

Statistical Analysis Plan: I6T-MC-AMBZ

A Multicenter, Phase 3b, Open-Label, Single-Arm Study to Investigate Bowel Urgency and its Relationship with Other Outcome Measures in Adults with Moderately to Severely Active Ulcerative Colitis Treated with Mirikizumab

NCT05767021

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## Abbreviations and Definitions

Term	Definition
<b>5-ASA</b>	5-aminosalicylic acid
<b>ADA</b>	anti-drug antibody
<b>AE</b>	adverse event
<b>AESI</b>	adverse event of special interest
<b>ALP</b>	alkaline phosphatase
<b>ALT</b>	alanine aminotransferase
<b>ANCOVA</b>	analysis of covariance
<b>AP</b>	abdominal pain
<b>APU</b>	absorbent product use
<b>AST</b>	aspartate aminotransferase
<b>ATC</b>	anatomical therapeutic chemical
<b>AZA</b>	azathioprine
<b>BMI</b>	body mass index
<b>BOCF</b>	baseline observation carried forward
<b>CCI</b>	
<b>CAP</b>	continued access period
<b>CFB</b>	change from baseline
<b>CI</b>	confidence intervals
<b>CMI</b>	clinically meaningful improvement
<b>CCI</b>	
<b>CSR</b>	Clinical Study Report
<b>ECG</b>	electrocardiogram
<b>eCRF</b>	Electronic case report form; an electronic document designed to record all the protocol-required information to be reported to the sponsor for each trial participant
<b>EIM</b>	extraintestinal manifestation
<b>ES</b>	endoscopic subscore
<b>FAS</b>	Full Analysis Set










			<p>Updated definition of location of disease</p> <p>Added a footnote for definition of S1P.</p> <p>Added prior advanced therapy exposure and prior advanced and biologic therapy failure.</p> <p>Updated prior therapy exposure and failure</p>
		<a href="#">Table AMBZ.6.4.</a>	<p>Updated language for daily diary time window calculation.</p>



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Objectives	Endpoints
	

Objectives	Endpoints
	

Abbreviations: QoL = quality of life; UC = ulcerative colitis; UNRS = urgency numeric rating scale.



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The image shows the letters 'CCI' in a large, bold, red, sans-serif font. The letters are set against a solid black rectangular background. The 'C's are slightly open at the top and bottom, and the 'I' is a simple vertical bar.

## 1.2. Study Design

This is a multicenter, open-label, single-arm Phase 3b study to investigate bowel urgency and its relationship with other outcome measures in participants with moderately to severely active UC treated with mirikizumab over a **CC** week period.

### Design

The study will have 4 study periods:

#### *Period 1 (CC days)*

Participants must complete all Visit 1 screening activities within **CC** days prior to Visit 2. The screening endoscopy must occur within **CC** days prior to Visit 2.

**Period II (CCI weeks)**

Participants will receive CCI mg mirikizumab CCI

**Period III (CCI weeks)**

Participants will receive CCI mg mirikizumab CCI

Note: Participants planning to participate in continued access must complete self-administration training during at least 2 visits between Visits 6 and 9 (see Section 6.1.1 of protocol). Upon completion of all Visit 10 activities, eligible participants may enter the Continued Access Period.

**Period IV**

Participants who meet the following criteria should enter posttreatment follow-up, including completion of Visit 801:

- [Redacted]
- [Redacted]

**Continued Access Period (CAP)**

Participants who successfully completed Visit 10 and are eligible to enter the CAP. Participants will enter the CAP on the same day that they complete Visit 10 and remain until they discontinue from treatment in the CAP portion of the study. The CAP period will begin at dose of Visit 501 minus 1 minute and end at treatment discontinuation visit.

**Continued Access Follow-up Period**

Participants who entered the CAP and then discontinued treatment will enter the CAP follow-up period. They exit the CAP follow-up period when they complete Visit 901.

See [Figure AMBZ.1](#) in this SAP for schema. The Schedule of Activities (SoA) is described in Section 1.3 of protocol.



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<sup>a</sup> Participants who are eligible for continued access should move directly from Visit 10 to Visit 501, on the same day, if possible. Visit 801 should not be performed.

<sup>b</sup> Optional Continued Access Period is described in Section 10.12 of the protocol.

## **2. Statistical Hypotheses**

The primary objective is to assess the improvement from baseline in UNRS in participants treated with mirikizumab at Week **CC**. No formal hypothesis testing will be performed on the primary endpoint.

### **2.1. Multiplicity Adjustment**

Multiplicity control is not applicable for this study.

### 3. Analysis Sets

Analysis sets are defined in [Table AMBZ.3.1](#) along with the planned analysis for each set. For both analysis sets, participants will be analyzed according to their assigned treatment unless otherwise specified.

**Table AMBZ.3.1. Analysis sets**

<b>Population</b>	<b>Description</b>
Full Analysis Set (FAS)	<b>Definition:</b> All participants who are assigned to treatment and receive at least 1 (partial or complete) dose of study treatment (regardless of whether the participant does not receive the correct treatment, or otherwise does not follow the protocol). <b>Purpose:</b> Used for efficacy and health outcomes analysis
Safety Analysis Set	<b>Definition:</b> All participants who are assigned to treatment and receive at least 1 (partial or complete) dose of study treatment (regardless of whether the participant does not receive the correct treatment, or otherwise does not follow the protocol). <b>Purpose:</b> Used for safety-related analysis

## 4. Statistical Analyses

### 4.1. 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 version of the Medical Dictionary for Regulatory Activities (MedDRA®) will be 24.0 or higher.

Any change to the data analysis methods in the protocol will require an amendment only if it changes a principal feature of the protocol. Additional exploratory analyses of the data will be conducted as deemed appropriate. 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 instead of or in addition to a static display.

#### 4.1.1. Analysis Methods

When reported, descriptive statistics will include the number of participants; mean, standard deviation, median, minimum, first and third quartile, and maximum for continuous measures; frequency counts and percentages for categorical measures; and estimate and 95% confidence intervals (CI) for correlation coefficients.

#### 4.1.2. Definition of Baseline

For efficacy and health outcomes analysis, baseline refers to the values or observations collected prior to or on the day of the initiation of study treatment in Study AMBZ, unless otherwise specified.

The baseline for variables collected as part of the daily diary (including the patient-reported outcomes components of the Modified Mayo Score, stool frequency (SF) and rectal bleeding (RB) subscores) will be calculated from valid daily diary entries obtained prior to baseline endoscopy preparation (see [Appendix 6](#)). The baseline endoscopy component of the Mayo Score will use the endoscopic appearance of the mucosa at the AMBZ screening endoscopy. For other efficacy and health outcome 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) in Study AMBZ.

Baseline for safety analysis is described in the [Section 4.6.2](#) and [Section 4.6.3](#).

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.

#### 4.1.3. Definition of Study Period Time Interval

[Table AMBZ.4.1](#) 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 (refer to [Appendix 6](#) for additional details on study visits and study weeks). See Section 10.12 of protocol for more details about Continued Access Period (CAP).

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

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

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

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

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

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

Only for the purpose of calculating the length of study period time intervals, the words "prior to" in [Table AMBZ.4.1](#) should be understood to mean "the day/time before" while the words "after" should be understood to mean "the day/time 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 AMBZ.4.1. Definition of Main Study Period Time Intervals (excluding Continued Access Period)**

Main Study Period	Interval Start Definition	Interval End Definition
<b>Period I (Screening):</b> All participants who sign informed consent are considered as entering the Screening Period.	Informed consent date	Prior to the start of study treatment.
<b>Period II (CCI mg mirikizumab CCI):</b> All participants who received any amount of mirikizumab CCI are considered as entering Period II and the treatment period.	At the date/time of first administration of CCI mg mirikizumab CCI	Prior to first administration of CCI mg mirikizumab CCI, or discontinuation of study treatment, whichever is earlier
<b>Period III (CCI mg mirikizumab CCI):</b> All participants who received any amount of mirikizumab CCI are considered as entering Period III.	At the date/time of first administration of CCI mg mirikizumab CCI	Week CCI Visit, or discontinuation of study treatment, whichever is earlier
<b>Period IV (Follow up)</b> All participants who discontinued mirikizumab treatment prior to Visit 10, or completed Visit 10 and who did not enter CAP are considered to have entered the follow-up period.	After last date of any study treatment period for patients who did not enter CAP.	The maximum of the last study visit and study disposition date for patients who did not enter CAP.

Abbreviations: CCI CAP = continued access period.

The CCI

The CCI week analysis will include analysis through Week CCI (Period III) but will not include analysis during the CAP. All safety and efficacy data will be included unless otherwise specified.

The CAP analysis will include a basic safety analysis, including disposition, analysis of AEs, vital signs, and lab data. Additional analysis during CAP will be performed as appropriate. All data from screening to end of CAP will be generally included.

**4.1.4. Missing Data Imputation**

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#### **4.1.5. Protocol Deviations**

Protocol deviations will be identified throughout the study. The protocol deviation categories will be described per Protocol Deviation Management Plan and Trial Issues Management Plan by clinical team. Important protocol deviations are defined in Protocol Deviation Management Plan as those deviations from the protocol that may significantly impact the completeness, accuracy and/or reliability of study data or that may significantly affect a subject's rights, safety or well-being.

## 4.2. Participant Dispositions, Baseline Characteristics and Medical History

The treatment disposition and study disposition will be summarized for the FAS population. The reason for discontinuation from treatment and from study will be included.

All FAS participants who discontinued from the study and/or study treatment during any period of the study will be listed with the reported study treatment discontinuation and study discontinuation times. If known, a reason for their discontinuation will be given.

### 4.2.1. Demographics and Baseline Characteristics

Summaries and listings of the demographic and baseline characteristics detailed in [Appendix 3](#) will be presented.

### 4.2.2. Non-UC Medical History

Non-UC medical history will be collected on the Pre-Existing Conditions and Medical History case report form (CRF) and coded using MedDRA version 24.0 or higher. The version used to code medical history will be displayed in the outputs. All medical history will be summarized for the Safety Set by system organ class and preferred term. Prespecified medical history of liver and concurrent disease, hypersensitivity event, and associated person medical history of liver disease collected on the respective CRFs will also be summarized.

## 4.3. Primary Endpoint Analysis

### 4.3.1. Definition of Endpoint(s)

The primary endpoint is defined in [Table AMBZ.1.1](#), description and derivation of endpoints are described in [Table AMBZ.6.1](#).

### 4.3.2. Main Analytical Approach

Analysis of the primary endpoint is described in [Table AMBZ.6.2](#).

The UNRS score at each time point of interest (baseline and Week CC) will be summarized as a continuous measure for each participant as the average daily diary score over a CC day period. The difference between the UNRS score at Week CC and at baseline will be calculated for each participant and averaged. CCI

CCI

[Section 4.1.4](#).

## 4.4. Secondary Endpoints Analysis

### 4.4.1. Definition of Endpoint(s)

The secondary endpoint is defined in [Table AMBZ.1.1](#) Derivation details are described in [Table AMBZ.6.1](#).

### 4.4.2. Main Analytical Approach

The analysis of the secondary endpoints is described in [Table AMBZ.6.2](#). Descriptive summaries and CI will be provided for continuous and binary secondary endpoints as indicated in [Section 4.1.1](#).

Analysis of association between secondary endpoints is described in [Table AMBZ.4.2](#) and [Table AMBZ.4.3](#). At Week [redacted] or Week [redacted], these analyses will be performed among participants with available data that do not discontinue prior to the time point of interest.

**Table AMBZ.4.2. Type of Endpoints and Association Analyses**

Dependent Outcome	Explanatory Outcome	Analysis
Continuous	Continuous	[redacted]
Continuous	Binary	
Binary	Binary	

Abbreviations: [redacted] (Kadel 2012); YI = Youden’s index (Youden 1950)

**Table AMBZ.4.3. Type of Assessments and Endpoints for Association Analyses**

Assessments	Endpoint Type	Endpoint
Bowel Urgency Assessments	Continuous	UNRS, BUF, SDT, [redacted]
	Binary	UNRS CMI, UNRS Remission
QoL/Function Measures	Continuous	[redacted]
	Binary	[redacted]
Symptom/ Symptom Severity of UC	Continuous	[redacted]
	Binary	[redacted]
Histological Features	Continuous	[redacted] (Analysis value, and CFB if applicable)

Assessments	Endpoint Type	Endpoint
	Binary	CCI
Additional Exploratory Measures	Continuous	

Abbreviations: CCI [redacted]  
[redacted]  
[redacted]  
[redacted]  
[redacted]  
[redacted]  
[redacted]  
[redacted]  
[redacted]

CCI [redacted] and 95% confidence interval CCI [redacted] [redacted] are implemented in SAS PROC CORR.

The odds ratio (OR) is calculated using logistic regression with 95% Wald confidence intervals, as implemented in SAS PROC LOGISTIC.

The Youden’s Index (YI) and corresponding 95% confidence intervals are calculated using the equations presented in Youden, W.J. (1950).

The standardized mean difference (SMD) is calculated by mean difference divided by pooled standard deviation, where pooled standard deviation is obtained by taking the square root of the weighted average of the variances of each group in binary outcome, where the weights are the degrees of freedom of each group.

#### 4.5. Exploratory Endpoints Analysis

Analysis of the exploratory endpoints other than gene expression endpoints are described in [Table AMBZ.6.2](#). Analysis of associations between exploratory endpoints is described in [Table AMBZ.4.2](#) and [AMBZ.4.3](#).





## 4.6. Safety Analyses

Safety will be assessed by describing the following: AEs, laboratory analytes, vital signs, and adverse events of special interest (AESIs). Additional analysis will be included if applicable.

### 4.6.1. Extent of Exposure

Duration of exposure to study treatment will be summarized for the safety population. For the study periods of interest, exposure will be calculated as the time period length in years (see [Section 4.1.3](#)) with start and end dates described in [Table AMBZ.4.1](#).

Total participant-years of exposure will be reported by treatment. Descriptive statistics will be provided for participant-weeks of exposure and the frequency of participants falling into different exposure ranges will be summarized. Exposure ranges will generally be reported in weeks using the following as a guide:

- >0 to <4 weeks,  $\geq 4$  weeks to <8 weeks,  $\geq 8$  weeks to < 12 weeks,  $\geq 12$  weeks to < 16 weeks,  $\geq 16$  weeks to < 20 weeks,  $\geq 20$  weeks to < 24 weeks,  $\geq 24$  weeks to 28 weeks.
- >0,  $\geq 4$  weeks,  $\geq 8$  weeks,  $\geq 12$  weeks,  $\geq 16$  weeks,  $\geq 20$  weeks,  $\geq 24$  weeks,  $\geq 28$  weeks.

Additional exposure ranges may be considered if necessary.

Treatment compliance will be summarized as described in [Appendix 4](#). Interruption of study treatment and the reasons drug not administered will be summarized for injection and infusion separately.

### 4.6.2. Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after baseline. Pre-existing events will be considered to determine TEAE. 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. The treatment period will be included as postbaseline for the analysis. 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 AE will be used to determine whether the event was pre-versus posttreatment. If start time for the AE is missing, it will be assumed to have started in the postbaseline period.

In an overview table, the number and percentage of participants with at least 1 TEAE, serious adverse event (SAE), fatal SAE, or discontinuation from study treatment due to an AE will be summarized. TEAEs (all and by maximum severity), SAEs, including deaths, and AEs that lead to treatment discontinuation will be summarized and analyzed by MedDRA system organ class (SOC) and PT or by PT alone. Potential AESIs will be summarized, which include:





See [Section 4.6.2.1](#) for detailed description on AESI.

Summary tables as described in [Table AMBZ.4.4](#) will be presented. Summary tables will include the number and percentage of participants reporting an event. For events that are gender-specific (as defined by MedDRA), the number of participants at risk will include only participants from the given gender. Listing of AEs may be provided as deemed appropriate.

**Table AMBZ.4.4. Summary Tables Related to Adverse Events**

<b>Analysis</b>
Overview of AEs
Summary of TEAE PTs by decreasing frequency
Summary of TEAE PTs occurring in $\geq 1\%$ of participants by decreasing frequency
Summary of TEAE PTs by decreasing frequency within SOC
Summary of TEAE PTs by maximum severity by decreasing frequency within SOC
Summary of SAE PTs by decreasing frequency within SOC
Summary of fatal SAE PTs by decreasing frequency within SOC
Summary of AEs leading to study treatment discontinuation by decreasing frequency of PTs within SOC
Listing of SAEs

Abbreviations: AE = adverse event; AESI = adverse event of special interest; PT = preferred term; SAE = serious adverse event; SOC = system organ class; TEAE = treatment-emergent adverse event.

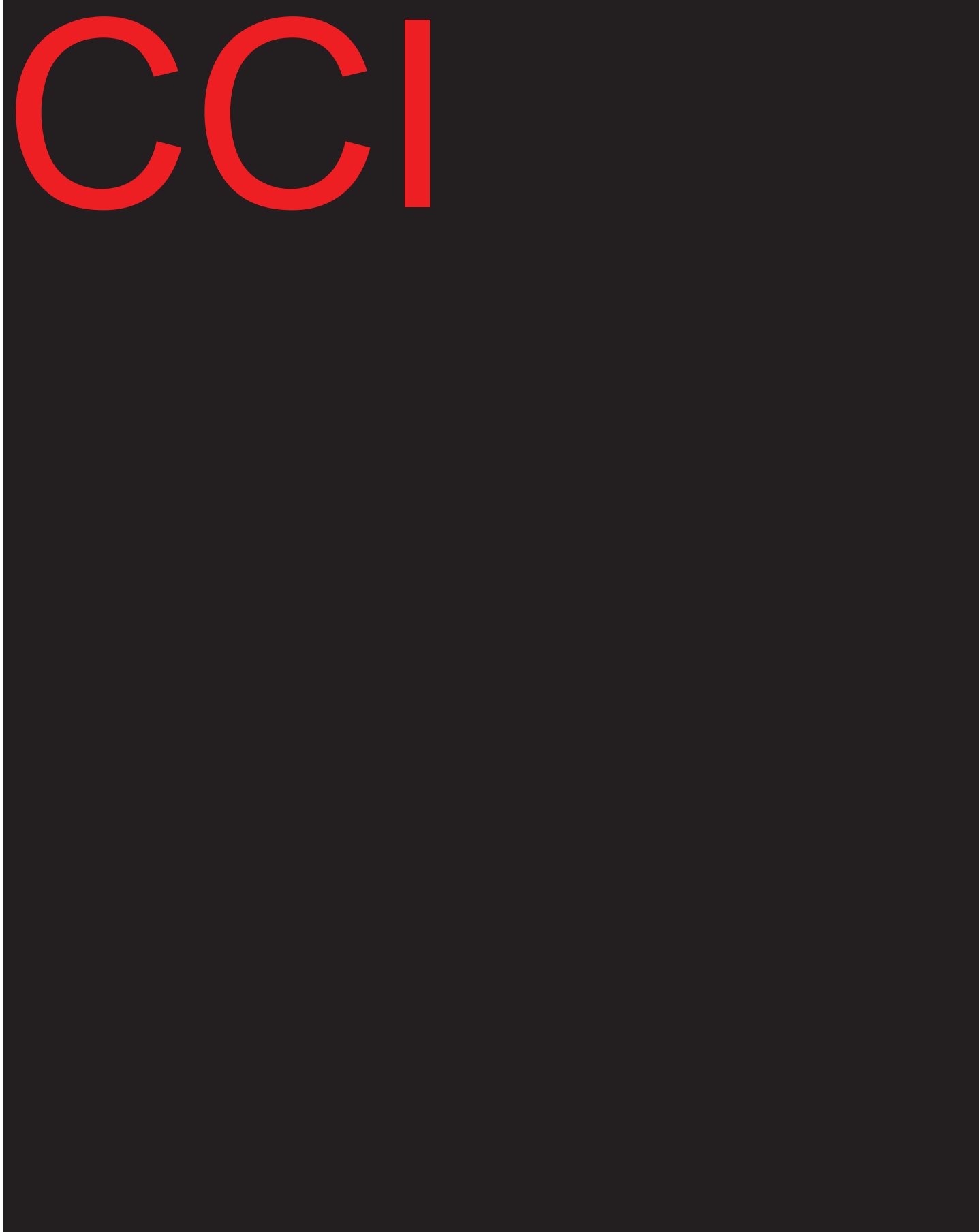
#### **4.6.2.1. Special Safety Topics including Adverse Events of Special Interest**

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 AESIs 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 TE relevant laboratory changes, as described below. Additional special safety topics may be added as warranted.

Unless otherwise specified, the treatment-emergent AESIs will be summarized for the safety population.

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.

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### 4.6.3. Clinical Laboratory Evaluations

As described more fully in compound level safety standards and in the laboratory-related PhUSE white papers [PhUSE 2013; PhUSE 2015], the clinical laboratory evaluations will be summarized with the following displays described in [Table AMBZ.4.5](#):

**Table AMBZ.4.5. Summaries/Displays/Analysis for Clinical Laboratory Evaluations**

<b>Analysis</b>
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.
Treatment-emergent abnormal high lab values (i.e., participants shifting from a normal/low maximum baseline value to a high maximum postbaseline).
Scatter plot of maximum (minimum) postbaseline value vs. maximum (minimum) baseline value if appropriate.
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 cutoffs defined in the compound level safety standards.

For these displays, the postbaseline periods will be identical to those described in [Table AMBZ.4.1](#). Postbaseline measurement for continuous analysis (e.g., boxplots) will include *only*

scheduled measurements, while postbaseline categorical analysis (e.g., shifts) will include *both* scheduled and unscheduled measurements.

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 (i.e., 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.

Hepatic serology, hematology, chemistry and coagulation tests will be done by local laboratory. Descriptive statistics of the test results will be summarized in a table. Summary will be done using standardized units (SI).

Screening assessment of Tuberculosis (TB) and evaluation of TB during the study will be listed, as appropriate.

**4.6.4. 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; PhUSE 2015], vital signs will be summarized similarly to the clinical laboratory evaluation (see [Section 4.6.3](#)). For vital signs, the low and high limits are based on a combination of a specified value and a change or percentage change. In this case, the PhUSE white paper recommends providing scatter plots and shifts to low/high. Boxplots will also be presented.

**4.6.5. Electrocardiograms**

Complete electrocardiogram (ECG) data will not be part of the clinical database for this study. Any clinically significant findings from ECGs that result in a diagnosis and that occur after the participant 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.

**4.6.6. Immunogenicity**

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[Redacted text block]

Compound level safety standards will be followed in the analyses of immunogenicity. Listings of immunogenicity assessments may be provided along with the summary of specified TEAEs by TE ADA status. The summary of TE ADA and NAb status may be produced as appropriate. Additional assessments of the relationship between immunogenicity and efficacy will be performed as deemed appropriate.

**4.6.7. Concomitant Therapy/ Procedure**

Medications will be classified into anatomical therapeutic chemical (ATC) drug classes using the latest version of the World Health Organization (WHO) drug dictionary. Medication start and stop

dates will be compared to the date of first dose of treatment to allow medications to be classified as Concomitant for 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 dose of study treatment and end on or after the date of first dose of study treatment or are ongoing at the end of the study. If it cannot be determined whether a medication is concomitant or not due to a partial or missing date, the medication will be treated as concomitant.

Concomitant medications may be summarized by ATC and preferred term for the Safety Set and sorted by descending frequency. Prespecified concomitant therapy of acetaminophen/paracetamol may also be summarized.

Concomitant UC-related surgeries will be summarized by procedure type for the Safety Set, as needed. The other procedures including hepatic monitoring procedures and endoscopic procedures will be listed.

Prior and concomitant use of vaccines may be listed as appropriate.

#### **4.6.8. Substance Use**

Substance use of alcohol, caffeine, tobacco, nicotine, and recreational drug at screening and change in substance use by visit may be listed, as appropriate.

#### **4.6.9. Extraintestinal Manifestations of Inflammatory Bowel Disease**

Extraintestinal manifestations (EIM) of inflammatory bowel disease will be reported in the Inflammatory Bowel Disease (IBD) EIM eCRF by visit and will be summarized by prespecified term.

### **4.7. Other Analyses**

Reference the analyses described in [Appendix 5](#) in this section.

#### **4.7.1. Other variables and parameters**

The pharmacokinetic/pharmacodynamics (PK/PD) analyses will be conducted by the PK/PD and Pharmacometrics group at Eli Lilly.

#### **4.7.2. Subgroup analyses**

Subgroup analyses may be conducted for all primary and secondary endpoints in the FAS population. The subgroups to be analyzed are listed in [Table AMBZ.6.3](#).

### **4.8 Interim Analyses**

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### **4.9 Changes to Protocol-Planned Analyses**

There are no changes to the analyses described in the protocol.

## 5. Sample Size Determination

Approximately 160 participants will be assigned to study intervention. The sample size was determined by considering the precision of the estimated correlation between endpoints. Simulations were performed for both binary and continuous measures where the true correlation varied between [CCI]. The average half width of the 95% CI for the correlations at Week [CC] varied between [CCI] under considered assumptions for an overall sample size of 160. The average half width of the 95% CI varied between [CCI] for endpoints during the maintenance period under the assumption that [CCI] of participants could discontinue early from the study.

Additionally, the proposed sample size of 160 participants is considered sufficient to have [CCI] power to detect a significant (non-zero) change from baseline in UNRS at Week [CC] (primary endpoint).

**6. Supporting Documentation**


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



All binary endpoints will be coded as Yes/No, unless otherwise specified.









**Table AMBZ.6.1. Description and Derivation of Efficacy, Safety and 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:	SF subscore	CCI	
	CCI [Redacted text]	RB subscore		
	[Redacted text]	ES subscore		



Measure	Description	Variable	Derivation / Comment	Definition of Missing
	CCI		CCI	
	PGA subscore	PGA subscore		
	Clinical Remission	Clinical Remission		
	Alternate Clinical Remission	Alternate Clinical Remission		
	Modified Mayo Score (MMS)	Modified Mayo Score (MMS)		
	Clinical Response	Clinical Response		
	Symptomatic Remission	Symptomatic Remission		
	SF component of clinical remission	SF component of clinical remission		
	RB component of clinical remission	RB component of clinical remission		


Measure	Description	Variable	Derivation / Comment	Definition of Missing
		Endoscopic Normalization		
		Absolute SF		
		Endoscopic Remission		
Urgency NRS	The Urgency numeric rating scale (NRS) is a single 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		
		Change from Baseline Urgency NRS		
		Urgency NRS CMI ( $\geq 3$ Point Improvement)		
		Alternate Urgency NRS Remission		
		Urgency NRS Remission		


Measure	Description	Variable	Derivation / Comment	Definition of Missing
		CCI		
		Change from Baseline in CCI		
		CCI [Redacted]		
		Change from Baseline in CCI  CCI [Redacted]		

Measure	Description	Variable	Derivation / Comment	Definition of Missing	
					
		 			
					
					
					
					

Measure	Description	Variable	Derivation / Comment	Definition of Missing
CCI		CCI		CCI
		CCI		
CCI		Loose Stool		CCI
		APU		


Measure	Description	Variable	Derivation / Comment	Definition of Missing
				
		Normal Number of Stools	Use the single item collected	
		CCI	Use the single item collected	
		CCI	CCI [REDACTED]	
		CCI [REDACTED]	CCI [REDACTED] [REDACTED] [REDACTED] [REDACTED]	


Measure	Description	Variable	Derivation / Comment	Definition of Missing
				

Measure	Description	Variable	Derivation / Comment	Definition of Missing
				

Measure	Description	Variable	Derivation / Comment	Definition of Missing
				CCI
CCI	[REDACTED]	Employment Status	Yes/No	CCI

Measure	Description	Variable	Derivation / Comment	Definition of Missing
				

Measure	Description	Variable	Derivation / Comment	Definition of Missing
				

Measure	Description	Variable	Derivation / Comment	Definition of Missing
				


6.2. Appendix 2: Description of Analyses


Table AMBZ.6.2. Description of Efficacy/Health Outcomes Analyses

Measure	Variable	Analysis Method	Population	Time Point(s)		
Urgency NRS	CFB in Urgency NRS Score (Primary Endpoint)	Descriptive summaries, including 95% CI	FAS	Baseline (if applicable), CCI [REDACTED]		
	UNRS CMI	Descriptive summaries, including 95% CI				
	UNRS Remission	Descriptive summaries, including 95% CI				
	Alternate UNRS Remission	Descriptive summaries, including 95% CI				
CCI [REDACTED]	CCI [REDACTED]	Descriptive summaries, including 95% CI				
	CCI [REDACTED]	Descriptive summaries, including 95% CI				
CCI [REDACTED]	CCI [REDACTED]	Descriptive summaries, including 95% CI				
	CCI [REDACTED]	Descriptive summaries, including 95% CI				
CCI [REDACTED] [REDACTED]	CCI [REDACTED]	Descriptive summaries, including 95% CI				
	CCI [REDACTED]	Descriptive summaries, including 95% CI				
Mayo Score and Urgency NRS	Clinical Remission and Urgency NRS CCI [REDACTED]	Descriptive summaries, including 95% CI				
	Clinical Response and Urgency NRS CCI [REDACTED] point Improvement	Descriptive summaries, including 95% CI				
<b>Bowel Urgency Analysis</b>						
Urgency NRS	UNRS	CCI [REDACTED] coefficient with CCI [REDACTED]			FAS	Baseline (if applicable), CCI [REDACTED]
	CFB UNRS	CCI [REDACTED] coefficient with CFB CCI [REDACTED]				
	UNRS CMI, UNRS Remission	ANCOVA with CCI [REDACTED] and CFB CCI [REDACTED]				
CCI [REDACTED]	CCI [REDACTED]	CCI [REDACTED] coefficient with CCI [REDACTED]				
	CCI [REDACTED]	CCI [REDACTED] coefficient with CFB CCI [REDACTED]				
<b>QoL Analysis</b>						
CCI [REDACTED]	CCI [REDACTED]	Descriptive summaries, including 95% CI	FAS	Baseline (if applicable), CCI [REDACTED]		
	CCI [REDACTED]	Descriptive summaries,				

Measure	Variable	Analysis Method	Population	Time Point(s)
		including 95% CI		
CCI		Descriptive summaries, including 95% CI	FAS	Baseline (if applicable), CCI
		Descriptive summaries, including 95% CI		
		Descriptive summaries, including 95% CI		
		Descriptive summaries, including 95% CI		
		Descriptive summaries, including 95% CI		
Bowel Urgency Analysis	UNRS, CCI	CCI Score and component subscores		
		CCI component scores		
		CCI coefficient with CCI		
		Pearson + Spearman correlation coefficient with APU		
	CFB UNRS, CFB CCI CFB	CCI coefficient with CFB CCI and component scores		
		CCI coefficient with CFB CCI component scores		
		Pearson + Spearman correlation coefficient with CFB CCI		
		CCI coefficient with CFB APU		
		ANCOVA with CCI		
		ANCOVA with CCI		
Bowel Urgency Analysis	UNRS CMI, UNRS Remission	ANCOVA with CFB CCI and component scores		
		ANCOVA with CCI and components score		
		ANCOVA with CCI components score		
		ANCOVA with CFB CCI components score		
		ANCOVA with CFB CCI		
		ANCOVA with CCI		
		ANCOVA with CFB CCI		
		ANCOVA with CCI		
		OR, YI with CCI remission		
		OR, YI with CCI response		
UC Symptom/Symptom Severity Analysis				
CCI	CCI	Descriptive summaries, including 95% CI	FAS	Baseline (if applicable), CCI
CCI	CCI	Descriptive summaries,		

Measure	Variable	Analysis Method	Population	Time Point(s)
		including 95% CI		
Absolute SF	Absolute SF Score	Descriptive summaries, including 95% CI		
Mayo	SF subscore	Descriptive summaries, including 95% CI		
	RB subscore	Descriptive summaries, including 95% CI		
	MMS	Descriptive summaries, including 95% CI		
	Symptomatic Remission	Descriptive summaries, including 95% CI		
	Clinical Remission	Descriptive summaries, including 95% CI		
	Clinical Response	Descriptive summaries, including 95% CI		
	Alternate Clinical Remission	Descriptive summaries, including 95% CI		
Mayo	Endoscopic Normalization	Descriptive summaries, including 95% CI	FAS	Baseline (if applicable), CCI
	Endoscopic Remission	Descriptive summaries, including 95% CI		
Fatigue NRS	Fatigue NRS Score	Descriptive summaries, including 95% CI		
Abdominal Pain NRS	Abdominal Pain NRS Score	Descriptive summaries, including 95% CI		
Nocturnal stool	Nocturnal Stool Score	Descriptive summaries, including 95% CI		
CCI	CCI	Descriptive summaries, including 95% CI		
	CCI	Descriptive summaries, including 95% CI		
Bowel Urgency Analysis	UNRS, CCI	CCI coefficient with CCI		
		CCI coefficient with CCI		
		CCI coefficient with Mayo SF		
		CCI coefficient with Absolute SF		
		CCI coefficient with Mayo RB		
		CCI coefficient with AP NRS		
		CCI coefficient with Fatigue NRS		
		Pearson + Spearman correlation coefficient with Nocturnal Stool		
		ANCOVA with clinical response		
		ANCOVA with clinical remission		
		ANCOVA with endoscopic remission		
		ANCOVA with endoscopic normalization		
		ANCOVA with symptomatic		

Measure	Variable	Analysis Method	Population	Time Point(s)
	CFB UNRS, CFB CCI CFB CCI [REDACTED] [REDACTED]	remission		
		ANCOVA with CCI [REDACTED]		
		CCI [REDACTED] coefficient with CFB CCI [REDACTED]		
		CCI [REDACTED] coefficient with CFB Mayo SF		
		CCI [REDACTED] coefficient with CFB Absolute SF		
		CCI [REDACTED] coefficient with CFB Mayo RB		
		CCI [REDACTED] coefficient with CFB AP NRS		
		CCI [REDACTED] coefficient with CFB Fatigue NRS		
		CCI [REDACTED] coefficient with CFB Nocturnal Stool		
		ANCOVA with clinical response		
		ANCOVA with clinical remission		
		ANCOVA with endoscopic remission		
		ANCOVA with endoscopic normalization		
		ANCOVA with symptomatic remission		
		Bowel Urgency Analysis		
UNRS CMI, UNRS Remission	ANCOVA with CFB CCI [REDACTED] ANCOVA with CFB Mayo SF ANCOVA with CFB Absolute SF ANCOVA with CFB Mayo RB ANCOVA with CFB AP NRS ANCOVA with CFB Fatigue NRS ANCOVA with CFB Nocturnal Stool OR, YI with clinical response OR, YI with clinical remission OR, YI with endoscopic remission OR, YI with endoscopic normalization OR, YI with symptomatic remission OR, YI with Bristol Loose Stool			
Exploratory Analyses				
		Descriptive summaries, including 95%CI	FAS	Baseline (if applicable), CCI [REDACTED] [REDACTED]
		Descriptive summaries, including 95% CI		
		Descriptive summaries, including 95% CI		
		Descriptive summaries, including 95% CI		
		Descriptive summaries, including 95% CI		
		Descriptive summaries, including		

Measure	Variable	Analysis Method	Population	Time Point(s)
		95% CI		
		Descriptive summaries, including 95% CI		
		Descriptive summaries, including 95% CI		
		Descriptive summaries, including 95% CI		
		Descriptive summaries, including 95% CI		
		Descriptive summaries, including 95% CI		
		Descriptive summaries, including 95% CI		
		Descriptive summaries, including 95% CI		
Bowel Urgency Analysis	UNRS, CCI [REDACTED]	CCI [REDACTED] coefficient with CCI [REDACTED]	FAS	Baseline (if applicable), CCI [REDACTED]
		CCI [REDACTED] coefficient with CCI [REDACTED]		
		CCI [REDACTED] coefficient with WIS		
		CCI [REDACTED] coefficient with SAA		
		ANCOVA with CCI [REDACTED]		
		ANCOVA with CCI [REDACTED]		
		ANCOVA with CCI [REDACTED]		
		ANCOVA with CCI [REDACTED]		
		CCI [REDACTED] coefficient with CCI [REDACTED]		
		CCI [REDACTED] coefficient with CCI [REDACTED]		
	CFB UNRS, CFB CCI [REDACTED] CFB CCI [REDACTED]	CCI [REDACTED] coefficient with CFB CCI [REDACTED]		
		CCI [REDACTED] coefficient with CFB CCI [REDACTED]		
		CCI [REDACTED] coefficient with CCI [REDACTED]		
		CCI [REDACTED] coefficient with CCI [REDACTED] CFB		
	UNRS CMI, UNRS Remission	OR, YI with CCI [REDACTED]		
		OR, YI with CCI [REDACTED]		
		OR, YI with CCI [REDACTED]		
		OR, YI with CCI [REDACTED]		
		OR, YI with CCI [REDACTED]		

Measure	Variable	Analysis Method	Population	Time Point(s)
		OR, YI with CCI [REDACTED]		
		OR, YI with CCI [REDACTED]		
		OR, YI with CCI [REDACTED]		
	UNRS CMI, UNRS Remission,	ANCOVA CCI [REDACTED]		
		ANCOVA with CCI CFB		
		ANCOVA with CCI		
		ANCOVA with CCI CFB		

Abbreviations: CCI [REDACTED]  
 [REDACTED]  
 [REDACTED]  
 [REDACTED]  
 [REDACTED]  
 [REDACTED]  
 [REDACTED]  
 [REDACTED]

Additional exploratory analysis will be performed as appropriate.

### 6.3. Appendix 3: Demographic and Baseline Characteristics

Participant demographic variables and baseline characteristics will be summarized for the FAS. The baseline characteristics of participants entering additional study periods may also be summarized if necessary. The continuous variables will be summarized using descriptive statistics and the categorical variables will be summarized using frequency counts and percentages. No inferential analysis for the comparability of baseline covariates across treatment groups will be performed. By-participant listings of basic demographic characteristics (i.e., gender, age, body weight, race, ethnicity, geographic region, prior biologic/ Janus Kinase (JAK)/ Sphingosine-1-phosphate (S1P) use and/or failure, corticosteroid use at baseline, duration of disease, and disease location) for the FAS will be provided as deemed appropriate.

Table AMBZ.6.3 describes the specific variables and how they will be summarized. The final column specifies variables used for the efficacy subgroup analysis.

**Table AMBZ.6.3. Participant Characteristics (and Variables for Subgroup Analysis)**

Variable	Continuous Summary	Categorical Summary	Subgroup Analysis <sup>a</sup>
<i>Demographic Characteristics</i>			
Age <sup>b</sup>	Yes	<65 years, ≥65 years <40 years, ≥40 years	
Sex	No	Male, Female	
Age within Sex	No	Male <40 years, Male ≥40 years, Female <40 years, Female ≥40 years	
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	

Variable	Continuous Summary	Categorical Summary	Subgroup Analysis <sup>a</sup>
Geographic Region	No	North America, Europe	
	No	North America, East Europe, West Europe	X
	No	By Country (listed in other documents)	
Height (cm)	Yes	None	
Weight (kg)	Yes	<80 kg, ≥80 kg	
		<100 kg, ≥100 kg	
BMI <sup>c</sup>	Yes	Underweight (<18.5 kg/m <sup>2</sup> ), Normal (≥18.5 and <25 kg/m <sup>2</sup> ), Overweight (≥25 and <30 kg/m <sup>2</sup> ), Obese (≥30 and <40 kg/m <sup>2</sup> ), Extreme obese (≥40 kg/m <sup>2</sup> )	
<i>Prior UC Therapies</i>			
Prior corticosteroid <sup>d</sup> failure <sup>e</sup>	No	Failed, Not failed	
Prior immunomodulator <sup>f</sup> failure <sup>e</sup>	No	Failed, Not failed	
Prior JAK inhibitor <sup>h</sup> exposure	No	Ever, Never	
Prior JAK inhibitor <sup>h</sup> failure <sup>e</sup>	No	Failed, Not failed	
Prior biologic agents exposure	No	Ever, Never	
Prior biologic agents failure	No	Failed, Not failed	
Number of prior biologic agents <sup>g</sup> used	No	0, 1, 2, 3, >3	
Number of failed <sup>e</sup> biologic agents <sup>g</sup>	No	0, 1, 2, 3, >3	
Number of prior JAK inhibitor <sup>h</sup> used	No	0, 1, 2	
Number of failed <sup>e</sup> JAK inhibitor <sup>h</sup>	No	0, 1, 2	
Prior advanced <sup>i</sup> therapy exposure	No	Ever, Never	
Prior advanced <sup>i</sup> therapy failure	No	Failed, Not failed	X
Number of prior advanced <sup>i</sup> therapy used	No	0, 1, 2, 3, >3	
Number of failed advanced <sup>i</sup> therapy	No	0, 1, 2, 3, >3	
Prior S1P therapy <sup>n</sup> exposure <sup>e</sup>	No	Ever, Never	
Prior S1P therapy <sup>n</sup> failure <sup>e</sup>	No	Failed, Not Failed	
<i>Baseline UC Therapies</i>			
Baseline Corticosteroid use <sup>j</sup>	No	Yes, No	X
Baseline Prednisone equivalent dose	Yes	None	
Baseline Budesonide MMX <sup>k</sup>	No	Yes, No	
Baseline Beclomethasone dipropionate	No	Yes, No	
Baseline Oral Aminosalicylates <sup>l</sup> dose	Yes	None	
Baseline immunomodulator use <sup>j</sup>	No	Yes, No	
Baseline Antidiarrheals/ Antispasmodics use	No	Yes, No	
<i>Baseline Disease Characteristics</i>			
Duration of UC <sup>m</sup>	Yes	<1 year, ≥1 to <3 years, ≥3 year to <7 years, ≥7 years	
Age at Diagnosis of UC <sup>b</sup>	Yes	<6, ≥6 to <10 year, ≥10 to <17 years, ≥17	

Variable	Continuous Summary	Categorical Summary	Subgroup Analysis <sup>a</sup>
		year to <40 years, ≥40 years	
Baseline Disease Location <sup>o</sup>	No	Ulcerative Proctitis, Left-sided UC (distal UC), Extensive UC (pancolitis)	X
Baseline Fecal Calprotectin	Yes	≤250 µg/g, >250 µg/g	X
Baseline Modified Mayo Score	Yes	Mild (1-3), Moderate (4-6), Severe (7-9)	X
Baseline Total Mayo Score	Yes	Mild (3-5), Moderate (6-9), Severe (10-12)	
Baseline Endoscopic Mayo Subscore	No	Possible values of 4-point scale in <a href="#">Table AMBZ.6.1</a>	X
Baseline Stool Frequency Mayo Subscore	Yes	Possible values of 4-point scale in <a href="#">Table AMBZ.6.1</a>	
Baseline Absolute Value Stool Frequency Mayo Subscore	Yes	Possible values of 4-point scale in <a href="#">Table AMBZ.6.1</a>	
Baseline Absolute Stool Frequency	Yes	None	
Baseline Rectal Bleeding (RB) Mayo Subscore	Yes	Possible values of 4-point scale in <a href="#">Table AMBZ.6.1</a>	
Baseline IBDQ Total Score and Domain Scores	Yes	None	
Baseline Urgency NRS	Yes	None	
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)	
Baseline Fatigue NRS	Yes	Yes (1-10), No (0)	
Baseline Bristol Stool Scale	Yes	Not Loose Stool (1 – 5), Loose Stool (6 – 7)	
Baseline Stool Deferral Time	Yes	No	
Baseline Stool Deferral Time Category	Yes	0: ≥ 15 min 1: ≥ 5 to < 15 min 2: ≥ 2 to < 5 min 3: ≥ 1 to < 2 min 4: < 1 min	
Baseline Bowel Urgency Frequency	Yes	None	
<i>Other Baseline Patient-Reported Outcomes</i>			
Alcohol Use	No	Never, Current, Former	
Caffeine Use	No	Never, Current, Former	
Tobacco Use	No	Never, Current, Former	
Nicotine Use	No	Never, Current, Former	
Recreational Drug Use	No	Never, Current, Former	

Abbreviation: 5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; ATC= Anatomical Therapeutic Chemical; AZA = azathioprine; eCRF = electronic clinical report form; IBDQ = Inflammatory Bowel Disease Questionnaire; JAK = Janus Kinase; MMX = multi matrix colonic delivery technology; MTX = Methotrexate; NRS = numeric rating scale; PGA = Physician's Global Assessment; S1P = Sphingosine-1-phosphate; TB = tuberculosis; TNF = tumor necrosis factor; UC = ulcerative colitis.

a. Subgroup analysis will be used for efficacy endpoints only.

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]



#### 6.4. Appendix 4: Treatment Compliance

Treatment compliance with IP will be summarized for participants who enter the treatment period. The treatment compliance of patents while being treated during other study periods may also be summarized if necessary. Treatment compliance for each participant will be calculated as:

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

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

- For visits where the participant is to receive an IV infusion, they received the planned dose (i.e., a partial dose does not count) as derived from the Exposure eCRF page
- For visits where the participant is to receive SC injections, they received the planned number of injection doses (i.e., 2 doses) as derived from the Exposure eCRF page

“Overall compliance” with therapy is defined as having at least 80% treatment compliance. Proportions of participants who satisfy the definition of overall compliance during the treatment period will be summarized for FAS population.

#### 6.5. Appendix 5: 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 MedDRA PT.

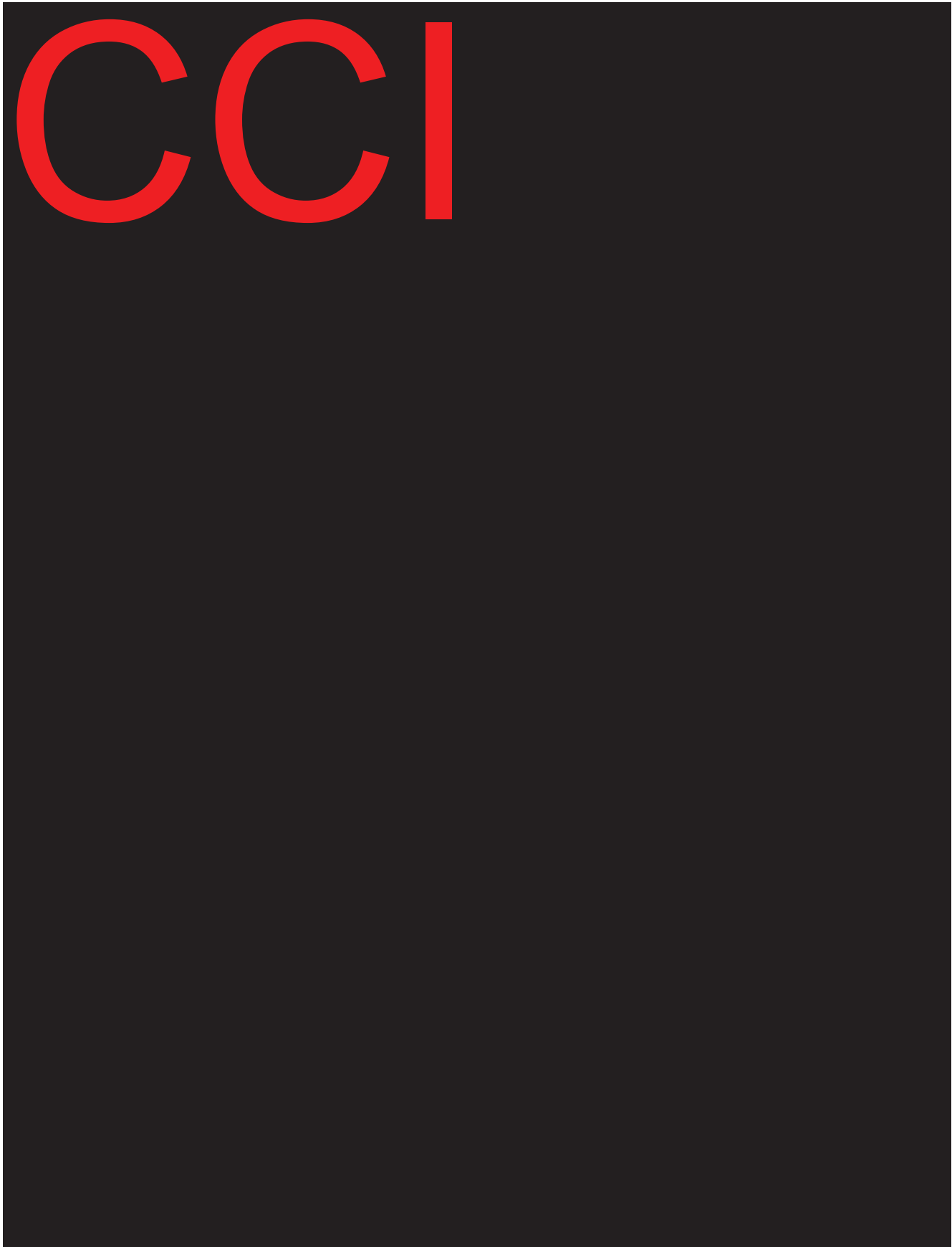
- An AE is considered ‘Serious’ whether or not it is a TEAE.
- An AE is considered in the ‘Other’ category if it is both a TEAE and is not serious. For each SAE and ‘Other’ AE, for each term, the following are provided:
  - the number of participants at risk of an event
  - the number of participants who experienced each event term
  - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, ‘Other’ AEs that occur in fewer than 5% of participants/subjects 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.

#### 6.6. Appendix 6: Study Visit or Week Definition for Daily Diary

Weekly summary measures of daily diary data will be created for each participant. 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.

**Table AMBZ.6.4. Study Visit and Week Definition for Daily Diary**





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