives and Endpoints

Objectives	Endpoints
Exploratory	
To summarize the change in baseline in biomarkers	Change from baseline in fecal calprotectin Change from baseline in C-reactive protein
To evaluate the time to **symptomatic response**	CCI [redacted]
To evaluate the time to **symptomatic remission**	Time to **symptomatic remission** (defined as SF = 0, or SF = 1 with a ≥1-point decrease from baseline, and RB = 0)
To summarize the change from baseline of individual MMS subscores and the composite symptomatic subscore over time in patients receiving mirikizumab	The numerical value and change from baseline in each of the following items: SF (at each visit) RB (at each visit) ES (Weeks 12 and 52) The composite clinical endpoint of the sum of the SF and RB subscores (at each visit)
CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]

Abbreviations: ES = Endoscopic subscore; MMS = Modified Mayo Score; NRS = numeric rating scale; PGIC = Patient's Global Impression of Change; PGRS = Patient's Global Rating of Severity; RB = rectal bleeding; SF = stool frequency; UC = ulcerative colitis.

5. Study Design

5.1. Summary of Study Design

Study AMBU is a multicenter, open-label study designed to evaluate the safety, pharmacokinetics (PK), pharmacodynamics (PD), and clinical response of mirikizumab in pediatric patients (ages 2 to <18 years old) and to provide data for dose confirmation for Phase 3. The study population includes pediatric patients with moderately to severely active ulcerative colitis (UC), who have an inadequate response to, loss of response to, or are intolerant to nonbiologic therapy for UC (biologic-naive), and/or those who have been exposed to at least 1 biologic and/or Janus kinase inhibitor therapy for UC (biologic/ Janus kinase inhibitor-experienced).

Patients weighing >40 kg will receive a mirikizumab induction dose of 300 mg via intravenous (IV) infusion and patients weighing ≤40 kg will receive 5 or 10 mg/kg via IV infusion at Weeks 0, 4, and 8. Patients who have met the clinical response criteria at Week 12 will receive subcutaneous (SC) maintenance doses of 200 mg (weight >40 kg), or 100 mg (weight >20 kg to ≤40 kg), or 50 mg (weight ≤20 kg) every 4 weeks from Weeks 12 to 48. Patients who have not achieved clinical response at Week 12 may receive extended induction at the next higher available dose, or will be discontinued. In cases where there is no higher dose, patients may receive extended induction dosing at the current dose. Approximately 60 patients with moderately to severely active UC will be screened to enroll approximately 30 patients.

Figure AMBU.5.1 illustrates the study design.

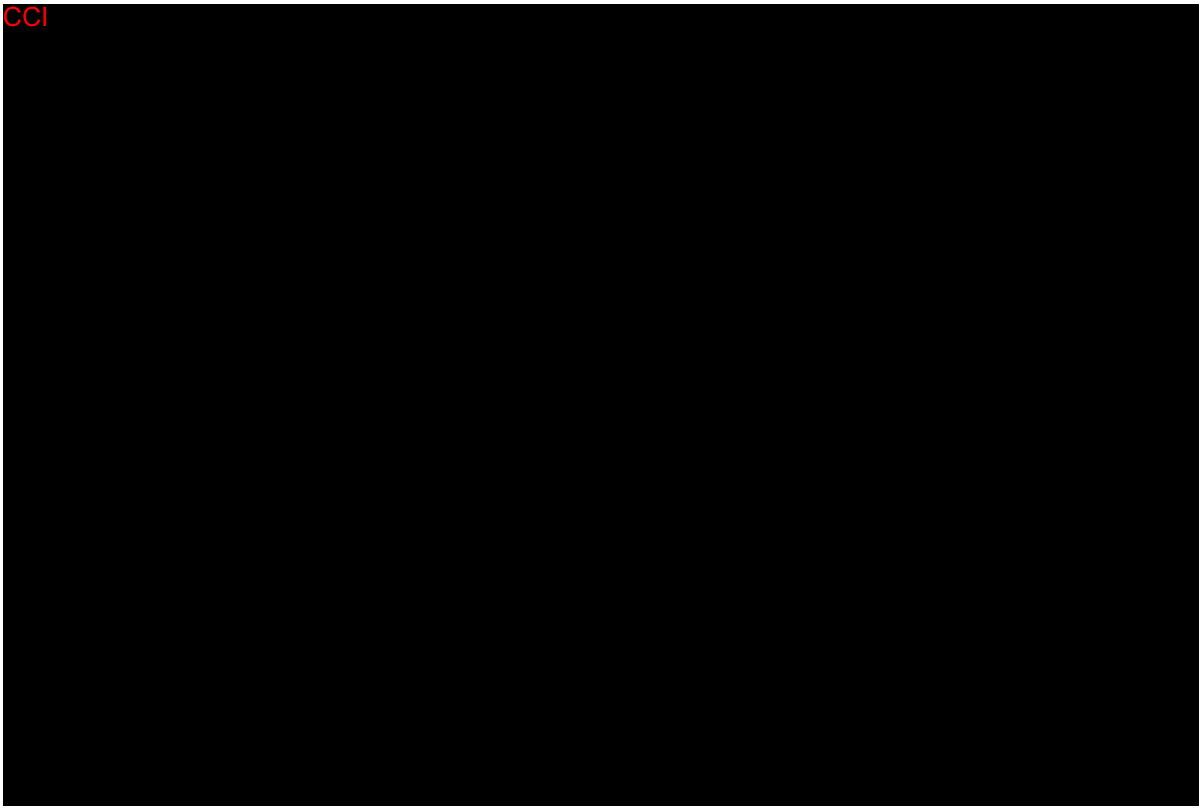

Figure AMBU.5.1. Illustration of study design for clinical protocol I6T-MC-AMBU.

5.2. Determination of Sample Size

Lilly plans to enroll approximately 30 patients into Study AMBU, to achieve at least 25 evaluable patients with respect to evaluating mirikizumab PK. The enrollment target includes approximately 10 patients in the >40 kg category and approximately 20 patients in the ≤40 kg category.

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

5.3. Method of Assignment to Treatment

Study AMBU is open-label and patients will be assigned to mirikizumab dose groups based o[redacted]

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (hereafter, Lilly) or its designee. The statistical analyses will be performed using SAS® Version 9.4 or higher. The latest version of the Medical Dictionary for Regulatory Activities (MedDRA®) will be used.

Analyses and summaries from assessment of endpoints described in the protocol (described in Section 4 of this SAP and Section 4 of I6T-MC-AMBU [AMBU] protocol) are planned to be included in the clinical study report (CSR). Analyses and summaries for key safety data are also planned to be included in the CSR. Results from additional efficacy analysis predefined below and other safety analyses may also be provided in the CSR, as deemed appropriate. Any analysis or summary not included in the CSR may 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 analyses of the data may be conducted, as deemed appropriate. Some of the analyses described in this document will be incorporated into interactive display tools instead of or in addition to static displays.

The Schedule of Activities outlined in the protocol specifies the allowable windows for assessments. Assessments performed outside these windows will not be excluded from any analysis, but will be reported as a protocol deviation (see Section 6.15).

6.1.1. Analysis Populations

Patient populations are defined in Table AMBU.6.1 along with the analysis they will be used to conduct. Patients will be analyzed according to the weight/treatment dose group to which they were assigned for all populations, found in Table AMBU.6.2.

Table AMBU.6.1. Definition of Population

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

Abbreviation: PK = pharmacokinetic.

[a] Safety population to include induction period and overall (combined induction and maintenance period). Any additional population or subpopulations that are of interest may also be considered for safety assessment. This is a revision to the safety population text in Section 10.2 of the protocol.

Table AMBU.6.2. Weight/Treatment Dose Groups for Each Analysis Study Period and Population

Study Period	Analysis Population	Weight/Treatment Dose Groups
Induction Period	mITT; Safety	≤40 kg 5mg/kg miri IV; ≤40 kg 10mg/kg miri IV; >40 kg 300mg miri IV; All miri
Induction and Maintenance Periods	mITT; Safety	≤40 kg 5mg/kg miri IV; ≤40 kg 10mg/kg miri IV; >40 kg 300mg miri IV; All miri
Maintenance Period	mITT	≤20 kg 50mg miri SC >20 kg and ≤ 40 kg 100mg miri SC >40 kg 200 mg miri SC; ≤20 kg NR 10mg/kg miri IV & 50mg miri SC >20 kg and ≤ 40 kg NR 10mg/kg miri IV & 100mg miri SC >40 kg NR 300mg miri IV & 200 mg miri SC; All miri

Abbreviations: IV = intravenous; mITT = modified intent-to-treat; miri = mirikizumab; NR = non-responder (at Week 12); SC = subcutaneous.

The weight/treatment dose groups shown in Table AMBU.6.2 reference the specific treatment regimens to which pediatric patients are assigned at Week 0 (for the induction period) and at Week 12 (for the maintenance period) and are dependent on the participants' weight at those respective visits and their clinical response status at Week 12 for the maintenance period as

defined in the protocol. The analyses for Week 12 endpoints will be summarized by the weight/treatment dose groups indicated for the induction period. Analyses of maintenance and Week 52 endpoints will primarily be summarized by the weight/treatment dose groups indicated for the combined induction and maintenance periods. Additional summaries of some Week 52 and maintenance period endpoints will be provided for the weight/treatment groups indicated for the maintenance period. Additional details are found in Section 6.10.

6.1.2. Baseline Definition

The baseline for variables collected as part of the CCI diary (including the SF and rectal bleeding (RB) components of the Modified Mayo) will be calculated from valid CCI diary entries obtained prior to baseline endoscopy preparation (see Appendix 1). The baseline endoscopy component of the Mayo will use the endoscopic appearance of the mucosa at the screening endoscopy. For other efficacy, health outcome, and safety assessments, baseline is defined as the last non-missing assessment recorded on or prior to the date of the first study drug administration at Visit 2 (Week 0).

Baseline for safety analysis is described in the safety section.

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.

6.1.3. Analysis Methods

For assessments of the binary efficacy endpoints and binary health outcomes, proportions for each weight class/treatment group along with the 95% confidence intervals (CIs) using the Wilson Score method (Wilson 1927; Newcombe 1998) will be provided. Non-responder imputation method will be used to estimate the percentage of patients achieving response across post-baseline visits.

Assessments of the continuous endpoints, descriptive statistics (n, mean, standard deviation [SD], minimum, first quartile, median, third quartile, and maximum) will be provided for each specified visit. Where appropriate, the mean and mean change from baseline with corresponding 95% CIs will be presented at each specified visit.

6.2. Adjustments for Covariates

This study is a multicenter, open-label PK study designed to evaluate the safety, PK, PD, and clinical response of mirikizumab in pediatric patients, and to provide data for dose confirmation for Phase 3. All patients will receive mirikizumab based on their baseline weight class for the Induction Period and Week 12 weight class for the Maintenance Period. Treatment comparisons are not planned to be performed, hence no adjustments for covariates will be warranted.

6.3. Handling of Dropouts or Missing Data

Intercurrent events (FDA 2021) are events which occur after the treatment initiation and make it impossible to measure a variable or influence how it should be interpreted. Examples of such

events include treatment discontinuation due to death or adverse events (AEs), rescue treatment, and loss to follow-up. The missing data methods described below handle intercurrent events in different ways and thus are relevant to different estimands.

The Schedule of Activities outlined in the protocol specifies the allowable windows for assessments. Assessments performed outside these windows will not be excluded from any analysis, but will be reported as a protocol deviation (see Section 6.15). While every effort will be made to reduce missing data, the missing data imputation method of NRI will be used when patients are permanently discontinued from study drug or otherwise have missing data. For the "as observed" analysis, only data from completers at the visit are relevant, and therefore the analysis does not need to deal with missing data.

For any interim analyses that occur, patients who, based on their treatment start date, would not have completed the visit corresponding to the selected endpoint at the time of the database lock will not be included in the analysis of that endpoint unless otherwise specified. Patients who have discontinued or otherwise have missing data and would have otherwise completed that visit at the time of database lock will be counted as non-responders for the interim analysis. For example, if a patient who discontinued at Week 12 of the study would have been in Week 24 of the study at the time of database lock, would not be included in the analysis of endpoints at Week 36 or Week 52. If that same patient who discontinued would have been at Week 48 at the time of the interim database lock if they had remained in the study, they would be counted as a non responder for Week 36, but not included in the Week 52 analysis.

6.3.1. Non-Responder Imputation (NRI)

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

The NRI method may be used when the estimand of interest uses the composite strategy (FDA 2021) for handling intercurrent events. In this strategy, patients with any intercurrent events that lead to the permanent discontinuation of assigned study treatment are defined to have failed treatment for all subsequent time points.

In addition, patients who were not adequately assessed to determine if they meet the clinical requirements for response at the time point of interest are also considered to have failed treatment.

For any interim analyses that occur, patients who, based on their treatment start date, would not have completed the visit corresponding to the selected endpoint at the time of the database lock will not be included in the analysis of that endpoint. Patients who have discontinued or otherwise have missing data and would have otherwise completed that visit at the time of database lock will be counted as non-responders for the interim analysis.

6.3.2. Modified Baseline Observation Carried Forward (mBOCF)

For patients discontinuing investigational product due to an AE, the baseline observation for the endpoint will be carried forward to the corresponding visit for all missing observations after the patient discontinued study treatment. For patients discontinuing investigational product for any other reason, the last nonmissing postbaseline observation before discontinuation will be carried forward to the corresponding visit for all missing observations after the patient discontinued. For all patients with sporadically missing observations prior to discontinuation, the last nonmissing observation before the sporadically missing observation will be carried forward to the corresponding visit. Randomized patients without at least 1 postbaseline observation will not be included for evaluation with the exception of patients discontinuing study treatment due to an AE.

The mBOCF method is based on an estimand that handles the intercurrent event of discontinuing study drug due to an AE by defining the patient as not receiving any benefit from study drug after the event. That is, the patient is defined as reverting back to baseline regardless of any continuing efficacy benefits they may still have received after the event. For other intercurrent events (eg, discontinuation due to reasons other than an AE) or sporadic missingness the "while on treatment" strategy is applied. That is, the endpoint is defined as the last observed value at or before the visit of interest before the patient discontinued study treatment.

For any interim analyses that occur, patients who, based on their treatment start date, would not have completed the visit corresponding to the selected endpoint at the time of the database lock will not be included in the analysis of that endpoint. Patients who have discontinued or otherwise have missing data and would have otherwise completed that visit at the time of database lock will be treated using mBOCF for the interim analysis.

6.4. Multicenter Studies

This study will be conducted by multiple investigators at multiple sites internationally. No estimation of interaction effects or adjustments by country or region will be performed due to the limited sample size in each treatment group and nature of the study.

6.5. Multiple Comparisons/Multiplicity

No multiplicity adjustments will be made due to the nature of the study.

6.6. Patient Disposition

Screen failures and reason for screen failure will be summarized. The treatment disposition and study disposition will be summarized for the modified intent-to-treat (mITT) population. Disposition summaries will be by weight/treatment dose group and overall. Summaries will also include reason for discontinuation from the study tabulated by weight/treatment group for all patients.

Additionally, a listing of all patients who are enrolled and received at least one dose of miri (ie, the mITT population) and discontinued from study treatment during any period from the study

will be provided, and the timing of discontinuing the study will be reported. If known, a reason for their discontinuation will be given.

6.7. Patient Characteristics

Patient demographic variables and baseline characteristics will be summarized by weight/treatment dose groups and overall for the mITT populations with the baseline values. The continuous variables will be summarized using descriptive statistics (N, mean, SD, minimum, Q1, median, Q3, and maximum) and the categorical variables will be summarized using frequency counts and percentages. No inferential analysis for the comparability of baseline covariates across groups will be performed. By-patient listings of basic demographic characteristics (ie, age, sex, race, racial subgroup, ethnicity, country, body weight) will be provided.

Table AMBU.6.3. Patient Characteristics (and Variables for Analysis)

Variable	Continuous Summary	Categorical Summary
Demographic Characteristics		
Age[a]	Yes	2 – <8 years, 8 – <12 years, 12 – <18 years
Sex	No	Male, Female
Ethnicity	No	Hispanic/Latino, Non-Hispanic/Non-Latino
Race	No	American Indian/Alaska Native, Asian, Black/African American, Native Hawaiian or other Pacific Islander, White, or Multiple
Geographic Region	No	By Country (listed in other documents)
Height (cm)	Yes	None
Weight (kg)	Yes	>40 kg, ≤40 kg and >20 kg, ≤20 kg
BMI[b]	Yes	Underweight (<18.5 kg/m^2), Normal (≥18.5 and <25 kg/m^2), Overweight (≥25 and <30 kg/m^2), Obese (≥30 and <40 kg/m^2), Extreme obese (≥40 kg/m^2)
Tobacco/Nicotine Replacement use (for ages ≥12)	No	Never, Current, Former
Alcohol use (for ages ≥12)	No	Never, Current, Former
Caffeine use (for ages ≥12)	No	Never, Current, Former
Prior UC Therapy		
Prior biologic[c] exposure	No	Ever, Never
Prior biologic[c] failure[d]	No	Failed, Not failed
Prior biologic[c] failure[d] excluding JAK[g] inhibitors	No	Failed, Not failed
Inadequate response or loss of response to a biologic[c]	No	Ever, Never
Inadequate response to a biologic[c]	No	Ever, Never
Loss of response to a biologic[c]	No	Ever, Never
Intolerance to a biologic[c]	No	Ever, Never
Number of prior biologics used[c]	No	0, 1, 2, >2
Number of failed[d] biologics[c]	No	0, 1, 2, >2
Prior biologic failure[d] and prior biologic exposures	No	Not exposed, Exposed but not failed, Exposed and failed at least one
Prior anti-TNF[e] failure[d]	No	Failed, Not failed

Variable	Continuous Summary	Categorical Summary
Number of failed[d] (unique) prior anti-TNFs[e]	No	0,1, 2, >2
Prior anti-integrin[f] failure[d]	No	Ever, Never
Prior failure[d] of a JAK[g] inhibitor	No	Ever, Never
Prior corticosteroid failure[d]	No	Ever, Never
Prior immunomodulator failure[d, h]	No	Ever, Never
Baseline UC Therapies		
Baseline corticosteroid use[h]	No	Yes, No
Baseline prednisone equivalent dose	Yes	None
Budesonide MMX	No	Yes, No
Baseline immunomodulator use[h]	No	Yes, No
Baseline corticosteroid and immunomodulator use[h]	No	Corticosteroid only, Immunomodulator, Neither, Both
Baseline use of oral aminosalicilates[i]	No	Yes, No
Baseline use of methotrexate[h]	No	Yes, No
Baseline use of thiopurine[h]	No	Yes, No
Baseline Disease Characteristics		
Duration of UC[j]	Yes	<1 year, ≥1 to <3 years, ≥3 year to <7 years, ≥7 years
Age at Diagnosis of UC[k]	Yes	<6, ≥6 to <10 year, ≥10 to <17 years
Historical Disease Severity	No	Ever Severe, Never Severe
Baseline Disease Extent	No	Ulcerative proctitis (rectum), Left-sided (descending or sigmoid colon), Extensive (transverse colon), Pancolitis (cecum or ascending colon)
Baseline Fecal Calprotectin	Yes	≤250 µg/g, >250 µg/g
Baseline C-reactive Protein (CRP)	Yes	≤6 mg/L, >6 mg/L
Baseline Modified Mayo Score	Yes	Moderate (4-6), Severe (7-9)
Baseline Total Mayo Score	Yes	Moderate (6-9), Severe (10-12)
Baseline Partial Mayo Score	Yes	None
Baseline Endoscopic Mayo Subcore	No	Possible values of 4-point scale in Table AMBU.6.4
Baseline Stool Frequency Mayo Subscore	No	Possible values of 4-point scale in Table AMBU.6.4
Baseline Rectal Bleeding Mayo Subscore	No	Possible values of 4-point scale in Table AMBU.6.4
Baseline PGA Mayo Subscore	No	Possible values of 4-point scale in Table AMBU.6.4
Baseline PUCAI	No	Severe (65-85), Moderate (35-60), Mild (10-30), None (<10)
CCI		
Baseline Abdominal Pain NRS	Yes	<4, ≥4
Baseline Patient's Global Rating of Severity (PGRS)	Yes	None
Baseline Nocturnal Stool	Yes	Yes (≥1), No (0)
CCI		
Baseline Bristol Stool Scale	No	Not Loose Stool (1 – 3), Loose Stool (4-5)
CCI		

Abbreviations: ATC = Anatomical Therapeutic Chemical; BMI = body mass index; DOB = date of birth; eCRF = electronic case report form; JAK = Janus kinase; NRS = numeric rating scale; PGA = Physician's Global Assessment; PUCAI = Pediatric Ulcerative Colitis Activity Index; TNF = tumor necrosis factor; UC = ulcerative colitis.

[a] Age in years will be calculated as length of the time interval from the DOB to the informed consent date.

[b] Body mass index (BMI) will be calculated as: $BMI\ (kg\ /\ m^2) = Weight\ (kg)\ /(Height\ (m))^2$.

[c] Biologic systemic therapies include: adalimumab, adalimumab biosimilar, alemtuzumab, brazikumab, certolizumab, golimumab, guselkumab, infliximab, infliximab biosimilar, interferon therapy, other TNF biosimilar, risankizumab, rituximab, tildrakizumab, ustekinumab, vedolizumab, visilizumab, tofacitinib, and other JAK inhibitors. For the purpose of counting the number of prior biologics, adalimumab and adalimumab biosimilar will be counted as one biologic. Also, infliximab and infliximab biosimilar will be counted as one biologic

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

[e] Anti-TNF alpha biologics include: infliximab, infliximab biosimilar, adalimumab, adalimumab biosimilar, golimumab, certolizumab pegol.

[f] Possible anti-integrin treatments include vedolizumab.

[g] Options on the prior medications eCRF for JAK inhibitors include: tofacitinib and other JAK inhibitor.

[h] ATC codes for immunomodulators including methotrexate and thiopurines are listed in the compound level safety standards.

[i] Aminosalicilates will be defined using ATC code A07EC (all members).

[j] Length of the interval from the date of UC diagnosis to the date of informed consent.

[k] Age at diagnosis in years will be calculated as the time interval from the DOB to the date of UC diagnosis.

6.8. Treatment Compliance

Treatment compliance with investigational product will be summarized for patients who have at least one dose (that is, mITT population) for the Induction Period and for the combined Induction and Maintenance Periods. Treatment compliance for each patient will be calculated as:

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

The "total number of study drug administration visits planned per protocol" is based on the number of planned administration visits before the patient discontinued study drug. Each patient will be defined as having had a study drug administration visit on a given date if:

- For visits where the patient is to receive an IV infusion, they received at least 80% of the planned infusion dose as derived from the infusion electronic case report form (eCRF) page.
- For visits where the patient is to receive SC injections, they received the planned number of injection doses as derived from the injection eCRF page.

"Overall compliance" with therapy is defined as having at least 80% treatment compliance. Patient treatment compliance will be summarized for the mITT population by weight/treatment dose group.

6.9. Prior and Concomitant Therapy

Medications will be classified into Anatomical Therapeutic Chemical drug classes using the latest version of the World Health Organization drug dictionary. Medication start and stop dates will be compared to the date of first dose of treatment in each treatment period to allow medications to be classified as concomitant for each treatment period.

Prior medications are those medications that start and stop prior to the date of first dose of study treatment. *Concomitant medications* are those medications that start before, on, or after the first day of study treatment of the defined treatment period and continue into the treatment period. Concomitant medications are assigned to the treatment period in which they are actually ongoing. For all summary tables of concomitant medications, preferred terms of concomitant medication will be summarized by weight/treatment dose group:

- summary of prior medications for mITT population,
- summary of concomitant medication for mITT population for the Induction and the combined Induction and Maintenance periods, and
- summary of concomitant medication for mITT population within class of interest (corticosteroid therapy, immunomodulatory therapy) for the Induction and the combined Induction and Maintenance periods. The definition of these two classes of interest will be based on compound level safety standards.

6.10. Efficacy Analyses

The description and derivation of the efficacy/health outcomes measure and endpoints are provided in Table AMBU.6.4.

Table AMBU.6.5 provides the detailed analyses including analysis type, method and imputation, population, time point, and dosing regimen comparisons for secondary efficacy/health outcomes analyses. Note that the details of each analysis will follow the general principles described in Section 6.13.

6.10.1. Primary Outcome and Methodology

The primary objective of this study is to evaluate the PK of mirikizumab treatment in pediatric patients. Analysis of primary endpoints is described in separate PK/PD analysis plan as mentioned in Section 6.11.1.

Table AMBU.6.4. Description and Derivation of Efficacy/Health Outcomes Measures and Endpoints

Measure	Description	Variable	Derivation / Comment	Definition of Missing
Mayo Score and components	The Mayo score is a composite instrument to measure Ulcerative Colitis disease activity. It is comprised of the following 4 subscores: Stool Frequency (SF): The SF subscore is a patient-reported measure. This item reports the number of stools in a 24-hour period, relative to the normal number of stools for that patient in the same period. The normal reference is collected at baseline/screening. Rectal Bleeding (RB): The RB subscore is a patient-reported measure. This item reports the most severe amount of blood passed for a given day Endoscopic Subscore (ES): The ES is a physician-reported measure that reports the worst appearance of the mucosa on flexible sigmoidoscopy or colonoscopy. Physician's Global Assessment (PGA): The PGA is a physician-reported measure that summarizes the investigator's assessment of the patient's UC disease activity. Each subscore is on a 4-point scale, ranging from 0 to 3.	SF subscore	Calculated by averaging and rounding the 4-point daily SF subscore over 3 days as described in Appendix 1. Possible values are: (0) Normal number of stools for subject; (1) 1 to 2 stools more than normal; (2) 3 to 4 stools more than normal; (3) 5 or more stools than normal.	Missing if fewer than 3 available measurements in the relevant 7 days.
		RB subscore	Calculated by averaging and rounding the 4-point daily RB subscore over 3 days as described in Appendix 1. Possible values are: (0) No blood seen; (1) Streaks of blood with stool less than half of the time; (2) Obvious blood (more than just streaks) or streaks of blood with stool most of the time; (3) Blood alone passed	Missing if fewer than 3 available measurements in the relevant 7 days.
		ES subscore	Possible values are: (0) Normal or inactive disease; (1) Mild disease (erythema, decreased vascular pattern); (2) Moderate disease (marked erythema, absent vascular pattern, friability, erosions); (3) Severe disease (spontaneous bleeding, ulceration)	Single item. Missing if missing.
		PGA subscore	Possible values are: (0) Normal (1) Mild disease	Single item. Missing if missing.

Measure	Description	Variable	Derivation / Comment	Definition of Missing
			(2) Moderate disease (3) Severe disease	
		Modified Mayo Score (MMS)	Calculated as: SF + RB + ES.	Missing if SF, RB or ES subscores are missing.
		Partial Mayo Score	Calculated as: SF + RB + PGA.	Missing if SF, RB or PGA subscores are missing.
		Alternate MMS Clinical Remission	SF subscore = 0, or SF = 1 with a ≥1-point decrease from baseline, and RB subscore = 0, and ES subscore = 0 or 1 (excluding friability)	Missing if SF, RB, or ES subscores are missing.
		MMS Clinical Remission	SF subscore = 0 or 1 RB subscore = 0, and ES subscore = 0 or 1 (excluding friability)	Missing if SF, RB, or ES subscores are missing.
		MMS Clinical Response	A decrease in the MMS of ≥2 points and ≥30% decrease from baseline, and A decrease of ≥1 point in the RB subscore from baseline or a RB score of 0 or 1	Missing if baseline or Week 12 MMS is missing.
		Endoscopic Remission	ES = 0 or 1 (excluding friability).	Missing if ES is missing.
		Symptomatic Remission	SF = 0, or SF = 1 with a ≥1-point decrease from baseline and RB = 0	Missing if SF or RB is missing.
		CCI [redacted]		
		Time to first symptomatic remission	For patients who are observed to meet the remission criteria during the Induction Period, time will be from the start of the Induction Period to the first measurement date where the patient met the remission criteria based on weekly averages.	Patients not observed to meet remission criteria during the Induction Period will be censored after the date of their last measurement during the Induction Period.
		CCI [redacted]		

Measure	Description	Variable	Derivation / Comment	Definition of Missing
			CCI	
		Time to first symptomatic response	For patients who are observed to meet the response criteria during the Induction Period, time will be from the start of the Induction Period to the first measurement date where the patient met the response criteria based on weekly averages.	Patients not observed to meet response criteria during the Induction Period will be censored after the date of their last measurement during the Induction Period.
		Endoscopic subscore of 0	ES = 0.	Missing if ES is missing.
		Total Symptomatic Score	Calculated as SF + RB.	Missing if SF or RB is missing.
		Endoscopic Response	A decrease in the ES of ≥1 point compared to baseline.	Missing if ES is missing.
		SF component of clinical remission	SF = 0, or SF = 1	Missing if SF is missing.
		RB component of clinical remission	RB = 0	Missing if RB is missing.
		Corticosteroid-free remission at Week 52	Corticosteroid-free remission without surgery at Week 52, defined as: Clinical remission at Week 52, and No corticosteroid use or UC-related surgery for ≥12 weeks prior to Week 52	NRI if any component is missing.
		Loss of Clinical Response	CCI	

Measure	Description	Variable	Derivation / Comment	Definition of Missing
Urgency NRS	CCI	Urgency NRS Score	Calculated by averaging data from all available CCI diary entries of Urgency NRS for a 7 day period as described in Appendix 1.	Missing if fewer than 4 available measurements in the relevant 7 days (see Appendix 1).
Abdominal Pain NRS	The Abdominal Pain NRS is a single patient-reported item that measures the "worst abdominal pain in the past 24 hours" using a 6-point scale ranging from 0 (no pain) to 5 (worst possible pain) for 8-11 years old, and 11-point NRS ranging from 0 (no pain) to 10 (worst possible pain) for children < 8 years old as completed by a caregiver and those 12-17 years old.	Abdominal Pain NRS Score	Calculated by averaging data from all available CCI diary entries of Abdominal Pain NRS for a 7 day period as described in Appendix 1.	Missing if fewer than 4 available measurements in the relevant 7 days.
PGIC	The Patient's Global Impression of Change (PGIC) scale is a patient-rated instrument designed to assess a patients' rating of change in their symptom(s). Responses are graded on a 7-point Likert scale. Patients or caregivers will record their response on the PGIC electronically as source data in the tablet device at appropriate visits.	PGIC Score	Single Item	Single item, missing if missing. No imputation.
PGRS	Patient's Global Rating of Severity (PGRS) is a 1-item patient-rated questionnaire designed to assess the patients' rating of their disease symptom severity over the past	PGRS Score	Calculated by averaging data from all available CCI diary entries of PGRS for a 7 day period as described in Appendix 1.	Missing if fewer than 4 available measurements in the relevant 7 days.

Measure	Description	Variable	Derivation / Comment	Definition of Missing
	24 hours. Responses are graded on a 6-point scale in which a score of 0 indicates the patient has no symptoms (that is, "none") and a score of 5 indicates that the patient's symptom(s) are "very severe."			
Nocturnal Stool	The Nocturnal Stool instrument is a single item asking the patient to record the number of stools they had during the night (or day, for shift workers) causing them to wake from sleep.	Nocturnal Stool Score	Calculated by averaging data from all available CCI diary entries of Nocturnal Stool for a 7 day period as described in Appendix 1.	Missing if fewer than 4 available measurements in the relevant 7 days.
Fatigue NRS	CCI	Fatigue NRS Score	Calculated by averaging data from all available CCI diary entries of Fatigue NRS for a 7 day period as described in Appendix 1.	Missing if fewer than 4 available measurements in the relevant 7 days.
Bristol Stool Scale	The Bristol Stool Scale is a single item that provides a pictoral and verbal description of stool consistency and form ranging from Type 1 (Hard Lumps) to Type 5 (Watery/liquid). An additional option provided was "6. Did not poop."	Bristol Stool Scale score	Calculated by using the worst value (ie, largest number from 1 to 5) from all available CCI diary entries of Bristol Stool Scale for a 7-day period as described in Appendix 1. Responses of "Did not poop," will be counted as missing for that day.	Missing if fewer than 4 available measurements in the relevant 7 days.
		Loose Stool	Bristol Stool Scale score of 4 or 5.	Bristol Stool Scale score is missing
PUCAI	The PUCAI (Turner et al. 2007) is a clinician-administered, 6-item questionnaire that measures: abdominal pain; RB; stool	PUCAI Score	All items are answered as an average over the 'past 2 days'. A total disease activity score is calculated from 0 to 85, with	Missing if any component is missing.

Measure	Description	Variable	Derivation / Comment	Definition of Missing
	consistency; number of stools; nocturnal stools; and activity level (see Appendix 7 of the protocol).		Severe: 65-85 Moderate: 35-60 Mild: 10-30, and None: <10. The clinician will record the patient or caregiver/legal guardian responses for the PUCAI electronically as source data in the tablet device at appropriate visits.	
		PUCAI clinical remission	PUCAI clinical remission is defined as a PUCAI score of <10 points	Missing if any component is missing.
		PUCAI clinical response	PUCAI clinical response is defined as a reduction in baseline PUCAI score of ≥20 points.	Missing if any component is missing.
Histopathology	CCI [redacted]			

Measure	Description	Variable	Derivation / Comment	Definition of Missing
	CCI			
Histo-Endo	Combined histology and endoscopic endpoints.	Histologic-endoscopic mucosal improvement	Histologic improvement and endoscopic remission.	Missing if any component of the definition is missing.
		Histologic-endoscopic mucosal remission	Defined as achieving both histologic remission and endoscopic remission	Missing if any component of the definition is missing.
CRP	C-reactive protein (CRP) is a biomarker of inflammation.	CRP	Lab value. May be transformed if needed.	Single lab value. Missing if missing.
Fecal calprotectin	Fecal calprotectin is used as a biomarker of intestinal inflammation in clinical practice.	Fecal calprotectin	Lab value. May be transformed if needed.	Single lab value. Missing if missing.
Growth and Pubertal Assessments	Occipital head circumference	Head circumference	Occipital head circumference measurements will be performed on patients less than 3 years of age at baseline. Measurements will be taken at baseline and then approximately Q12W thereafter, until the patient reaches the age of 3 years.	Data will be missing for patients who are 3 years or older at entry. Missing if missing.
	Change from baseline in height (cm)	Height CFB	Change from baseline in height (cm) at all study visits. Height is measured 3 times at all visits, height at each visit is calculated	Missing if baseline height or height at visit is missing.

Measure	Description	Variable	Derivation / Comment	Definition of Missing
			using the average of the 3 measurements.	
	Change from baseline in weight (kg)	Weight CFB	Change from baseline in weight (kg) at all study visits.	Missing if baseline weight or weight at visit 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 Height Percentile	Observed height z-score and percentile by sex and age	Missing if height at visit is missing.
	Height Percentile Change from Baseline	Height Percentile CFB	Change from Baseline is calculated as Present height percentile – Baseline height percentile	Missing if baseline height or height at visit is 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 Weight Percentile	Observed weight z-score and percentile by sex and age	Missing if weight at visit is missing.
	Weight Percentile Change from Baseline	Weight Percentile CFB	Change from Baseline is calculated as Present weight percentile – Baseline weight percentile	Missing if baseline weight or weight at visit is missing.
	Observed height velocity by gender and age group. Age groups for which	Height velocity	Observed height velocity by gender and age group will be calculated at baseline	Data will be missing if either present height or previous height

Measure	Description	Variable	Derivation / Comment	Definition of Missing
	this will be summarized are 2 to <8, 8 to <12, and 12 to <18.		according to the following formula: (Present Height [cm] - Previous Height [cm])/Interval (months) Between Measurements × 12	is missing.
Assessment of Puberty	Total testosterone levels will be collected from male patients ≥9 years of age. Estradiol levels will be collected from female patients ≥9 years of age, until the female begins menstruating. If the patient is 9 years of age and has already begun menstruation, estradiol levels will not be required.	Hormone level	Total testosterone levels for male patients ≥9 years of age and estradiol levels for female patients ≥9 years of age, until the female begins menstruating.	Missing if patients are less than 9 years old or if date of onset of menstruation for females if exists. Missing if missing.
EIMs	Extraintestinal manifestations (EIMs) are collected using the medical history and adverse event eCRFs. Extraintestinal manifestations include, but are not limited to: uveitis, peripheral arthritis, ankylosing spondylitis, aphthous stomatitis, arthralgia, autoimmune hepatitis, cholelithiasis, deep vein thrombosis, iritis, nephrolithiasis, erythema nodosum, osteopenia, osteoporosis, pancreatitis, sclerosing cholangitis, pyoderma gangrenosum, sacrolitis and skin vasculitis NOS.	Baseline EIMs	EIMs ongoing at first dose of study treatment.	No Imputation.
		Resolution of Baseline EIMs	Complete resolution of baseline EIMs at Week 12 or 52. If a patient has multiple baseline EIMs, then at least one of the EIMs must have resolved.	No Imputation

Abbreviations: CFB = change from baseline; NOS = not otherwise specified; NRI = non-responder imputation; NRS = Numeric Rating Scale; PUCAI = Pediatric Ulcerative Colitis Activity Index; Q12W = every 12 weeks.

Table AMBU.6.5. Description of Secondary Efficacy/Health Outcomes Analyses

Measure	Variable	Analysis Method (Section 6.1.3)	Population (Section 6.1.1)	Time Point(s)
Mayo Score and components	MMS Clinical Remission	Proportion for each weight/treatment dose group along with the 95% 2-sided CI with NRI and as observed	mITT	Weeks 12 and 52
			mITT who are remitters from Week 12	Week 52
			mITT who are MMS clinical responders from Week 12	Week 52
	MMS Clinical Response	Proportion for each weight/treatment dose group along with the 95% 2-sided CI with NRI and as observed.	mITT	Weeks 12 and 52
			mITT who achieve MMS clinical response at Week 12	Week 52
	Corticosteroid-free remission	Proportion for each weight/treatment dose group along with the 95% 2-sided CI with NRI and as observed.	mITT	Week 52
	Endoscopic Remission	Proportion for each weight/treatment dose group along with the 95% 2-sided CI with NRI and as observed.	mITT;	Weeks 12 and 52
			mITT who are in endoscopic remission at Week 12	Week 52
	Endoscopic subscore of 0	Proportion for each weight/treatment dose group along with the 95% 2-sided CI with NRI and as observed.	mITT	Weeks 12 and 52
	Symptomatic remission	Proportion for each weight/treatment dose group along with the 95% 2-sided CI with NRI and as observed.	mITT	At all scheduled visits
PUCAI	PUCAI clinical remission	Proportion for each weight/treatment dose group along with the 95% 2-sided CI with NRI and as observed.	mITT	Weeks 12 and 52
			mITT who achieve PUCAI clinical remission at Week 12	Week 52
			mITT who achieve PUCAI clinical response at Week 12	Week 52
	PUCAI clinical response	Proportion for each weight/treatment dose group along with the 95% 2-sided CI with NRI and as observed.	mITT	Weeks 12 and 52
			mITT who achieve PUCAI clinical response at Week 12	Week 52
	PUCAI CFB	Descriptive statistics and 95% CI for mean with mBOCF and as observed.	mITT	Weeks 12, 24, 36, and 52

Measure	Variable	Analysis Method (Section 6.1.3)	Population (Section 6.1.1)	Time Point(s)
Height	Height Velocity	Descriptive statistics and 95% CI for mean.	mITT, by gender and age group	Weeks 12, 24, and 52
	Height CFB	Descriptive statistics and 95% CI for mean.	mITT	Weeks 12, 24, and 52
	Height Percentiles CFB	Descriptive statistics and 95% CI for mean.	mITT	Weeks 12, 24, and 52
Weight	Weight CFB	Descriptive statistics and 95% CI for mean.	mITT	At each scheduled visit.
	Weight Percentiles CFB	Descriptive statistics and 95% CI for mean.	mITT	Weeks 12, 24, and 52
Occipital head circumference	Head circumference	Descriptive statistics and 95% CI for mean.	mITT only on those patients less than 3 years at baseline	At all applicable visits (Week 12 + Q12W)
Puberty Development	Testosterone CFB	Descriptive statistics and 95% CI for mean.	mITT – males who are 9 years or older	Weeks 12, 36, and 52
	Estradiol CFB	Descriptive statistics and 95% CI for mean.	mITT – females who are 9 years or older without the date of onset of menstruation.	Weeks 12, 36, and 52
Abdominal Pain NRS	Abdominal Pain NRS score CFB	Descriptive statistics and 95% CI for mean with mBOCF and as observed.	mITT, summarized by age group	Weeks 12 and 52
	CCI			Week 12 and 52
CCI			mITT	Weeks 12 and 52
Histopathology	Histologic Remission	Proportion for each weight/treatment dose group along with the 95% 2-sided CI with NRI and as observed.	mITT	Weeks 12 and 52
	Histologic Improvement	Proportion for each weight/treatment dose group along with the 95% 2-sided CI with NRI and as observed.	mITT	Weeks 12 and 52

Measure	Variable	Analysis Method (Section 6.1.3)	Population (Section 6.1.1)	Time Point(s)
	Histologic-Endoscopic Mucosal Improvement	Proportion for each weight/treatment dose group along with the 95% 2-sided CI with NRI and as observed.	mITT	Weeks 12 and 52
	Histologic-Endoscopic Mucosal Remission	Proportion for each weight/treatment dose group along with the 95% 2-sided CI with NRI and as observed.	mITT	Weeks 12 and 52

Abbreviations: CFB change from baseline; CI = confidence interval; mBOCF = modified baseline observation carried forward; mITT = modified intent-to-treat; MMS = Modified Mayo Score; NRI = non-responder imputation; NRS = Numerical Rating Scale; PUCAI = Pediatric Ulcerative Colitis Activity Index; Q12W = every 12 weeks.

Table AMBU.6.6. Description of Exploratory Efficacy/Health Outcomes Analyses

Measure	Variable	Analysis Method (Section 6.1.3)	Population (Section 6.1.1)	Time Point(s)
Mayo Score and components	Change from baseline in SF, RB, and Total Symptomatic Score	Descriptive statistics and 95% CI for mean with mBOCF and as observed.	mITT	At each scheduled visit
	Change from baseline in ES	Descriptive statistics and 95% CI for mean with mBOCF and as observed.	mITT	Weeks 12 and 52
	Time to first symptomatic response	Descriptive statistics and 95% CI for mean.	mITT	During Induction Period
	Time to first symptomatic remission	Descriptive statistics and 95% CI for mean.	mITT	During Induction Period
	MMS Alternative Clinical Remission	Proportion for each weight/treatment dose group along with the 95% 2-sided CI with NRI and as observed.	mITT	Weeks 12 and 52
CRP	CRP CFB	Descriptive statistics and 95% CI for mean with mBOCF and as observed.	mITT	Week 12 Week 52
Fecal calprotectin	Fecal calprotectin CFB	Descriptive statistics and 95% CI for mean with mBOCF and as observed.	mITT	Week 12 Week 52
PGIC	Mean PGIC Score	Descriptive statistics and 95% CI for mean as observed.	mITT	Week 4, Week 8, Week 12, and Week 52
PGRS	PGRS Score CFB	Descriptive statistics and 95% CI for mean with mBOCF and as observed.	mITT	At each scheduled visit.
Nocturnal Stool	Nocturnal Stool Score CFB	Descriptive statistics and 95% CI for mean with mBOCF and as observed.	mITT - In patients with a nocturnal stool score ≥1 at baseline	At each scheduled visit.
CCI [redacted]				At each scheduled visit.
Bristol Stool Scale	Loose stool	Proportion for each weight/treatment dose group along with the 95% 2-sided CI with NRI and as observed	mITT, in patients with loose stool at baseline	At each scheduled visit.

Measure	Variable	Analysis Method (Section 6.1.3)	Population (Section 6.1.1)	Time Point(s)
EIMs	Resolution of Baseline EIMs	Proportion for each weight/treatment dose group along with the 95% 2-sided CI with NRI and as observed.	mITT – in patients with EIMs at baseline	Weeks 12 and 52

Abbreviations: CFB = change from baseline; CI = confidence interval; CRP = c-reactive protein; ES = Endoscopic subscore; mBOCF = modified baseline observation carried forward; mITT = modified intent-to-treat; MMS = Modified Mayo Score; NRI = non-responder imputation; NRS = Numerical Rating Scale; PGIC = Patient's Global Impression of Change; PGRS = Patient's Global Rating of Severity; RB = rectal bleeding; SF = stool frequency.

6.10.2. Secondary Efficacy Analyses

Table AMBU.6.4 includes the description and derivation of the efficacy/health outcomes measures and endpoints. The analysis of secondary efficacy/health outcomes measures and endpoints is described in Table AMBU.6.5.

6.10.3. Exploratory Efficacy Analyses

The analysis of predetermined exploratory efficacy/health outcomes measures and endpoints is described in Table AMBU.6.6. Other exploratory analyses may be added as deemed appropriate.

6.11. Health Outcomes Analyses

6.11.1. Health Care Utilization

Hospitalization is recorded in the Healthcare Visit eCRF. Categories of healthcare visits include: acute care, emergency room, immediate care, intensive care, physical rehabilitation, outpatient office/clinic, professional healthcare at home, infusion center, and other. Ulcerative colitis-related hospitalizations may be determined from the related AE eCRF. Summary statistics will be reported for the number and percentage of patients with UC-related hospitalization overall and within each category by weight/treatment dose group.

Ulcerative colitis-related surgery is recorded in the Surgical Procedures eCRF. Types of surgery include proctocolectomy, total colectomy, partial colectomy, colostomy, ileoanal anastomosis, and ileostomy. As with hospitalizations, summary statistics will be reported for the number and percentage of patients with any surgery, a colectomy surgery (ie, proctocolectomy, total colectomy, partial colectomy) and within each surgery category by weight/treatment dose group.

6.12. Pharmacokinetic/Pharmacodynamic Methods

The bioanalytical and PK/PD analyses will be conducted by the PK/PD and Pharmacometrics group at Eli Lilly. Pharmacokinetic/PD analyses to address primary objectives of this study will be described by Lilly in a separate PK/PD analysis plan.

6.13. Safety Analyses

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

Analyses of safety data will be based on the Safety population as defined in Table AMBU.6.1. The analysis treatment periods of interest will be the Induction and the combined Induction and Maintenance period; the associated weight/treatment dose groups for each period are described

in Table AMBU.6.2. Unless otherwise stated, safety data collected during the follow-up periods for patients that do not enroll in the long-term extension Study I6T-MC-AMAZ will be listed.

6.13.1. Extent of Exposure

Duration of exposure to study treatment will be summarized by weight/treatment dose groups for the Safety population in the combined Induction and Maintenance period. For the treatment period of interest associated with the safety analysis population, exposure will be calculated as (date of last study visit during the treatment period – date of first dose for the treatment period +1 day).

Total patient-years (PY) of exposure will be reported for each of the weight/treatment dose groups. Descriptive statistics (n, mean, SD, minimum, first quartile, median, third quartile, and maximum) will be provided for patient-weeks of exposure and the frequency of patients falling into different exposure ranges will be summarized. Exposure ranges will generally be reported in weeks using the following as a guide:

- >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.

6.13.2. Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after baseline. The MedDRA Lowest Level Term (LLT) will be used in the treatment-emergent computation. 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 periods 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 AE will be used to determine whether the event was pre- versus post-treatment. If start time for the AE is missing, it will be assumed to have started in the postbaseline period.

Summary tables of AEs to include the following:

- overview of AEs
- summary of TEAE Preferred Terms (PTs) by decreasing frequency
- summary of TEAE PTs by decreasing frequency within System Organ Class (SOC)
- summary of TEAE PTs by maximum severity by decreasing frequency within SOC
- summary of serious adverse event (SAE) PTs by decreasing frequency
- summary of AEs leading to study discontinuation, and

- listing of SAEs.

Summary tables will include the number and percentage of patients reporting an event. For events that are gender-specific (as defined by MedDRA), the number of participants at risk will include only patients from the given gender

The baseline period and postbaseline periods will be defined as follows:

- the baseline period is the Screening period, and
- the postbaseline periods will be a) the Induction period and b) the combined Induction and Maintenance period (see Table AMBU.6.2).

6.13.3. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events

The number and percentage of patients who reported a SAE (including those resulting in death) during the safety analysis treatment periods will be summarized by weight/treatment dose group using MedDRA PT nested within SOC. Events will be ordered by decreasing frequency within SOC. A listing of SAEs will be provided.

The number and percentage of patients who permanently discontinued from study treatment due to an AE (including AEs that led to death) during each period will be summarized by weight/treatment dose group using MedDRA PT nested within SOC. Events will be ordered by decreasing frequency within SOC.

6.13.4. Clinical Laboratory Evaluation

As described more fully in compound level safety standards and in the laboratory-related PhUSE white papers [PhUSE 2015], the clinical laboratory evaluations will be summarized by weight/treatment dose group with the following displays:

- Box plots of observed values (and change from baseline values) by visit.
- Change from baseline to last observation will be summarized within the box plot of changes (rightmost column), and descriptive summary statistics will be included in a table below the box plot as described in Section 6.1.3.
- Treatment emergent abnormal high lab values (ie, patients shifting from a normal/low maximum baseline value to a high maximum post-baseline value) or low lab values (ie, patients 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 patients 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.

For these displays, the postbaseline period for continuous variables will be the combined Induction and Maintenance period and for categorical variables will be the Induction period and the combined Induction and Maintenance period. Postbaseline measurement for continuous analysis (eg, boxplots) will include *only* scheduled measurements, while postbaseline categorical analysis (eg, shifts) will include *both* scheduled and unscheduled measurements.

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

- for analyses of continuous measurements: the last scheduled or unscheduled nonmissing measurement recorded during the Screening Period, and
- for analyses of categorical measurements: all scheduled or unscheduled nonmissing measurements recorded during the Screening Period.

For any lab performed on the day of first taking study medication at the start of the postbaseline period, the start time of the study treatment 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 (ie, we assume the protocol defined order of procedures was followed). Following the compound level safety standards, for some labs a safety concern may exist for only high (or only low) values. For these labs, displays with only maximum (or minimum) values will be used and shift tables will be presented accordingly.

6.13.5. Vital Signs and Other Physical Findings

As described more fully in compound level safety standards and in the vital signs-related PhUSE white papers [PhUSE 2013], vital signs will be summarized similarly to the clinical laboratory evaluation (see Section 6.13.4). For vital signs, the low and high limits are based on a combination of a specified value and a change or percentage change by age, as shown in Table AMBU.6.7. In this case, the PhUSE white paper recommends providing scatter plots and shifts to low/high. Boxplots will also be presented.

Table AMBU.6.7. Categorical Criteria for Abnormal Treatment-Emergent Blood Pressure and Pulse Measurement for Children by Age Group

Age at IC (years)		Systolic BP mm HG	Diastolic BP mm HG	Pulse/HR bpm
≥2 and <5	Low	≤75 and DFB ≥15	≤40 and DFB ≥10	≤60 and DFB ≥25
	High[a]	≥110 and IFB ≥15	≥76 and IFB ≥10	>160 and IFB ≥25
≥5 and <10	Low	≤80 and DFB ≥15	≤45 and DFB ≥10	≤60 and DFB ≥25
	High[a]	≥119 and IFB ≥15	≥78 and IFB ≥10	>150 and IFB ≥25
≥10 and <13	Low	≤85 and DFB ≥20	≤50 and DFB ≥10	≤60 and DFB ≥25
	High[a]	≥126 and IFB ≥20	≥82 and IFB ≥10	>140 and IFB ≥25
≥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; HR = heart rate; DFB = decrease from baseline; IFB = increase from baseline; IC = Informed Consent.

[a] The high limit values shown 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.

6.13.6. Electrocardiograms

Complete electrocardiogram (ECG) data will not be part of the clinical database for the individual studies. Any clinically significant findings from ECGs that result in a diagnosis and that occur after the patient receives the first dose of the investigational treatment will be reported to Lilly or its designee as an AE via eCRF. Aside from standard AE summary tables no additional analysis of ECG data will be performed.

6.13.7. Adverse Events of Special Interest

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 PT listing based upon the review of the most current MedDRA version, or by treatment emergent relevant laboratory changes, as described below. Additional special safety topics may be added as warranted.

Unless otherwise specified, the AESIs will be summarized by weight/treatment dose group for the safety population during the Induction and combined Induction and Maintenance periods using the baseline and postbaseline definitions described in Section 6.13.2.

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.

6.13.7.1. CCI

CCI

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

6.13.8. Immunogenicity

An individual sample is potentially examined multiple times in a hierarchical procedure to produce a sample anti-drug antibody (ADA) assay result and potentially a sample neutralizing anti-drug antibodies assay result. A patient has treatment-emergent anti-drug antibodies (TE ADA) when ADAs are induced or boosted by exposure to study drug. That is, when at least one postbaseline ADAs 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 along with the summary of specified TEAEs by TE ADA status. The summary of TE ADA and neutralizing anti-drug antibodies status will be produced. Analyses of the relationship between immunogenicity and PK will be conducted as part of the PK/PD analyses as described in Section 6.11.1. Additional assessments of the relationship between immunogenicity and efficacy will be performed as deemed appropriate.

6.14. Subgroup Analyses

Subgroup analyses may be conducted for secondary endpoints and safety endpoints. Subgroups to be evaluated may include sex, age, race, geographic region, baseline disease severity, duration of disease, previous use of biologic therapy, and any other baseline characteristic subgroups as deemed appropriate.

6.15. Protocol Violations

Protocol deviations will be identified throughout the study. Important protocol deviations (IPDs) are defined as those deviations from the protocol that would potentially compromise patients' safety, data integrity, or study outcome.

A separate document known as the "The AMBU Trial Issues Management Plan" will describe the categories and subcategories of important protocol deviations, and how the IPDs would be identified.

The number and percentage of patients having IPDs will be summarized within category and subcategory of deviations by dosing regimen for the mITT population. A by-patient listing of IPDs will be provided.

6.16. Data Snapshots and Interim Analyses

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

6.16.1. Data Snapshots

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

The first snapshot will be taken when at least 5 patients reach Week 4. This will provide an early assessment of PK and safety data. This analysis is planned to enable dose confirmation for the Phase 3 study for patients >40 kg.

The second snapshot will be taken when approximately 5 patients in the ≤40 kg group (5 mg/kg IV Q4W) reach Week 4. This analysis is planned to enable the enrollment of the 10 mg/kg treatment group.

6.16.2. Interim Analyses

An interim analysis is planned when approximately 15 patients in the ≤40 kg group reach Week 12. This analysis will allow confirmation of dose for patients ≤40 kg to begin the Phase 3 study.

Interim analyses provided will include assessments and summaries of disposition, demographics, safety, PK, and efficacy endpoints. Safety analyses will include, but are not limited to summaries of exposure, AEs/SAEs, labs, vitals, AESIs, and immunogenicity and will be performed according as described in Section 6.13. Efficacy analyses will include summaries of MMS clinical remission, response, and the associated component scores at Week 12 and Week 52. Pediatric Ulcerative Colitis Activity Index remission, response, and associated scores will also be summarized at relevant visits. Refer to Section 6.10.1 for details regarding the analysis of each endpoint.

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

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

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

6.17. Annual Report Analyses

Based on regulatory requirements for the Development Safety Update Report, reports will be produced (if not already available from the study CSR) for the reporting period covered by the Development Safety Update Report.

6.18. 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 Serious AEs and 'Other' AEs are summarized: by treatment/weight group and 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 Serious AE and 'Other' AE, for each term and weight class, 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 patients/subjects in every weight class may not be included if a 5% threshold is chosen (5% is the minimum threshold).

AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

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8. Appendices

Appendix 1. CCI Diary Calculations

Weekly summary measures of CCI diary data will be created for each patient. The 7-day period associated with each week will be defined using a visit centric approach. The table below displays the interval for each week.

Week (Visit)	Start Day[a]	End Day[a]
Screening	Max(Informed Consent Date, Week 0 Visit Date – 14)	Week 0 Visit Date – 8
Baseline	Week 0 Visit Date – 7	Week 0 Visit Date – 1
Week 2 (V3)	Max(Week 0 Visit Date, Week 2 Visit Date – 7)	Week 2 Visit Date – 1
Week 4 (V4)	Max(Week 2 Visit Date, Week 4 Visit Date – 7)	Week 4 Visit Date – 1
Week 8 (V5)	Max(Week 4 Visit Date, Week 8 Visit Date – 7)	Week 8 Visit Date – 1
Week 12 (V6)	Max(Week 8 Visit Date, Week 12 Visit Date – 7)	Week 12 Visit Date – 1
Continue the algorithm as above.		
Week 48 (V15)	Max(Week 44 Visit Date, Week 48 Visit Date – 7)	Week 48 Visit Date – 1
Week 52 (V16)	Max(Week 48 Visit Date, Week 52 Visit Date – 7)	Week 52 Visit Date – 1

[a] If End Day < Start Day, do not assign specified visit week. Visit date will be calculated by selecting the first date from the following list (ie, first in list order): (1) date of endoscopy preparation if endoscopy preparation was performed, (2) date of endoscopy if endoscopy was performed, (3) date of treatment if treatment was given, (4) office visit date if available, or (5) imputed date of visit center of the protocol-defined window for that visit.

For the Mayo SF and RB subscores, the most recent 3 nonmissing days of the 7-day period in the table above will be averaged and rounded to the nearest integer to calculate the weekly score for each patient. Patients with less than 3 measurements in the 7-day period will be considered missing.

All diary data collected on the following days will be excluded from any calculations:

- any day(s) of bowel preparation
- day after any day(s) of bowel preparation (will most often be associated with date of endoscopy)
- day of endoscopy
- day after endoscopy, and
- two days after endoscopy (patients will be answering questions in a 24-hour recall fashion, so two days following endoscopy, they may be reporting their patient-reported outcomes from the day after the endoscopy).

For the Bristol Stool Scale the worst (ie, maximum) of the available measures during the 7-period in the table above will be used to calculate a weekly score for each patient. If fewer than

4 days are available (ie, not missing), the patient will be considered to be missing data for that week.

For all other CCI diary measures, all available days of the 7 days will be averaged to calculate the weekly score for each patient. If fewer than 4 days are available (ie, not missing), the patient will be considered to be missing data for that week.

If multiple diary assessments on a single day are present, use the latest assessment.

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