| STATISTICAL ANALYSIS PLAN | |
|---|---|
| Study Code | D5272C00002 (Legacy #3151-202-008) |
| Edition Number | 1.0 |
| Date | 12-Oct-2022 |

# A Phase 2 Open-label, Long-term Extension Safety Study of Brazikumab in Participants with Moderately to Severely Active Ulcerative Colitis

# (EXPEDITION OLE)

Redacted for Public Disclosure

# TABLE OF CONTENTS

TITLE PAGE ..... 1
TABLE OF CONTENTS ..... 2
LIST OF ABBREVIATIONS ..... 6
AMENDMENT HISTORY ..... 8
1 INTRODUCTION ..... 9
2 CHANGES TO PROTOCOL PLANNED ANALYSES ..... 10
3 DATA ANALYSIS CONSIDERATIONS ..... 11
3.1 Timing of Analyses ..... 11
3.2 Analysis Populations ..... 11
3.3 General Considerations ..... 12
3.3.1 General Study Level Definitions ..... 12
3.3.1.1 Study Day 1 ..... 12
3.3.1.2 Baseline ..... 12
3.3.1.3 Study Periods ..... 13
3.3.2 Visit Window ..... 14
3.3.2.1 Study day ..... 14
3.3.2.2 Conventions for the analysis windows ..... 14
3.3.2.3 Early discontinuation visits ..... 15
3.3.2.4 Multiple observations ..... 15
3.3.3 Handling of Unscheduled Visits ..... 16
3.3.4 Multiplicity/Multiple Comparisons ..... 16
3.3.5 Handling of Protocol Deviations in Study Analysis ..... 16
4 STATISTICAL ANALYSIS ..... 17
4.1 Study Population ..... 17
4.1.1 Participant Disposition and Completion Status ..... 17
4.1.1.1 Definitions and Derivations ..... 17
4.1.1.2 Presentation ..... 18
4.1.2 Analysis Sets ..... 19
4.1.2.1 Definitions and Derivations ..... 19
4.1.2.2 Presentation ..... 20
4.1.3 Protocol Deviations ..... 20
4.1.3.1 Definitions and Derivations ..... 20
4.1.3.2 Presentation ..... 20
4.1.4 Demographics ..... 20
4.1.4.1 Definitions and Derivations ..... 20
4.1.4.2 Presentation ..... 20
4.1.5 Disease Characteristics ..... 21
4.1.5.1 Definitions and Derivations ..... 21
4.1.5.2 Presentation ..... 22

4.1.6 Medical History and Concomitant Disease ..... 22
4.1.6.1 Definitions and Derivations ..... 22
4.1.6.2 Presentation ..... 22
4.1.7 Prior and Concomitant Medications ..... 23
4.1.7.1 Definitions and Derivations ..... 23
4.1.7.2 Presentation ..... 24
4.1.8 Study Intervention Compliance ..... 25
4.1.8.1 Definitions and Derivations ..... 25
4.1.8.2 Presentation ..... 25
4.2 Endpoint Analyses ..... 25
4.2.1 Primary Endpoint ..... 28
4.2.2 Secondary Endpoint ..... 28
4.2.3 Exploratory Endpoint: mMS ..... 28
4.2.3.1 Definition ..... 28
4.2.3.2 Derivation ..... 28
4.2.3.3 Handling of Dropouts and Missing Data ..... 28
4.2.3.4 Primary Analysis of Exploratory Endpoint ..... 28
4.2.4 Exploratory Endpoint: Change from Baseline in Patient Reported Outcomes in Site Visits ..... 28
4.2.4.1 Definition ..... 28
4.2.4.2 Derivation ..... 29
4.2.4.3 Handling of Dropouts and Missing Data ..... 30
4.2.4.4 Primary Analysis of Exploratory Endpoints ..... 31
4.2.5 Exploratory Endpoint: Evening Diary ..... 31
4.2.5.1 Definition ..... 31
4.2.5.2 Derivation ..... 31
4.2.5.3 Handling of Dropouts and Missing Data ..... 31
4.2.5.4 Primary Analysis of Exploratory Endpoints ..... 31
4.2.6 Exploratory Endpoint: GHI and RHI ..... 31
4.2.6.1 Definition ..... 31
4.2.6.2 Derivation ..... 33
4.2.6.3 Handling of Dropouts and Missing Data ..... 33
4.2.6.4 Primary Analysis of Exploratory Endpoints ..... 33
4.2.7 Exploratory Endpoints: Binary outcomes ..... 34
4.2.7.1 Definition ..... 34
4.2.7.2 Derivation ..... 34
4.2.7.3 Handling of Dropouts and Missing Data ..... 34
4.2.7.4 Primary Analysis of Exploratory Endpoints ..... 34
4.2.8 Exploratory Endpoint: Physicians' Global Assessment ..... 35
4.2.8.1 Definition ..... 35
4.2.8.2 Derivation ..... 35
4.2.8.3 Handling of Dropouts and Missing Data ..... 35
4.2.8.4 Primary Analysis of Exploratory Endpoints ..... 35
4.3 Pharmacodynamic Endpoint(s) ..... 35

4.4 Pharmacokinetics ..... 36
4.5 Immunogenicity ..... 36
4.5.1 Derivations ..... 36
4.5.2 Primary analysis of ADA ..... 37
4.6 Safety Analyses ..... 37
4.6.1 Exposure ..... 38
4.6.1.1 Definitions and Derivations ..... 38
4.6.1.2 Presentation ..... 38
4.6.2 Adverse Events ..... 38
4.6.2.1 Definitions and Derivations ..... 38
4.6.2.2 Presentation ..... 39
4.6.3 Clinical Laboratory, Blood Sample ..... 41
4.6.3.1 Definitions and Derivations ..... 41
4.6.3.2 Presentation ..... 44
4.6.4 Clinical Laboratory, Urinalysis ..... 44
4.6.4.1 Definitions and Derivations ..... 44
4.6.4.2 Presentations ..... 45
4.6.5 Other Laboratory Evaluations ..... 45
4.6.5.1 Definitions and Derivations ..... 45
4.6.5.2 Presentations ..... 45
4.6.6 Physical Examinations ..... 45
4.6.6.1 Definitions and Derivations ..... 45
4.6.7 Vital Signs ..... 45
4.6.7.1 Definitions and Derivations ..... 45
4.6.7.2 Presentation ..... 46
4.6.8 Electrocardiogram ..... 46
4.6.8.1 Definitions and Derivations ..... 46
4.6.8.2 Presentation ..... 47
4.6.9 Other Safety Assessments ..... 47
4.6.9.1 Definitions and Derivations ..... 47
4.6.9.2 Presentation ..... 48
5 INTERIM ANALYSIS ..... 48
6 REFERENCES ..... 49
7 APPENDIX ..... 51
7.1 Modified Mayo Score ..... 51
7.2 Evening diary ..... 51
7.3 Missing start and stop dates ..... 53
7.3.1 Incomplete Start Date ..... 53
7.3.2 Incomplete Stop Date ..... 54

## TABLES

Table 1-1 Treatment details footnotes for listings ..... 10
Table 3-1 Populations for Analysis ..... 11
Table 3-2 Analysis Windows ..... 14
Table 4-1 Drug names and ATC codes ..... 22
Table 4-2 Permitted rescue medications ..... 24
Table 4-3 Objectives and endpoints ..... 26
Table 4-4 IBDQ subscores ..... 29
Table 4-5 GHI and RHI grading ..... 32
Table 4-6 RHI derivation ..... 33
Table 4-7 Protocol-Required Safety Laboratory Assessments ..... 41
Table 4-8 Normal ranges for laboratory values (Central Laboratory Services Manual) ..... 42
**Table 4-9** Criteria for Potentially Clinically Significant Laboratory Values ..... 43
Table 4-10 Criteria for Potentially Clinically Significant Vital Signs ..... 46
Table 4-11 Criteria for Potentially Clinically Significant Electrocardiograms ..... 47
Table 7-1 Items Included in mMS ..... 51
Table 7-2 Daily recall items ..... 52

# LIST OF ABBREVIATIONS

| *Abbreviation or Specialized Term* | *Definition* |
|---|---|
| ADA | Anti-drug antibodies |
| AE | Adverse event |
| AESI | Adverse Event of Special Interest |
| ALP | Alkaline Phosphatase |
| ALT | Alanine Aminotransferase |
| AP | Abdominal Pain |
| AST | Aspartate Aminotransferase |
| BMI | Body mass index |
| CI | Confidence Interval |
| CRF | Case Report Form |
| CRP | C-Reactive Protein |
| CS | Corticosteroid |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| ED | Early discontinuation of study intervention |
| EQ-5D-5L | 5-level European Quality of Life - 5 Dimensions |
| ET | Early termination |
| FAS | Full Analysis Set |
| FCP | Fecal Calprotectin |
| GHI | Geboe's Histological Index |
| HRQoL | Health-Related Quality of Life |
| IBD | Inflammatory Bowel Disease |
| IBDQ | Inflammatory Bowel Disease Questionnaire |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonization |
| IP | Investigational Product |
| IPD | Important Protocol Deviation |
| ITT | Intent-to-Treat |
| IV | Intravenous |
| JAK | Janus kinase |
| LLN | Lower Limit of Normal |
| Max | Maximum |

| | |
|---|---|
| MCS | Mental Component Score |
| MedDRA | Medical Dictionary for Regulatory Activities |
| Min | Minimum |
| mMS | modified Mayo Score |
| nAb | Neutralizing antibody |
| NRI | Non-responder imputation |
| NRS | Numerical Rating Scale |
| PCS | Potentially Clinically Significant |
| PD | Pharmacodynamic |
| PFS | Physical Functioning scale |
| PGA | Physician's Global Assessment |
| PK | Pharmacokinetics |
| PRO | Patient Reported Outcome |
| PT | Preferred Term |
| Q1 | 1st Quartile |
| Q3 | 3rd Quartile |
| RHI | Robart's Histopathology Index |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis System |
| SC | Subcutaneous |
| SD | Standard Deviation |
| SE | Standard Error |
| SF-36 | Short-Form 36 Health Survey |
| SI | International System of Units |
| SOC | System Organ Class |
| TBL | Total Bilirubin |
| UC | Ulcerative Colitis |
| ULN | Upper Limit of Normal |
| VAS | Visual Analog Scale |
| WHO | World Health Organization |

# AMENDMENT HISTORY

| CATEGORY Change refers to: | Date | Description of change | In line with CSP? | Rationale |
|---|---|---|---|---|
| N/A | 12Oct2022 | Initial approved SAP | N/A | N/A |
| | | | | |
| | | | | |

# 1 INTRODUCTION

This study is a global, multicenter open-label extension study of brazikumab limited to participants previously enrolled in the lead-in (LDI) Study D5272C00001 (Legacy #3151-201-008). Participants in the LDI study are eligible to enroll in Study D5272C00002 (Legacy #3151-202-008) provided they continue to meet eligibility criteria and have not had adverse experiences considered to be related to study medication that resulted in discontinuation of the initial lead-in study intervention, or that in the judgment of the investigator, would disqualify them from participating. Eligible participants do not need to complete the 18-week Safety Follow-up Period of the lead-in study if they rollover into this study after they complete the final visit of the lead-in study.

It is anticipated that the enrolled population will consist of participants who have had varying endoscopic and clinical symptom responses during the lead-in study, ranging from complete clinical remission to no response or worsening of their signs and symptoms of ulcerative colitis (UC). Participants who completed the lead-in Study D5272C00001 (Legacy #3151-201-008) and met criteria for clinical response at Week 54, will receive subcutaneous (SC) brazikumab dosing. Participants who did not meet criteria for clinical response at Week 54 or who met criteria for early termination (rescue treatment) prior to Week 54 in the lead-in study will be administered intravenous (IV) induction dosing with brazikumab.

This Statistical Analysis Plan (SAP) provides a technical and detailed elaboration of the statistical analyses of the efficacy and safety data as outlined and/or specified in the most recent Clinical Study Protocol (CSP) (Amendment 3 version 4, dated 13 May 2022). Specifications of tables, figures, and data listings are contained in a separate document. The advanced analysis of pharmacokinetic data may be specified in a separate analysis plan and reported outside of the Clinical Study Report (CSR).

This is an extension study and the sample size is determined by the number of participants in the lead-in study who are eligible and choose to participate in this study. No separate sample size calculation was performed. Up to a maximum of 255 participants may enter the study, based on the expected number of participants in the lead-in Study D5272C00001.

The 240 mg SC dose of brazikumab will be administered every 4 weeks to all completers who met criteria for clinical response at Week 54 in the lead-in study. Participants in the lead-in study who did not meet criteria for clinical response at Week 54 or who met criteria for early termination (rescue treatment) prior to Week 54 are considered inadequate/non-responders and will receive IV induction dosing with 1440 mg of brazikumab at Week 0, Week 4, and Week 8, followed by brazikumab 240 mg SC administered every 4 weeks thereafter (up to Week 52).

The study will consist of a maximum 52-week open-label treatment period and an 18-week safety follow-up period (no study intervention will be administered), for a total of up to 70 weeks.

For reporting purposes, there will be 3 treatment groups in the extension study, defined by treatment in the lead-in study: Brazikumab/Brazikumab, Placebo/Brazikumab, and Vedolizumab/Brazikumab. Vedolizumab/Brazikumab will be excluded from efficacy analyses and only listed for safety reporting. As part of the changes to the development program in the LDI study, the highest brazikumab induction dose (2100 mg IV) arm and the vedolizumab arm have been removed in the Protocol Amendment 5 of study D5272C00001 (Legacy #5151-201-008).

For listings, treatment details for the lead-in and OLE studies will be footnoted as in Table 1-1.

Table 1-1 Treatment details footnotes for listings

| ***Footnote*** | ***Study treatment*** | ***Footnote text*** |
|---|---|---|
| a | LDI Brazikumab | Brazikumab 700 mg IV or brazikumab 720 IV + 105-240 mg SC |
| b | LDI Brazikumab | Brazikumab 1400 mg IV or brazikumab 1440 mg IV + 105-240 mg SC |
| c | LDI Brazikumab | Brazikumab 2100 mg IV + 105-240 mg SC |
| d | OLE Brazikumab | Brazikumab 120 mg SC |
| e | OLE Brazikumab | Brazikumab 120 mg SC + brazikumab 240 mg SC |
| f | OLE Brazikumab | Brazikumab 240 mg SC |
| g | OLE Brazikumab | Brazikumab 1440 mg IV + 240 mg mg SC |
| h | OLE Brazikumab | Brazikumab 2160 mg IV (incl. administration at Day 15) + 240 mg mg SC |

The schedule of assessments for the open label extension study can be found in the Clinical Study Protocol (CSP) Section 1.3, Tables 1, 2, and 3.

# 2 CHANGES TO PROTOCOL PLANNED ANALYSES

This SAP has been authored to account for the different protocol versions, assuring that all data collected will be presented in an appropriate fashion.

# 3 DATA ANALYSIS CONSIDERATIONS

## 3.1 Timing of Analyses

The analysis will be undertaken after the last participant has completed the last visit of the study (second safety follow-up visit) or discontinued early. All analyses described in this SAP will be included in the clinical study report (CSR).

## 3.2 Analysis Populations

The following populations are defined in Table 3-1 :

**Table 3-1 Populations for Analysis**

| Population/Analysis set | Description |
|---|---|
| Screened Analysis Set | This includes all participants screened for the study. |
| Full Analysis Set | All participants who are assigned to an IV or SC brazikumab study intervention in the OLE, excluding participants randomized to vedolizumab in the double-blind, lead-in study. Participants will be summarized according to the randomized study treatment in the double-blind, lead-in study. Treatment groups will be presented as Brazikumab/Brazikumab for participants randomized to brazikumab study intervention in the LDI study, and Placebo/Brazikumab for participants randomized to placebo study intervention in the LDI study. |
| Safety Analysis Set | All participants who receive 1 or more administration of study intervention in this extension study; participants will be summarized according to the actual study treatment received in the double-blind, lead-in study. Treatment groups will be presented as Brazikumab/Brazikumab for participants who received brazikumab study intervention in the LDI study, and Placebo/Brazikumab for participants who received placebo study intervention in the LDI study. Participants who received Vedolizumab/Brazikumab will only be included in listings. |
| PK Analysis Set | This includes participants who receive at least 1 dose of study intervention in the OLE and have at least 1 PK sample containing detectable brazikumab concentration. Participants randomized to vedolizumab in the double-blind lead-in study are excluded from the PK population. |
| ADA Evaluable Analysis Set | This includes Safety Set participants having non-missing baseline ADA result and at least one non-missing post-baseline ADA result; participants will be summarized according to the actual study treatment group. |

ADA = anti-drug antibody; IV = intravenous; PK = pharmacokinetic; SC = subcutaneous

## 3.3 General Considerations

Statistical analysis will be performed using the SAS Software, Version 9.4 or higher.
All study-related raw data for enrolled participants, including derived data, will be presented in data listings. All listings will be sorted for presentation in order of treatment group, study site, participant number, date of event, and parameter name (if applicable).

Descriptive statistics for continuous variables include the number of participants (n), mean, standard deviation (SD), median, 1st (Q1) and 3rd (Q3) quartiles, minimum (Min), and maximum (Max). Summary statistics for categorical variables include the number of participants (n) and percent (%). All efficacy and safety data will be analyzed based on the analysis visits. The details of analysis visit windowing rules are described in Section 3.3.2.2.

All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise. Means and medians will be presented to 1 more decimal place than the recorded data. SD and standard errors will be presented to 2 more decimal places than the recorded data. Confidence intervals will be presented using the same number of decimal places as those recorded for the parameter point estimate. Percentages will be rounded to 1 decimal place, except 0 and 100%, which will be displayed without any decimal places.

### 3.3.1 General Study Level Definitions

#### 3.3.1.1 Study Day 1

Day 1 will be defined as the date of first dose of study intervention in this open-label study.

#### 3.3.1.2 Baseline

In general, baseline for this open-label study is defined as the last non-missing assessment before the first dose of study intervention administration in the lead-in study, with the following exceptions:

- The Baseline Patient Reported Outcomes (PRO) items (including stool frequency and rectal bleeding) will be based on the participant's average evening diary data completed over the most recent 3 days within a 7 consecutive day period prior to the lead-in Screening colonoscopy (exclusive of the days of bowel prep or endoscopy).
- The lead-in screening colonoscopy should take place within the time frame defined by the Amendment under which the participant was enrolled. For instance, in Amendment 4 the colonoscopy should occur within 35 days of randomization, while Amendment 5 specifies within 14 days of randomization. For a participant enrolled under Amendment 4 with a Baseline colonoscopy that is out of window according to Amendment 5, that is still a valid Baseline colonoscopy.

- For PK and ADA analyses, baseline for participants who received Brazikumab/Brazikumab is the same as the baseline in the double-blind lead-in study (as treated with brazikumab during the lead-in study); however, for participants who received Placebo/Brazikumab, baseline is the last non-missing assessment before the first dose of study intervention administration in this open-label extension study (as never treated with brazikumab during the lead-in study).

**Change from Baseline** is defined as (Value at Visit X – Value at Baseline).

**Percent Change from Baseline** is defined as (Value at Visit X – Value at Baseline)/(Value at Baseline)*100.

#### 3.3.1.3 Study Periods

**Screening assessments**

All assessments made at the final visit of the lead-in study D5272C00001 (Legacy #3151-201-008) will be used as screening assessments for this study, unless Week 0 for this study occurs greater than 28 days from the final assessment(s) of the lead-in study, in which case the participant will need to complete all screening assessments except the colonoscopy. Any repeated screening assessments or the final assessment for the lead-in study will not be considered in the current OLE study and will not be listed.

**Treatment Period**

The treatment period consists of:

- For participants who receive maintenance therapy only, the Maintenance Period (Days 1 to 365)

- For participants who receive Induction therapy, Induction Period (Days 1 to 85 until first administration of SC brazikumab) through Maintenance Period (Day 85 from first administration of SC brazikumab to Day 365).

**Safety Follow-up Period**

The Safety Follow-up Period consists of the 18 weeks after the last dose of brazikumab (Follow-up Visit 1 [8 weeks after last dose] and Follow-up Visit 2 [18 Weeks after last dose]) for all treatment groups.

**LDI+OLE Treatment Period**

The LDI+OLE Treatment Period is defined as starting on the date of first dose investigation product in the LDI until 28 days after the last dose of investigational product in the OLE.

### 3.3.2 Visit Window

#### 3.3.2.1 Study day

For assignment of data to analysis windows, study days will be defined in reference to Study Day 1 as defined in Section 3.3.1.1.

For any analysis visit time windows, if the assessment date is on or after the date of first dose of study intervention, the study day is calculated by:

assessment date – date of first dose of study intervention + 1.

If the assessment date is before the date of first dose of study intervention, the study day is calculated by:

assessment date – date of first dose of study intervention.

Therefore, a negative day indicates a day before the start dose of the study intervention.

If the assessment date is unavailable, the visit date will be used instead.

#### 3.3.2.2 Conventions for the analysis windows

Table 3-2 presents the analysis windows assigned for efficacy (except daily data parameters) and safety analyses and the corresponding range of treatment days (window) during which data for a particular nominal visit may be collected. The analysis windows will be calculated from the date of first dose for study intervention. These are analysis windows that contain, but are not the same as, the actual visit windows. Each analysis window is equidistant between the neighboring Scheduled Visit Days. For example, Week 24 = Day 169 and Week 28 = Day 197 (Table 3-2): the center of the analysis window is calculated as the average between the two Visit Days, or (169+197)/2= 183. Therefore, the end of the Week 24 analysis window is Day 182 and the beginning of the analysis window for Week 28 is Day 183.

**Table 3-2 Analysis Windows**

| ***Derived Visit*** | ***Scheduled Visit Day*** | ***Analysis Window*** |
|---|---|---|
| Lead-in Baseline | | See Section 3.3.1.2 |
| Screening OLE, last visit in LDI[a] | | Last assessment in the LDI |
| Screening OLE[a] | -28 | Days [-28, -1] |
| Week 0 | Day 1[b] | Day 1 |
| Week 4[c] | Day 29 | Days [2, 42] |
| Week 8[c] | Day 57 | Days [43, 70] |
| Week 12 | Day 85 | Days [71, 98] |
| Week 16 | Day 113 | Days [99, 126] |
| Week 20 | Day 141 | Days [127, 154] |
| Week 24 | Day 169 | Days [155, 182] |
| Week 28 | Day 197 | Days [183, 210] |
| Week 32 | Day 225 | Days [211, 238] |
| Week 36 | Day 253 | Days [239, 266] |
| Week 40 | Day 281 | Days [267, 294] |
| Week 44 | Day 309 | Days [295, 322] |
| Week 48 | Day 337 | Days [323, 350] |

| | | |
|---|---|---|
| Week 52 | Day 365 | Day ≥ 351 and within Treatment Period |
| End of Treatment Period[d] | Last visit or Termination Visit during the Treatment Period | |
| Follow-up Visit 1[e] | Last dose date +1 to Last dose date + 90 | |
| Follow-up Visit 2[e] | Last dose date +91 to End of Study | |

[a] Mapped to "Screening OLE" in Tables and Figures, and presented separately in listings. Any repeated screening assessments or the final assessment for the lead-in study will be presented in the listings.
[b] Relative to the date of the first dose of study intervention in the Induction Period. Day 1 = the date of the first dose of study intervention in the Induction Period. There is no Day 0.
[c] For participants assigned to lead-in treatment Group C (under the protocol D5272C00002 (Legacy #3151-202-008), Amendment 1, 17 Aug 2020), the Week 2 assessment will be mapped to Week 4, and the Week 6 assessment to Week 8, with subsequent mapping every 4 weeks throughout the study.
[d] Presented in analysis tables for safety parameters, including but not limited to electrocardiograms, clinical laboratory values, and vital signs.
[e] Follow-up Visits will only be carried out for participants who discontinue early.

#### 3.3.2.3 Early discontinuation visits

Early discontinuation visits for either discontinuation of study intervention or early discontinuation from study will be mapped to analysis windows following the conventions in Table 3-2. Early discontinuation visits will only be used in analysis if the nominal scheduled visit result is missing.

#### 3.3.2.4 Multiple observations

All observations will be assigned to their corresponding analysis window following the conventions in Table 3-2. If multiple assessments are recorded in a single analysis window, the following rules will be followed unless otherwise specified:

- If there are 2 or more observations within the same analysis window, then the observation closest to the Visit where study intervention was given will be used in the analysis.
- If there are 2 Visits with study intervention, the observation closest to the planned protocol Scheduled Visit day will be used. The other observation(s) will not be used for analysis but will be included in listings.
- If 2 observations are equidistant from the Visit where study intervention was given, the observation with the earlier collection date will be used in the analysis.
- Where study intervention is not scheduled, then the observation closest to the Scheduled Visit Day will be used in the analysis.

For mMS PRO components, apply the same rules as above using assessments that are:

- prior to bowel preparation
- before any endoscopy
- done during the analysis window.

Once the assessment date is determined, the most recent 3 days during the previous seven day window of the diary (PRO) data will be used to calculate the mMS score (excluding days of bowel prep and colonoscopy).

### 3.3.3 Handling of Unscheduled Visits

If the study intervention cannot be administered during a scheduled study visit, the rescheduled dose will be administered as an unscheduled visit.

Post-baseline unscheduled visits will be mapped to a visit based on the analysis windows in Table 3-2. Both unscheduled and scheduled visits will be used in case of multiple observations within an analysis visit window and same rules as in Section 3.3.2.4 will be applied.

All data from unscheduled visits will be presented in data listings.

### 3.3.4 Multiplicity/Multiple Comparisons

Efficacy endpoints are exploratory in this extension study. No formal hypothesis testing will be performed.

### 3.3.5 Handling of Protocol Deviations in Study Analysis

A per-protocol (PP) analysis is not planned for this study. Important protocol deviations will be listed and tabulated in the CSR. Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being.

The protocol deviations, definitions, process for identification and assessment are detailed in a separate protocol deviation plan.

# 4 STATISTICAL ANALYSIS

## 4.1 Study Population

The study population covers participant disposition, analysis sets, protocol deviations, demographics, baseline characteristics medical history, prior and concomitant medication, and study drug compliance.

### 4.1.1 Participant Disposition and Completion Status

#### 4.1.1.1 Definitions and Derivations

**Enrolled/Screened**

A participant is enrolled if they, or their legally acceptable representative, sign the informed consent form.

**Screen failure**

Screen failures are defined as participants who consent to participate in this open-label clinical study but subsequently do not receive open-label study intervention. Screen failure will be identified from the Disposition- Screening form of the eCRF as "What was the subject's status?" = "Screen Failure".

**Treatment assignment**

This is an open-label trial and participants are not randomized. Instead, each participant is assigned to one of two treatments (Induction or Maintenance Brazikumab) based on their clinical response in the lead-in study. OLE Treatment assignment can be found on the eCRF form Treatment Criteria. Treatment groups will be defined for presentation as specified in Section 1.

**Study discontinuation**

A study discontinuation will occur if a participant who signs the Informed Consent Form (ICF) and is dosed ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures. The day of discontinuation is the Study Day of last visit (or contact), that is, the date of discontinuation visit (or contact) – date of first dose of study intervention + 1. Date of last contact may be found in the CRF as:

- Date of death (Death form)
- What was the date of Completion/Discontinuation? (Disposition – Screening form)
- What was the date of Completion/Discontinuation? (Disposition – Induction form)
- What was the date of Completion/Discontinuation? (Disposition – Maintenance form)
- What was the date of Completion/Discontinuation? (Disposition –Follow-up form)

**Treatment discontinuation**

A study intervention discontinuation will occur if a participant who has taken at least one dose of the study intervention is discontinued from the study intervention before the completion of protocol-defined study procedures. Discontinuation of study intervention will be identified from the eCRF Form Study Drug Completion/Discontinuation if the question What was the subject's status? has any response except "Completed".

**Completer**

Study intervention completion is found on the Study Drug Completion/Discontinuation Form as "What was the date of Completion/Discontinuation?" and "What was the subject's status?" = "Completed".

#### 4.1.1.2 Presentation

Listings and summaries will be presented for the Screened Analysis Set. The listings will include but not be limited to completion status, including reasons for premature termination. The summary will include the number and percentage of participants in the Screened Analysis Set who:

- Were screened
- Failed screening, and reasons
- Were assigned to treatment
- Were assigned to treatment, not treated and reasons
- Started treatment
- Discontinued treatment in the Induction Period (if applicable), and reasons
- Completed the Induction Period (if applicable)
- Entered Maintenance Period
- Discontinued treatment in the Maintenance Period, and reasons
- Completed Maintenance treatment
- Completed Week 52
- Withdrew from the study, and reasons
- Completed the Safety Follow-up Period

Participants will be summarized overall and by treatment group.

**Summary of global/country situation** A summary of disposition due to the global/country situation will be provided by treatment group, to include the number of participants who

- Completed treatment
- Discontinued treatment due to the global/country situation, and reasons
- Completed the study
- Withdrew from the study due to the global/country situation

In addition, global/country situation disruptions will be summarized for the FAS by treatment group, to include the number of participants with at least one disruption due to global/country situation:

- Visit impacted
- Study drug impacted
- Concomitant medication impacted
- Discontinued treatment due to global/country situation
- Withdrew from the study due to global/country situation

### 4.1.2 Analysis Sets

#### 4.1.2.1 Definitions and Derivations

**Screened Analysis Set**

This analysis set includes all participants screened for the study.

The Screened flag is defined by the question "Did the subject meet all eligibility critera?" populated with either "Yes" or "No" on the Inclusion/Exclusion form of the eCRF.

**The Full Analysis Set (FAS)**

This analysis set includes all participants who are assigned to an IV or SC brazikumab study intervention in this study, excluding participants randomized to vedolizumab in the double-blind lead-in study. The FAS will be used for all efficacy analyses unless otherwise indicated. The FAS will be defined from the Disposition-Induction form "Will the subject continue?" ='Y' and from the randomization schedule from the lead-in study.

**The Safety (SAF) Analysis Set**

This analysis set includes all participants who receive 1 or more administration of study intervention. Participants will be summarized according to the actual study treatment group.

The Safety flag is defined by the question "Did the subject receive study treatment at this visit?" = 'Yes' is checked at any Visit on the Exposure-Intravenous Infusion Bag form or the Exposure – Subcutaneous form of the eCRF.

**The PK Analysis Set**

This includes Safety Set participants having at least 1 PK sample containing detectable brazikumab concentrations. Participants randomized to vedolizumab in the double-blind lead-in study are excluded from the PK population.

**The ADA Evaluable Analysis Set**

This includes Safety Set participants having a non-missing baseline ADA result and at least one non-missing post-baseline ADA result. Participants will be summarized according to the actual study treatment group.

#### 4.1.2.2 Presentation

The number of participants in each analysis set will be listed and summarized by treatment group as defined in Section 1, and overall, including reasons excluded from the Safety analysis set, PK analysis set, and ADA evaluable analysis set.

Recruitment per country and site will also be summarized for each analysis set.

### 4.1.3 Protocol Deviations

#### 4.1.3.1 Definitions and Derivations

The definition and derivation of IPDs is described in a separate Protocol Deviation plan. These important protocol deviations will be reviewed and documented before clinical data lock.

#### 4.1.3.2 Presentation

The number and percentage of participants with important protocol deviations will be listed and summarized overall and by treatment group.

Important Protocol Deviations include:

- Violations of inclusion criteria
- Violations of exclusion criteria
- Discontinuation Criteria for study intervention are met but the participant was not withdrawn from study intervention
- Discontinuation Criteria for withdrawal from study are met but the participant was not withdrawn from the study
- Excluded medication taken
- Deviations related to study procedures
- Other Important Protocol Deviations

In addition, the number of participants with at least one Important Protocol Deviation will be presented.

### 4.1.4 Demographics

#### 4.1.4.1 Definitions and Derivations

Demographic variables will include age, sex, region, country, race and ethnicity. Participant age is entered into the eCRF in years. Age will be further categorized in 3 groups (<40, 40-65, and >65).

Participants who reported multiple races will be counted in the category “multiple”.

#### 4.1.4.2 Presentation

Demographic variables will be listed and summarized by treatment group and overall for the FAS and include:

- Age
- Age group [<40, 40-65, and >65]

- Sex
- Region [US and Non-US]
- Country
- Race
- Ethnicity

### 4.1.5 Disease Characteristics

#### 4.1.5.1 Definitions and Derivations

The disease characteristics of interest include disease duration, immunomodulator use, baseline disease location, JAK inhibitor use, prior biologic use, number of different mechanisms of actions (MOA) of biologics, inadequate response on prior biologics, C-reactive protein (CRP), fecal calprotectin (FCP), and mMS at Baseline.

**Disease duration** will be calculated as the (Date of First Study Intervention - Date of Initial Diagnosis of Ulcerative Colitis)/365.25 years from the eCRF form Ulcerative Colitis History.

**Immunomodulators** will be abstracted from the form Prior and Concomitant Medications for Ulcerative Colitis and include either prior or concomitant use of azathioprine, 6-mercaptopurine, methotrexate, or other immunomodulator.

**Janus kinase (JAK) inhibitors** will be abstracted from the form Prior and Concomitant Medications for Ulcerative Colitis and include either prior or concomitant use of tofacitinib or upadacitinib.

**Prior biologic use** includes any use of biologics prior to the first dose of study intervention in this OLE study. Biologics will be abstracted from the form Prior and Concomitant Medications for Ulcerative Colitis and include adalimumab, infliximab, golimumab, certolizumab, vedolizumab, natalizumab, and ustekinumab.

**Number of different mechanism of actions** of prior biologics: each of the biologics entered into the form Prior and Concomitant Medications with the question “Type of Medication” = “Ulcerative Colitis Medication”, will be categorized as anti-TNF, selective immunosuppressants, or interleukin inhibitor. The number of different mechanisms will be 0-3.

**Inadequate response to biologics** will be determined for each prior biologic whose response to “reason for discontinuation” is either “intolerance” or “lack of efficacy”.

See Table 4-1 for examples of immunomodulators, JAK inhibitors, and biologics.

**Table 4-1 Drug names and ATC codes**

| Category | Drug Name | ATC code |
|---|---|---|
| Immunomodulator | Azathioprine<br>6-mercaptopurine<br>Methotrexate<br>Other | L04AX01<br>L01BB02<br>L01BA01/L04AX03 |
| JAK inhibitors | Tofacitinib<br>Upadacitinib | L04AA29<br>L04AA44 |
| BIOLOGICS | | |
| Anti-TNF | Infliximab<br>Adalimumab<br>Certolizumab<br>Golimumab | L04AB02<br>L04AB04<br>L04AB05<br>L04AB06 |
| Integrin receptor antagonist | Vedolizumab<br>Natalizumab | L04AA33<br>L04AA23 |
| IL-12 and IL-23 antagonist | Ustekinumab | L04AC05 |

ATC = Anatomic Therapeutic Chemical; IL = Interleukin; JAK = Janus kinase; TNF = Tumor necrosis factor.

**mMS total score** and subscores will be collected at Baseline (for the lead-in study). The endoscopic subscore will be collected by Baseline disease location subgroup (descending colon, pancolitis, other). mMS is defined in Appendix 7.1 and mMS Baseline in Section 3.3.1.2.

#### 4.1.5.2 Presentation

The Disease characteristics will be listed and summarized descriptively by treatment group and overall for the FAS Population.

### 4.1.6 Medical History and Concomitant Disease

#### 4.1.6.1 Definitions and Derivations

**General Medical and Surgical History**

Medical and Surgical history will be captured as verbatim terms on the eCRF form Medical and Surgical History and will be mapped to system organ class (SOC) and preferred term (PT). For each Finding, the item will be concurrent if the question "Ongoing (at time of enrollment)" is answered "Yes".

Participants' medical and surgical histories and concurrent procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 24.0 or newer.

#### 4.1.6.2 Presentation

Medical and surgical histories will be summarized applying MedDRA terms. Each SOC and PT will be summarized separately for data from the lead-in study, and for any new medical

history as collected from the OLE eCRF, by treatment group as defined in Section 1, and overall for the FAS Population. Concurrent procedures will also be presented in a listing.

### 4.1.7 Prior and Concomitant Medications

#### 4.1.7.1 Definitions and Derivations

The World Health Organization (WHO) Drug Dictionary Enhanced, March 2018 or newer, will be used to classify prior and concomitant medications by therapeutic class and drug name.

**Prior medication**

Prior medication is defined as any medication discontinued before the first dose of the study intervention in the OLE study.

**Concomitant medication**

Concomitant medication is defined as any medication taken on or after the date of the first dose of the study intervention in the OLE study.

Any medications started later than 18 weeks after the last dose of study intervention date will not be presented in the summary tables but will be included in the participant data listings.

**Permitted UC medication**

Permitted UC medication should be recorded as concomitant medications as specified in the CSP Section 6.5.1.

**Prohibited UC medications**

Prohibited UC medication should not be taken during the course of the study. In most cases, if prohibited medications are taken, the study intervention must be discontinued. Prohibited medications are specified in the CSP Section 6.5.4.

**Rescue treatment**

Permitted rescue medications are allowed as per investigator judgment. Participants will continue to receive study intervention unless a prohibited medication is used.

The definition of a medication as rescue treatment will be guided by CSP 4 Amendment 3, Section 6.5.3, regardless of which amendment a participant was enrolled under. A rescue treatment is defined as any new concomitant medication, or any increase in dose of a Baseline medication required to treat new or unresolved UC symptoms, except for antidiarrheal medications already used at Baseline, after Week 12 of the OLE Study D5272C00002 (Legacy #3151-202-008). Other investigational products are not permitted to be used as rescue treatment. Any **new** initiation (or dose increase) of medications or interventions in Table 4-2 for the treatment of UC after Week 12 of OLE Study D5272C00002 (Legacy #3151-202-008) will be considered as rescue treatment and will not require stopping study intervention.

**Table 4-2 Permitted rescue medications**

| ***Medication*** | ***ATC code*** |
|---|---|
| 5-aminosalicylates | A07EC02 |
| Corticosteroids | |
| Parenteral, oral, or rectal CS | L04AD01 |
| Oral CS doses above Day 1 dose | L04AD01 |
| Immunomodulators | |
| Azathioprine | L04AX01 |
| 6-mercaptopurine | L01BB02 |
| Methotrexate | L01BA01/L04AX03 |
| IV immunoglobulin | J06BA02 |

Administration of rescue treatment constitutes treatment failure.

The criteria for use of rescue treatment are found in the CSP Section 6.5.3.

#### 4.1.7.2 Presentation

Medications will be summarized for the FAS by the number and proportion of participants in each treatment group receiving each medication within WHO drug class and preferred term. If a participant took a specific medication multiple times or took multiple medications within a specific therapeutic class, that participant would be counted only once for the coded drug name or therapeutic class. Any prior and concomitant medications will be included in listings, including corticosteroid medications.

The following summaries will be provided:

- Prior medication use
- Prior corticosteroid use for UC
- Prior immunomodulator use (for UC and for other indication than UC)
- Concomitant rescue medication use during the lead-in study for UC
- Concomitant rescue medication use during the OLE for UC
- Permitted concomitant medications
- Concomitant corticosteroid use (for UC and for other indication than UC)
- Concomitant immunomodulator use (for UC and for other indication than UC)

Prior medication use will be reported for the time periods “prior to the first dose in the lead-in study”, and “after the first dose during the lead-in study but before the first dose in the OLE”.

### 4.1.8 Study Intervention Compliance

#### 4.1.8.1 Definitions and Derivations

Participants are dosed under the direct supervision of study center personnel. The date and time of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. Study intervention compliance will measure the number of doses received and will be calculated as the total number of doses taken during that period divided by the number of expected doses, multiplied by 100.

#### 4.1.8.2 Presentation

Study intervention compliance will be listed and summarized for the Induction Period with number and proportion of expected participants dosed for each Visit by treatment group and overall using the FAS. Mean study intervention compliance will also be descriptively summarized for the Maintenance Period and full treatment period by treatment group and overall.

## 4.2 Endpoint Analyses

This section covers details related to the endpoint analyses such as primary, secondary, and other endpoints.

The purpose of this OLE study is to permit participants who previously enrolled in the double-blind Study D5272C00001 (Legacy #3151-201-008) to receive brazikumab, allowing for long-term observation of safety and efficacy in these participants treated with brazikumab. There are no formal hypotheses to be tested.

**Table 4-3 Objectives and endpoints**

| *Statistical category* | *Endpoint* | *Analysis Population* | *Intercurrent event strategy* | *Population level summary (analysis)* | *Details in section* |
|---|---|---|---|---|---|
| **Objective 1:** To assess the safety of long-term treatment with brazikumab in UC participants who previously completed or discontinued participation due to lack of efficacy after Week 10 in the lead-in Study D5272C00001 (Legacy #3151-201-008) | | | | | |
| Primary | • AEs<br>• Clinical laboratory values<br>• Vital signs<br>• Physical exams<br>• ECGs | Safety | | Summary tables | 4.6 |
| **Objective 2:** To assess the efficacy of long-term treatment with brazikumab in UC participants who previously completed or discontinued participation due to lack of efficacy after Week 10 in the lead-in Study D5272C00001 (Legacy #3151-201-008) | | | | | |
| Exploratory | • Change from Baseline in mMS assessments | FAS | | Descriptive statistics | 4.2.3 |
| Exploratory | PRO: Change from Baseline in<br>• IBDQ at Weeks 0,12 and 52<br>• SF-36v2 at Weeks 0, 12 and 52<br>• EQ-5D-5L at Weeks 0, 12 and 52<br>• Evening Diary for 1 week prior to Weeks 0, 12, and 52 | FAS | | Descriptive statistics | 4.2.4 and 4.2.5 |
| Exploratory | • GHI and Change from Baseline in RHI at Week 52 | FAS | | Descriptive statistics | 4.2.6 |
| Exploratory | • Clinical remission at Week 52<br>• Symptomatic remission at Week 52 | FAS | NRI before Week 52 | Descriptive statistics | 4.2.7 |
| Exploratory | • Symptomatic remission at Week 12 | FAS | NRI before week 12 | Descriptive statistics | 4.2.7 |
| Exploratory | • PGA | | | | 4.2.7 |
| **Objective 3**: To evaluate the PK and immunogenicity of brazikumab. | | | | | |
| Exploratory | • Serum concentration of brazikumab | PK | N/A | Descriptive statistics | 4.2.5 |
| Exploratory | • Serum ADAs | ADA | N/A | Descriptive statistics | 4.5 |

| *Statistical category* | *Endpoint* | *Analysis Population* | *Intercurrent event strategy* | *Population level summary (analysis)* | *Details in section* |
|---|---|---|---|---|---|
| **Objective 4**: To explore transcriptional, histological, protein, microbiome, and clinical biomarkers in UC participants who previously completed or discontinued participation due to lack of efficacy after Week 10 in the lead-in Study D5272C00001 (Legacy #3151-201-008), and the effect of long-term brazikumab treatment on these biomarkers. | | | | | |
| Exploratory | • Serum, plasma, fecal, or gut tissue proteins; whole blood or gut transcriptional changes; histological, microbiome, and clinical lab assessments | FAS | N/A | Descriptive statistics will be presented for IL-22, CRP, and FCP. Analysis for other assessments to be developed in separate SAP and reported outside of the CSR. | 4.3 |

ADA = Anti-drug antibodies; AE = adverse event; CRP = C-reactive protein; CSR = Clinical study report; ECG = electrocardiogram; EQ-5D-5L = European Quality of Life-5 Dimensions; FAS = Full analysis set; FCP = Fecal calprotectin; GHI = Geboes Histological Index; IBDQ = Inflammatory Bowel Disease Questionnaire; IL-22 = Interleukin-22; mMS = modified Mayo Score; NRI = Non-responder imputation; PGA = Physician's Global Assessment; PK = Pharmacokinetic; PRO = patient reported outcome; RHI = Robarts Histopathology Index; SAP = Statistical analysis plan; SF36-v2 = 36-Item Health Survey Version 2; UC = Ulcerative colitis.

### 4.2.1 Primary Endpoint

The primary endpoints are safety endpoints (See Section 4.6).

### 4.2.2 Secondary Endpoint

There are no secondary endpoints in this study.

### 4.2.3 Exploratory Endpoint: mMS

#### 4.2.3.1 Definition

mMS is defined in Appendix 7.1. Baseline is defined in Section 3.3.1.2.

#### 4.2.3.2 Derivation

Change from Baseline will be calculated at Week 0 and at Week 52 as defined in Section 3.3.1.2.

#### 4.2.3.3 Handling of Dropouts and Missing Data

**Missing PRO components**

If there are not 3 days with data from the 7 days prior to the Week 52 endoscopy, the score will be set to missing and the participant will be imputed as a nonresponder.

**Missing endoscopy component**

Any endoscopy performed outside the 7 day window around the Week 52 scheduled visit will be considered missing. If the missing mMS score is due to missing endoscopy subscore, it may be imputed from the most recent data from any unscheduled visit during the Treatment Period. If mMS is still missing, then Change from Baseline will be set to missing.

#### 4.2.3.4 Primary Analysis of Exploratory Endpoint

mMS Change from Baseline will be descriptively summarized. Time points include Week 0 (i.e., the last assessment before the first dose of OLE treatment), and Week 52.

##### 4.2.3.4.1 Presentation

Descriptive statistics will be presented for the FAS at Week 0 and Week 52. The values of PRO components used in derivation of the mMS will be presented in a listing.

### 4.2.4 Exploratory Endpoint: Change from Baseline in Patient Reported Outcomes in Site Visits

- IBDQ Change from Baseline at Weeks 0, 12, and 52
- SF-36v2 Change from Baseline at Weeks 0, 12, and 52
- EQ-5D-5L Change from Baseline at Weeks 0, 12, and 52

#### 4.2.4.1 Definition

**Inflammatory Bowel Disease Questionnaire (IBDQ)**

The IBDQ is presented in Appendix F 2.1 of the CSP, and measures Health Related Quality of Life (HRQoL) in participants with inflammatory bowel disease (IBD). It will be assessed during the site visit at Weeks 0, 12 and 52 (Week 12 for Induction groups only). It covers how the participant has been feeling in the past two weeks (Guyatt et al, 1989). Four dimensions are covered: bowel symptoms (10 items), systemic symptoms (5 items), emotional function (12 items), and social function (5 items). Items are scored on a 7-point Likert scale (from 1 [worse] to 7 [better]). The total score is obtained by summing the score from each item, yielding a global score in the range 32 to 224 (with higher scores indicating better quality of life).

**SF-36v2**

The SF-36v2 (SF36) is presented in Appendix F 2.2 of the CSP and will be assessed at Baseline and during site visits at Weeks 0, 12, and 52 (Week 12 for Induction groups only). It is a standardized instrument used to measure self-reports of health status and functional well-being. It consists of 8 domains: physical functioning (10 questions, #3a to 3j), role physical (4 questions, #4a to 4b), bodily pain (2 questions, #7 and 8), general health (5 questions, #1,11a to 11d), vitality (4 questions, #9a, 9e, 9g, 9i), social functioning (2 questions, #6, #10), role emotional (3 questions, #5a to 5c), and mental health (5 questions, #9b to 9d, 9f, 9h). The subscores from the 8 dimensions can be directly calculated. Two summary indices can be scored: the Physical Component Score (PCS) and the Mental Component Score (MCS). The lower the score, the more disability (Brazier, Roberts, and Deverill, 2002).

**EQ-5D-5L**

The EQ-5D-5L is presented in Appendix F 2.1 of the CSP and will be assessed at Baseline and during site visits at Weeks 0, 12, and 52 (Week 12 for Induction groups only). The EQ-5D-5L includes a VAS that allows respondents to rate their own current health on a 101-point scale ranging from “best imaginable” to “worst imaginable” health.

#### 4.2.4.2 Derivation

For each Week, Change from Baseline will be calculated as defined in Section 3.3.1.2.

**IBDQ**

The mapping of items to the 4 subscores is found in Table 4-4 along with the maximum score per dimension, calculated by summing the response to each item in the subscore.

**Table 4-4 IBDQ subscores**

| *Subscore* | *Item numbers* | *Max points* |
|---|---|---|
| Bowel symptoms | 1,5,9,13,17,20,22,24,46,29 | 70 |
| Systemic symptoms | 2,6,10,14,18 | 35 |
| Emotional function | 3,7,11,15,19,21,13,15,17,30,31,32 | 84 |

| | | |
|---|---|---|
| Social function | 4,8,12,16,28 | 35 |

Each of the 4 IBDQ domain scores is calculated by summing the responses from the items in that domain, as defined in Table 4-4. The total score is calculated as the sum of each domain score (Irvine 1999) and will range from 32 to 224. Change from Baseline is calculated for the total score and subscores. A positive Change from Baseline value indicates increased quality of life compared to Baseline.

**SF-36v2**

The SF36 will be scored using the algorithm provided by Optum with the instrument license (Health Outcomes™ Scoring Software 4.5 or higher). Change from Baseline is calculated for the PCS and MCS.

**EQ-5D-5L**

Change from Baseline is calculated for the 101-point scale. A negative Change from Baseline value indicates a worse health state.

#### 4.2.4.3 Handling of Dropouts and Missing Data

IBDQ, SF36, and EQ-5D-5L will be administered at the site. If a participant discontinues early or misses a Visit, the scores for that Visit will be set to missing.

If more than half of the items in a subscore are missing for the IBDQ, the total score will be set to missing as well as that subscore. Otherwise, substitution of the mean of the remaining items in the subscore can be imputed for that subscore (Han 1998).

The SF36 is scored by averaging items in the same subscale. A missing value is given for a scale if over half of the items are missing. If a question is missing (not completed by the participant), the average for a subscale will be based on the non-missing questions and the total score calculated as usual. The PCS and the MCS can be calculated if:

1. at least 7 scale scores are available
2. the PF scale is not missing when evaluating the PCS
3. the MH scale is not missing when calculating the MCS

The scoring algorithm to apply to the calculation of summary scores depends on which scale score is missing from the eight-scale profile.

Per the EQ-5D-5L user guide (EQ-5D-5L User Guide, 2019), missing values should be coded as ‘9’, or ‘999’ for the VAS. These should be set to missing prior to analysis.

#### 4.2.4.4 Primary Analysis of Exploratory Endpoints

Descriptive statistics will be calculated for IBDQ subscores and total score, SF-36 PCS and MCS, and EQ-5D-5L VAS separately for each Visit, by treatment group and overall.

##### 4.2.4.4.1 Presentation

Descriptive statistics will be presented for each Visit, by treatment group and overall. Week 12 results will only be reported for participants receiving Induction treatment. A listing of IBDQ subscores and SF-36V2 domain and component scores will be presented. Listings of the 5 elements and the "current health" scale will be presented for the EQ-5D-DL.

### 4.2.5 Exploratory Endpoint: Evening Diary

#### 4.2.5.1 Definition

Stool frequency, rectal bleeding, urgency, worst abdominal pain, worst fatigue, worst tiredness, worst weakness, worst lack of energy, worst joint pain, and frequency/severity of flatulence are collected from the Evening Diary as described in the CSP Appendix F1.

#### 4.2.5.2 Derivation

For each item, the average value will be calculated as the mean over the most recent 3 days of the 7 days prior to the visit (exclusive of bowel prep and endoscopy). Change from Baseline for each Week will be calculated as defined in Section 3.3.1.2.

#### 4.2.5.3 Handling of Dropouts and Missing Data

If 3 days of data are not available for the 7 days prior to the visit, the value will be set to missing and their data will not be included in the summary table.

#### 4.2.5.4 Primary Analysis of Exploratory Endpoints

Descriptive statistics will be calculated for each item at each Visit, by treatment group and overall.

##### 4.2.5.4.1 Presentation

Descriptive statistics will be presented for each item at each Visit, by treatment group and overall. Week 12 results will be reported only for participants receiving Induction treatment. The responses for the days used for calculating the scores, as well as the derived scores, will be presented in a listing.

### 4.2.6 Exploratory Endpoint: GHI and RHI

#### 4.2.6.1 Definition

Geboes Histological Index (GHI) is a measure of the degree of mucosal inflammation as follows: 0 = structural change only; 1 = chronic inflammation; 2a = lamina propria

eosinophils; 2b = lamina propria neutrophils; 3 = neutrophils in epithelium; 4 = crypt destruction; and 5 = erosions or ulcers. The Geboe's score ranges from 0 to 5.4 (Geboes, et al, 2000). The Robarts Histopathology Index (RHI) is calculated based on information from the GHI and contains 4 histological descriptors: severity of chronic inflammatory infiltrate, the number of lamina propria neutrophils, the number of neutrophils in the epithelium, and the severity of erosions or ulceration. Table 4-5 lists the GHI scores and their translation to RHI scores.

**Table 4-5 GHI and RHI grading**

| *Grade* | *Subgrades* | *Conversion to RHI* |
|---|---|---|
| Grade 0: structural changes | 0.0 No abnormality<br>0.1 Mild abnormality<br>0.2 Mild or moderate diffuse or multifocal abnormalities<br>0.3 Severe diffuse or multifocal abnormalities | N/A |
| Grade 1: chronic inflammatory infiltrate | 1.0 No increase<br>1.1 Mild but unequivocal increase<br>1.2 Moderate increase<br>1.3 Marked increase | 0<br>1<br>2<br>3 |
| Grade 2A: eosinophils | 2A.0 No increase<br>2A.1 Mild but unequivocal increase<br>2A.2 Moderate increase<br>2A.3 Marked increase | N/A |
| Grade 2B: neutrophils | 2B.0 None<br>2B.1 Mild but unequivocal increase<br>2B.2 Moderate increase<br>2B.3 Marked increase | N/A |
| Grade 3: neutrophils in epithelium | 3.0 None<br>3.1 < 5% crypts involved<br>3.2 < 50% crypts involved<br>3.3 > 50% crypts involved | 0<br>1<br>2<br>3 |
| Grade 4: crypt destruction | 4.0 None<br>4.1 Probable- local excess of neutrophils in part of the crypt<br>4.2 Probable – marked attenuation<br>4.3 Unequivocal crypt destruction | |
| Grade 5: erosion or ulceration | 5.0 No erosion, ulceration, or granulation tissue<br>5.1 Recovering epithelium + adjacent inflammation<br>5.2 Probable erosion, focally stripped<br>5.3 Unequivocal erosion<br>5.4 Ulcer or granulation tissue | 0<br>1<br>1<br>2<br>3 |

The total RHI is calculated as follows in Table 4-6:

**Table 4-6 RHI derivation**

| *Descriptor* | *Responses* | *Scoring metric* |
|---|---|---|
| Severity of chronic inflammatory infiltrate | 0= none<br>1= mild but unequivocal increase<br>2= moderate increase<br>3= marked increase | × 1 |
| Lamina propria neutrophils | 0= none<br>1= mild but unequivocal increase<br>2= moderate increase<br>3= marked increase | × 2 |
| Neutrophils in epithelium | 0= none<br>1= < 5% crypts involved<br>2= <50% crypts involved<br>3= >50% crypts involved | × 3 |
| Erosion or ulceration | 0= no erosion, ulceration of granulation tissue<br>1= recovering epithelium + adjacent inflammation<br>1= probable erosion – focally stripped<br>2= unequivocal erosion<br>3= ulcer or granulation tissue | × 5 |
| | ***Total*** | Σ |

#### 4.2.6.2 Derivation

The biopsies that are obtained during the endoscopy at Screening and Week 52 will be scored according to the GHI by the central pathologist as 0, 1, 2a, 2b, 3, 4, or 5.

Each component of the RHI will also be graded between 0 and 3 based on information from the GHI. Using the scoring table above, the RHI can be calculated as: 1 × chronic inflammatory infiltrate level + 2 × lamina propria neutrophils + 3 × neutrophils in epithelium + 5 × erosion or ulceration, yielding a score that ranges from 0 (no disease activity) to 33 (severe disease activity) (Mosli, et al, 2015).

Change from Baseline for RHI will be calculated as defined in Section 3.3.1.2.

#### 4.2.6.3 Handling of Dropouts and Missing Data

If the Week 52 endoscopy is missing, data from the nearest ET or unscheduled visit prior to Week 52 may be used. Otherwise, GHI and RHI Change from Baseline will be set to missing.

#### 4.2.6.4 Primary Analysis of Exploratory Endpoints

GHI will be described as a categorical variable (1, 2A, 2B, 3, 4, 5) by treatment group and overall.

Descriptive statistics will be calculated for RHI Change from Baseline by treatment group and overall.

##### 4.2.6.4.1 Presentation

Descriptive statistics will be presented by treatment group and overall.

### 4.2.7 Exploratory Endpoints: Binary outcomes

- Clinical remission at Week 52
- Symptomatic remission at Week 12 (for participants receiving Induction treatment)
- Symptomatic remission at Week 52

#### 4.2.7.1 Definition

Intercurrent events are captured in the variable definition of binary endpoints as a participant who

- Discontinues the study intervention prematurely
- Takes rescue treatment (specified in Section 4.1.7)
- Uses prohibited medication (specified in Section 6.5.4 of the CSP)

Participants who experience any of these intercurrent events are considered as being unsuccessfully treated (Composite Strategy - ICH E9[R1]) and will be imputed as nonresponders (NRI).

#### 4.2.7.2 Derivation

Clinical remission at Week 52 is defined as meeting all of the following at Week 52:

- endoscopy subscore = 0 or 1, AND
- rectal bleeding subscore = 0, AND
- stool frequency subscore = 0 or 1, AND
- at least a 1 point decrease from Baseline.

Symptomatic remission is defined as

- rectal bleeding subscore =0 AND
- stool frequency subscore = 0 or 1, AND
- at least a 1 point decrease from Baseline.

#### 4.2.7.3 Handling of Dropouts and Missing Data

If the endoscopy subscore is missing for Week 52, it can be imputed using existing data from an unscheduled visit. Otherwise, the endoscopy score will be set to missing and clinical remission will be imputed as a nonresponder.

If PRO components (rectal bleeding subscore or stool frequency subscore) do not have 3 days with data from the 7 days prior to endoscopy, the score will be set to missing and the participant will be imputed as a nonresponder.

#### 4.2.7.4 Primary Analysis of Exploratory Endpoints

Descriptive statistics will be calculated by treatment group and overall.

#### 4.2.7.4.1 Presentation

Categorical descriptive statistics will be presented by treatment group and overall. Symptomatic remission at Week 12 will only be presented for participants receiving Induction treatment in the OLE. The responses for the days used for calculating the scores, as well as the derived scores, will be presented in a listing.

### 4.2.8 Exploratory Endpoint: Physicians' Global Assessment

- Physicians' Global Assessment (PGA) improvement at Weeks 12 and 52

#### 4.2.8.1 Definition

The PGA evaluates the participant's symptoms, as well as the participant's general sense of well-being and other observations such as laboratory findings. The PGA is performed by a qualified physician.

#### 4.2.8.2 Derivation

The PGA categorizes disease as 0=normal, 1=mild, 2=moderate, and 3=severe. Change from Baseline will be defined as worsening (1 point, 2 points, 3 points), no change (0), or improvement (1 point, 2 points, 3 points).

#### 4.2.8.3 Handling of Dropouts and Missing Data

If the PGA is missing for Week 12 or Week 52, it can be imputed using existing data from an unscheduled visit. Otherwise, PGA Improvement will be set to missing.

#### 4.2.8.4 Primary Analysis of Exploratory Endpoints

Categorical descriptive statistics will be calculated by treatment group and overall.

#### 4.2.8.4.1 Presentation

Categorical descriptive statistics will be presented by treatment group and overall. PGA will be presented as number and percentage in each of the seven categories for OLE Screening, Week 12, and Week 52. Week 12 results will only be presented for participants receiving Induction treatment in the OLE. The PGA scores and Change from Baseline will also be listed.

## 4.3 Pharmacodynamic Endpoint(s)

Pharmacodynamic variables collected for this study include IL-22, serum C-reactive protein (CRP), and fecal calprotectin (FCP). Absolute values, Change from Baseline, and percentage Change from Baseline will be listed and summarized by treatment group using descriptive statistics for the FAS. Mean absolute values, mean Change from Baseline, and mean percentage Change from Baseline will be presented graphically by treatment group.

## 4.4 Pharmacokinetics

Serum samples for determination of brazikumab concentrations will be collected at Baseline prior to first study intervention administration, and pre-dose at Weeks 0, 12, 24 and 52 for brazikumab concentration (Week 12 sample will be collected for participants receiving Induction only).

Individual brazikumab serum concentrations for each nominal sampling time will be listed and summary descriptive statistics will be presented and plotted versus time for the PK analysis set. Individual brazikumab serum concentrations will be graphically illustrated and summarized by ADA status.

For each time point, the geometric mean, geometric standard deviation, coefficient of variation (CV), arithmetic mean, SD, median, minimum, and maximum will be reported as summary statistics.

Linear and log-linear mean (± SE) concentration profile plots against time will be produced for each treatment group, with nominal sampling time on the x-axis.

These descriptive statistics will be reported in the CSR. Further model-based evaluation of PK will be detailed in a separate PK analysis plan and reported outside the CSR.

## 4.5 Immunogenicity

Serum samples to measure the presence of anti-drug antibodies (ADAs) against brazikumab (binding antibodies and neutralizing antibodies) will be collected at Week 0 and Week 24. ADA results from each sample will be reported as either positive or negative. If the sample is positive, the ADA titer will be reported as well. In addition, the presence of nAb will be tested for all ADA-positive samples.

### 4.5.1 Derivations

The number and percentage of ADA-evaluable participants in the following ADA categories in each treatment group and overall will be determined. The number of ADA-evaluable participants in the treatment group will be used as the denominator for percentage calculation.

- ADA positive at any visit (at baseline and/or post-baseline). The percentage of these participants in a population is known as ADA prevalence.
- Treatment-emergent ADA positive (sum of treatment-induced ADA positive and treatment-boosted ADA positive). The percentage of these participants in a population is known as ADA incidence.
- Treatment-induced ADA positive (ADA negative at baseline and ADA positive at >=1 post-baseline assessment).
- Treatment-boosted ADA positive (baseline ADA titer that was boosted by ≥4-fold following OLE study intervention administration).

- Treatment-emergent ADA negative (ADA positive but not fulfilling the definition of TE-ADA positive).
- ADA positive at baseline and post-baseline.
- ADA positive at baseline and not detected post-baseline.
- Treatment-emergent ADA (TE-ADA) persistently positive, defined as treatment-emergent ADA positive participants having at least 2 post-baseline ADA positive measurements at least 16 weeks (112 days) between the first and last positive measurement, or an ADA positive result at the last available assessment.
- Treatment-emergent ADA (TE-ADA) transiently positive is defined as treatment-emergent ADA positive participants not fulfilling the conditions for TE-ADA persistently positive.
- Neutralizing Antibody (nAb) positive is defined as nAb positive at any time baseline and/or post-baseline (nAb prevalence).
- Treatment-induced nAb positive (nAb incidence).
- Treatment-emergent ADA positive with maximum titre > median of maximum titre (calculated based on the maximum titre for each ADA positive subject within each treatment group).

### 4.5.2 Primary analysis of ADA

A summary of the number and percentage of participants who developed positive ADA by ADA categories (Section 4.5.1) in different treatment groups and overall will be presented based on the ADA evaluable analysis set. In addition, descriptive statistics of the maximum titer will be presented by ADA category. ADA results and titers will be summarized by visit and treatment group.
Additional immunogenicity outcomes may be described in separate analysis plans and will be reported separately.

## 4.6 Safety Analyses

Safety data will be summarized descriptively using the Safety analysis set. The safety parameters will include AEs, clinical laboratory, vital signs, physical examinations, and ECG parameters. Continuous variables will be summarized by the number of participants and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

### 4.6.1 Exposure

#### 4.6.1.1 Definitions and Derivations

Exposure to the study intervention will be calculated as the number of days from the first study intervention in the OLE to 28 days after the last study intervention for the study for the Safety Population. Any gaps in dosing will be ignored when calculating the total.

#### 4.6.1.2 Presentation

Exposure to the study intervention (in days) for the Safety Population will be listed and summarized by treatment group. Participants who received Vedolizumab/Brazikumab will only be included in the listings.

### 4.6.2 Adverse Events

Adverse events will be coded by system organ class and preferred term using the MedDRA, version 24.0 or newer.

#### 4.6.2.1 Definitions and Derivations

Adverse event data will be categorized according to their onset date based on the last dose of investigational product as follows:

- An AE occurring during the Treatment Period is defined as an AE with a date of onset ≥ the first dose of investigational product in the OLE and ≤ 28 days after the last dose of investigational product.
- An AE occurring during the Study Period that occurs during treatment, including follow-up, is defined as an AE with a date of onset ≥ day of first dose of investigational product in the OLE and ≤ 18 weeks after the last dose of investigational product.
- An AE occurring during the LDI Treatment Period and is still ongoing during the OLE treatment period is defined as an AE occurring during the LDI+OLE Treatment Period with a date of onset ≥ day of first dose of investigational product in LDI and ≤ 28 days after the last dose of investigational product in the OLE.

Per case report form instructions, a new AE record will be created for any AE that worsens.

**Treatment related**

An AE will be considered as treatment related if the investigator considers that there is a reasonable possibility that the event may have been caused by the investigational product.

**Serious**

An AE will be considered a serious AE (SAE) if it is an AE that additionally meets any SAE criteria (as recorded on the AE form of the eCRF).

**Missing Severity Assessment**

Adverse events with missing severity are assumed to be severe. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

**Missing Causal Relationship to Study Intervention**

If the causal relationship to the study intervention is missing for an AE that started on or after the date of the first dose of the study intervention, a causality of yes will be assigned. The imputed values for causal relationship during the Treatment Period will be used for the incidence summary; the values will be shown as missing in the data listings.

**Missing Date Information for Adverse Events**

See Appendix 7.3 for missing date imputation rules.

#### 4.6.2.2 Presentation

Adverse Events will be reported for the Treatment Period and Study Period (Treatment Period + Safety Follow-up Period). The end of the Treatment Period is defined as the date of last dose of study intervention + 28 days. The end of the Follow-up Period is defined as the date of last dose of study intervention + 18 weeks.

For the Safety analysis set, the following events will be summarized by treatment group:

- Overall summary of AE, including
  - Any AE
  - Any SAE
  - Any SAE with outcome death
  - Any AE leading to discontinuation of IP
  - Any possibly related AE
  - Any possibly related SAE
- AE by SOC and PT
- AE sorted by decreasing frequency on preferred term level
- AE by maximum reported intensity on preferred term level
- Possibly related AE by SOC and PT
- AE per subject year by SOC and PT.
- Adverse events of special interest (AESI)
- SAE with outcome death by SOC and PT
- SAE by SOC and PT
- Possibly related SAE by SOC and PT
- AE leading to discontinuation of investigational product by SOC and PT

The incidence of common (> 5% of participants in any treatment group) non-serious AEs will be summarized by system organ class, preferred term, and treatment group.

If more than 1 AE is coded to the same preferred term for the same participant, the participant will be counted only once for that preferred term using the most severe severity for the summaries by severity. Similarly, the participant will be counted using the closest relationship for summaries by causality.

Listings of AEs, deaths, SAEs, and AEs leading to discontinuation of the investigational product by participant will be presented, to include key subject information, including Participant identifier, sex, age, event term as reported, AE (PT), time from first dose to AE onset, treatment period, last dose prior to event, outcome, time from first dose to outcome, and AE relationship to study intervention. Key subject information will be presented for the Treatment Period and Study Period (Treatment Period + Safety followup Period). In addition, key subject information for subjects with an AE that occurred during the LDI study and has let to discontinuation of investigational product due to that AE in the OLE study will also be presented for the LDI+ OLE Treatment Period.

AESI will be summarized and include infusion related reactions, injection-site reactions, malignancies, hypersensitivity (including anaphylaxis), and infections.

### 4.6.3 Clinical Laboratory, Blood Sample

#### 4.6.3.1 Definitions and Derivations

The following are protocol-required laboratory parameters as listed in Table 4-7 through **Table 4-9**. Clinical chemistry, CRP, and hematology will be carried out at Weeks 12, 24, 36, 52, unscheduled visits and ED or ET.

**Table 4-7 Protocol-Required Safety Laboratory Assessments**

| ***Laboratory Assessments*** | ***Parameters*** | | |
|---|---|---|---|
| Hematology | Platelet count<br>RBC count<br>Hemoglobin<br>Hematocrit | RBC indices:<br>MCV<br>MCH<br>% Reticulocytes | WBC count with differential:<br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils |
| Clinical Chemistry | BUN<br>C-reactive protein<br>Creatinine<br>eGFR<br>Glucose (non-fasting)<br>Magnesium<br>Uric acid | AST<br>ALT<br>ALP<br>Albumin<br>Potassium<br>Sodium<br>Calcium<br>Chloride | Total and direct bilirubin<br>Total protein<br>Bicarbonate<br>Phosphate |
| Fecal tests | • Fecal calprotectin<br>• Fecal lactoferrin | | |
| Routine urinalysis | • Specific gravity<br>• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick<br>• Microscopic examination (reflexively as needed) | | |
| Other Tests | • FSH (as needed in women of non-childbearing potential only)<br>• Serum hCG pregnancy test or FSH when applicable is required at screening, as needed for women of childbearing potential. All other pregnancy testing will consist of urine pregnancy testing performed locally at each visit prior to administering study intervention and as outlined in the SoA. For participants who are postmenopausal, an FSH level is to be obtained at screening (see Section 5).<br>• All study-required laboratory assessments will be performed by a central laboratory unless indicated (eg, local urine hCG testing). | | |

ALP=Alkaline Phosphate ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; IgM = immunoglobulin M; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; PT = prothrombin time; RBC = red blood cell; TB = tuberculosis; WBC = white blood cell.

**Table 4-8 Normal ranges for laboratory values (Central Laboratory Services Manual)**

| *Laboratory Parameter* | *LLN - Male* | *ULN- Male* | *LLN – Female* | *ULN- Female* | *SI Unit* |
|---|---|---|---|---|---|
| **Hematology** | | | | | |
| Hemoglobin | Age 12-59: 127<br>Age >59: 125 | Age 12-59: 181<br>Age >59:170 | Age 12-59: 116<br>Age >59: 115 | Age 12-59: 164<br>Age >59: 158 | g/L |
| Hematocrit | Age 12-59: 0.39<br>Age >59: 0.37 | Age 12-59: 0.54<br>Age >59: 0.51 | 0.34 | 0.48 | Ratio |
| RBC | Age 12-59: 4.5<br>Age >59: 4.0 | Age 12-59: 6.4<br>Age >59: 5.8 | Age 12-59: 4.1<br>Age >59: 3.9 | Age 12-59: 5.6<br>Age >59: 5.5 | TI/L |
| Eosinophils | 0.00 | 0.57 | 0.00 | 0.57 | GI/L |
| Neutrophils | 40.5 | 75.0 | 40.5 | 75.0 | % |
| Basophils | 0.00 | 0.20 | 0.00 | 0.20 | GI/L |
| Monocytes | 0.12 | 0.92 | 0.12 | 0.92 | GI/L |
| Lymphocytes | Age 18-59: 0.91<br>Age >59: 0.80 | Age 18-59: 4.28<br>Age >59:3.00 | Age 18-59: 0.91<br>Age >59: 0.80 | Age 18-59: 4.28<br>Age >59: 3.00 | GI/L |
| Absolute neutrophil count | 1.96 | 7.23 | 1.96 | 7.23 | GI/L |
| Platelet count | Age 12-60: 140<br>Age > 60: 130 | Age 12-60: 400<br>Age > 60: 394 | Age 12-60: 140<br>Age > 60: 130 | Age 12-60: 400<br>Age > 60: 394 | 10^9/L |
| **Clinical chemistry** | | | | | |
| Albumin | Age 18-69: 33<br>Age >69: 33 | Age 18-69: 49<br>Age >69: 46 | Age 18-69: 33<br>Age >69: 33 | Age 18-69: 49<br>Age >69: 46 | g/L |
| Alkaline phosphatase | Age 18-19: 55<br>Age >19: 40 | Age 18-19: 149<br>Age > 19: 129 | Age 18-19: 45<br>Age > 19: 35 | Age 18-19: 87<br>Age > 19: 104 | U/L |
| Alanine aminotransferase (ALT) | Age 18-69: 6<br>Age > 69: 6 | Age 18-69: 43<br>Age > 69: 35 | Age 18-69: 6<br>Age > 69: 6 | Age 18-69: 34<br>Age > 69: 32 | U/L |
| Aspartate aminotransferase (AST) | 11 | 36 | 9 | 34 | U/L |
| Blood urea nitrogen or Urea | 1.4 | Age 18-70: 8.6<br>Age >70: 10.4 | 1.4 | Age 18-70: 8.6<br>Age >70: 10.4 | mmol/dL |
| Calcium | 2.07 | 2.64 | 2.07 | 2.64 | mmol/dL |
| Chloride | 94 | 112 | 94 | 112 | mmol/L |
| Creatinine | 40 | Age 18-50: 110<br>Age 50-70: 119<br>Age >70: 137 | 31 | Age 18-70: 101<br>Age >70: 110 | µmol/L |
| Glucose, nonfasting | 3.9 | 5.6 | 3.9 | 5.6 | mmol/L |
| Magnesium | Age 18-20: 0.70<br>Age 20-60: 0.66<br>Age >60: 0.66 | Age 18-20: 0.90<br>Age 20-60: 1.07<br>Age >60: 0.98 | Age 18-20: 0.70<br>Age 20-60: 0.66<br>Age >60: 0.66 | Age 18-20: 0.90<br>Age 20-60: 1.07<br>Age >60: 0.98 | mmol/L |
| Potassium | 3.5 | 5.2 | 3.5 | 5.2 | mmol/L |
| Sodium | Age 18-59: 132 | Age 18-59: 147 | Age 18-59: 132 | Age 18-59: 147 | mmol/L |

| *Laboratory Parameter* | *LLN - Male* | *ULN- Male* | *LLN – Female* | *ULN- Female* | *SI Unit* |
|---|---|---|---|---|---|
| | Age >59: 135 | Age >59: 145 | Age >59: 135 | Age >59: 145 | |
| Total bilirubin | 3 | 21 | 3 | 21 | µmol/L |
| Total protein | Age 18-59: 61<br>Age >59: 60 | Age 18-59: 84<br>Age >59: 80 | Age 18-59: 61<br>Age >59: 60 | Age 18-59: 61<br>Age >59: 60 | g/L |
| Uric acid or Urate | Age 18-50: 125<br>Age > 50: 149 | Age 18-50: 488<br>Age >50: 494 | Age 18-50: 125<br>Age >50: 149 | Age 18-50: 428<br>Age >50: 446 | mg/dL |

Blood urea nitrogen or Urea are the same parameters, and Uric acid or Urate are the same parameters.
LLN = lower limit of normal; ULN = upper limit of normal laboratory reference range.

## Table 4-9 Criteria for Potentially Clinically Significant Laboratory Values

| *Laboratory Parameter* | *SI Unit* | *Conversion Factor*[a] | *Conventional Unit* | *PCS Criterion*[b] *Low Value* | *PCS Criterion*[b] *High Value* |
|---|---|---|---|---|---|
| **Hematology** | | | | | |
| Hemoglobin | g/L | 0.1 | g/dL | < 0.9 × LLN | |
| Hematocrit | Volume fraction | 100 | % | < 0.9 × LLN | |
| Eosinophils | % | 1 | % | — | > 10 |
| Neutrophils | % | 1 | % | < 30 | > 90 |
| Basophils | % | 1 | % | — | > 6 |
| Monocytes | % | 1 | % | — | > 20 |
| Lymphocytes | % | 1 | % | < 10 | > 60 |
| Absolute neutrophil count | $\times 10^9$/L | 1 | 1000/µL | < 1.0 | — |
| Platelet count | $\times 10^9$/L | 1 | 1000/µL | ≤ 75 | ≥ 700 |
| White blood cell count with differential | $\times 10^9$/L | 1 | 1000/µL | ≤ 2.5 | ≥ 15 |
| **Chemistry** | | | | | |
| Albumin | g/L | 0.1 | g/dL | < 0.9 × LLN | > 1.1 × ULN |
| Alkaline phosphatase | U/L | 1 | U/L | — | ≥ 3 × ULN |
| Alanine aminotransferase (ALT) | U/L | 1 | U/L | — | ≥ 3 × ULN |
| Aspartate aminotransferase (AST) | U/L | 1 | U/L | — | ≥ 3 × ULN |
| Blood urea nitrogen or Urea | mmol/L | 2.8011 | mg/dL | — | > 1.2 × ULN |
| Calcium | mmol/L | 4.008 | mg/dL | < 0.9 × LLN | > 1.1 × ULN |
| Chloride | mmol/L | 1 | mg/dL | < 0.9 × LLN | > 1.1 × ULN |
| Creatinine | µmol/L | 0.0113 | mg/dL | — | > 1.3 × ULN |

| *Laboratory Parameter* | *SI Unit* | *Conversion Factor*[a] | *Conventional Unit* | *PCS Criterion*[b] *Low Value* | *PCS Criterion*[b] *High Value* |
|---|---|---|---|---|---|
| Glucose, nonfasting | mmol/L | 18.018 | mg/dL | < 0.8 × LLN | > 1.2 × ULN |
| Magnesium | mmol/L | 2 | mEq/L | < 0.9 × LLN | > 1.1 × ULN |
| Potassium | mmol/L | 1 | mEq/L | < 0.9 × LLN | > 1.1 × ULN |
| Sodium | mmol/L | 1 | mEq/L | < 0.9 × LLN | > 1.1 × ULN |
| Total bilirubin | µmol/L | 0.0585 | mg/dL | — | > 1.5 × ULN |
| Total protein | g/L | 0.1 | g/dL | < 0.9 × LLN | > 1.1 × ULN |
| Uric acid or Urate | µmol/L | 0.0168 | mg/dL | — | > 1.1 × ULN |

[a] Conversion factor from SI units to conventional (traditional) units.
[b] Criteria refer to SI units.
Blood urea nitrogen or Urea are the same parameters, and Uric acid or Urate are the same parameters.
LLN = lower limit of normal; PCS = potentially clinically significant; SI = *Le Système International d'Unités* (International System of Units); ULN = upper limit of normal laboratory reference range.

Clinical laboratory test values will be considered potentially clinically significant (PCS) if they meet either the lower-limit or higher-limit PCS criteria listed in Table 4-9.

#### 4.6.3.2 Presentation

Lead-in Baseline, Week 0 (i.e., the last assessment prior to OLE dose), Weeks 12, 24, 36, 52, and change from baseline for hematology and clinical chemistry parameters will be listed and summarized in SI units by treatment group for the Safety analysis set.

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table because, for example, a character string is reported for a parameter of the numeric type, a coded value must be appropriately determined for use in the statistical analyses. The actual values, however, as reported in the database will be presented in the data listings.

The number and percentage of participants who have PCS post baseline clinical laboratory values will be tabulated by treatment group. The percentages will be calculated relative to the number of participants with available baseline values and at least 1 post baseline assessment for the Treatment Period. The numerator will be the total number of participants with available baseline values and at least 1 PCS post baseline value for the Treatment Period. A supportive listing of participants with PCS post baseline values will be provided, including the PID number, baseline and all post baseline (including non-PCS) values.

In addition, a listing with key subject information showing all AEs that occurred in participants who had PCS post baseline clinical laboratory values will be provided.

Chemistry lab results will be similarly listed and summarized with descriptive statistics.

### 4.6.4 Clinical Laboratory, Urinalysis

#### 4.6.4.1 Definitions and Derivations

Urinalysis will be carried out at Week 52, unscheduled visit and ED or ET. Routine urinalysis includes specific gravity, glucose, protein, ketones, bilirubin, urobilinogen, nitrite, and

leukocyte esterase, all of which are considered a high value if 2+. In addition, pH normal range is ≥ 5 to ≤ 8. Microscopic examination is performed as needed.

#### 4.6.4.2 Presentations

Listing of urinalysis results, including Lead-in Baseline, for the Safety analysis set will be provided. A shift table from Baseline to the end of the Treatment Period will be presented by treatment group. Treatment emergent urinalysis abnormalities will be summarized by treatment group.

### 4.6.5 Other Laboratory Evaluations

#### 4.6.5.1 Definitions and Derivations

Other laboratory testing is presented in the CSP Appendix E 6.

#### 4.6.5.2 Presentations

Positive pregnancy and other screening tests will be listed.

### 4.6.6 Physical Examinations

#### 4.6.6.1 Definitions and Derivations

A complete physical examination will include assessments of the respiratory, cardiovascular, gastrointestinal, and neurological systems. Physical examinations will be performed at Weeks 0, 12, 24, 36, 52, and unscheduled as well as E/T or ED.

Any new findings or aggravated existing abnormalities, judged as clinically significant by the investigator, will be reported as an AE.

### 4.6.7 Vital Signs

#### 4.6.7.1 Definitions and Derivations

Vital signs will be collected at every Visit and include:

- Body temperature
- Pulse rate
- Respiratory rate
- Blood pressure
- Height (Screening Visit only) recorded in centimeters
- Weight, recorded in kilograms

Vital sign values will be considered PCS if they meet both the observed value criterion and the Change from Baseline value criterion, if both criteria are available, or meet either the observed value criterion or the change from baseline value criterion detailed in Table 4-10.

**Table 4-10 Criteria for Potentially Clinically Significant Vital Signs**

| *Parameter* | *Flag* | *Criteria*[a] | |
|---|---|---|---|
| | | *Observed Value* | *Change from Baseline* |
| Sitting systolic blood pressure, mm Hg | High | ≥ 140 | Increase of ≥ 20 |
| | Low | < 90 | Decrease of ≥ 20 |
| Sitting diastolic blood pressure, mm Hg | High | ≥ 90 | Increase of ≥ 15 |
| | Low | < 60 | Decrease of ≥ 15 |
| Sitting pulse rate, bpm | High | ≥ 100 | Increase of ≥ 15 |
| | Low | ≤ 60 | Decrease of ≥ 15 |
| Weight, kg | High | — | Increase of ≥ 7% |
| | Low | — | Decrease of ≥ 7% |

[a] A postbaseline value is considered potentially clinically significant if it meets both the observed-value and the change-from-baseline criteria.
bpm = beats per minute; hG = Mercury

#### 4.6.7.2 Presentation

A listing and summary of descriptive statistics for vital signs (systolic and diastolic blood pressures, pulse rate, body temperature, respiratory rate, and weight) values at lead-in Baseline, Week 0 (i.e., the last assessment prior to first OLE dose), all post baseline visits, and change from baseline values at each post baseline timepoint will be presented by treatment group for the Safety analysis set. This by-visit summary is based on the visit name as collected in eCRF.

The number and percentage of participants who have PCS post baseline vital sign values will be tabulated by treatment group for each assessment. The percentages will be calculated relative to the number of participants who have available baseline values and at least 1 post baseline assessment for the Treatment Period. The numerator will be the total number of participants with at least 1 PCS postbaseline value for the Treatment Period. A supportive listing with PCS postbaseline values will be provided.

In addition, a listing showing all AEs that occurred in participants who had PCS post baseline vital sign values will be provided.

### 4.6.8 Electrocardiogram

#### 4.6.8.1 Definitions and Derivations

Single 12-lead ECGs will be obtained during Week 52 and E/T visits using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. The upper limit for each measure is shown in Table 4-11.

**Table 4-11 Criteria for Potentially Clinically Significant Electrocardiograms**

| *Parameter* | *Unit* | *Low Value* | *Low Decrease* | *High Value* | *High Increase* |
|---|---|---|---|---|---|
| RR interval | msec | < 500 | NA | > 1500 | NA |
| PR interval | msec | NA | NA | ≥ 240 | NA |
| QRS duration | msec | ≤ 60 | NA | ≥ 140 | NA |
| QT | msec | ≤ 300 | NA | > 450 | > 60 |
| QTcF | msec | ≤ 300 | NA | > 480 | > 60 |
| QTcB | msec | ≤ 300 | NA | > 480 | > 60 |

QTc = QT interval corrected for heart rate.
QTcB = QT interval corrected for heart rate using the Bazett formula.
QTcF = QT interval corrected for heart rate using the Fridericia formula.

The outcome of the ECG evaluation is to be recorded as normal or abnormal in the eCRF, with any abnormalities recorded as either not clinically significant, or clinically significant.

#### 4.6.8.2 Presentation

A listing and summary of descriptive statistics for ECG parameters (i.e., heart rate, PR interval, QRS interval, QT interval, and QTc interval) at Baseline, Week 0 (i.e., the last assessment prior to first OLE dose), Week 52, and change from baseline values at Week 52 will be presented by treatment group for the Safety analysis set.

ECG parameter values are considered PCS if ECG values meet the value listed in Table 4-11. The number and percentage of participants with PCS post baseline values will be tabulated by treatment group. The percentages will be calculated relative to the number of participants with an available non-PCS Baseline value and at least one post baseline assessment during the Treatment Period. The numerator will be the total number of participants with an available non-PCS baseline value and at least one PCS post baseline ECG value during the Treatment Period. A supportive listing of participants with PCS post baseline values will be provided and will include the participant number and the baseline and post baseline values.

A listing of all AEs for participants with PCS ECG values will also be provided.

### 4.6.9 Other Safety Assessments

#### 4.6.9.1 Definitions and Derivations

Potential Hy's Law criteria is defined as a post baseline elevation of ALT or AST ≥ 3x ULN, and TBL ≥ 2x ULN, where at least one time Total Bilirubin ≥ 2x ULN occurred after the first occurrence of AST ≥ 3x ULN or ALT ≥ 3x ULN after start of treatment with investigational product.

Hy's Law is defined as ALT or AST ≥ 3× ULN together with total bilirubin ≥ 2× ULN, where for no other reason, other than study intervention, can be found to explain the combination of increases (e.g., elevated alkaline phosphatase indicating cholestasis, viral hepatitis, or another drug).

More information can be found in the CSP, Section 7.1 and CSP Appendix E3.

#### 4.6.9.2 Presentation

Participants with elevated liver tests based on measured laboratory values will be summarized for the Safety analysis set. Participants who meet the potential Hy's Law criteria from the first dose of the study intervention to within 18 weeks after the last dose of the study intervention will be listed and summarized by treatment group for the Safety.

# 5 INTERIM ANALYSIS

No interim analysis is planned for this study.

# 6 REFERENCES

Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology 1976; 70(3):439-44.

Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ. 2002 Mar;21(2):271-92. doi: 10.1016/s0167-6296(01)00130-8. PMID: 11939242.

EuroQol Research Foundation. EQ-5D-5L User Guide, 2019. Available from: https://euroqol.org/publications/user-guides.

Geboes K, Riddell R, Ost A, Jensfelt B, Persson T, Lofberg R. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. Gut. 2000 Sep:47(3):404-409.

Guyatt G, Mitchell A, Irvine EJ, et al. A New Measure of Health Status for Clinical Trials in Inflammatory Bowel Disease. Gastroenterology 1989;96:804-10.

Han SW, McCollE, Steen N, Barton JR, Welfare MR. The Inflammatory Bowel Disease Questionnaire: a valid and reliable measure in ulcerative colitis patients in the North East of England. Scand J Gastroenterol 1998;33:961-966.

Irvine EJ. Development and subsequent refinement of the inflammatory bowel disease questionnaire: a quality-of-life instrument for adult patients with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 1999 Apr;28(4):S23-7.

Loftus EV, Feagan BG, Colombel JF, Rubin DT, Wu EQ, Pollack PF, Chao J, Mulani P. Effects of adalimumab maintenance therapy on health-related quality of life of patients with Crohn's disease: patient-reported outcomes of the CHARM trial. Am J Gastroenterol 2008; 103:3132-3141.

Mosli MH, Feagan BG, Zou G, Sandborn WJ, D'Haens G, Khanna R et al. Development and validation of a histological index for UC. Gut. 2015;0:1-9. doi:10.1136/gutjnl-2015-310393.

Rubin GP, Hungin APS, Chinn DJ, Dwarakanath D. Quality of life in patients with established inflammatory bowel disease: a UK general practice survey. Aliment Pharmacol Ther 2004; 19:529-535.

Sandborn WJ, Vermeire S, Sands BE, et al. Defining Remission Using Patient-reported Outcome Components of the Crohn's Disease Activity Index: Post-hoc Analyses of Vedolizumab Data from the GEMINI 2 Study, American Journal of Gastroenterology: October 2015 - Volume 110 - Issue - p S792-S793.

Sands BE, Ooi CJ. A survey of methodological variation in the Crohn's disease activity index. Inflamm Bowel Dis. 2005; 11:133-38.

Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid 548 therapy for mildly to moderately active ulcerative colitis. N Engl J Med. 1987;317:1625-1629.

Spiegel B, Bolus R, Harris LA, et al. Measuring irritable bowel syndrome patient-reported outcomes with an abdominal pain numeric rating scale. *Aliment Pharmacol Ther*. 2009;30(11-12):1159-1170. doi:10.1111/j.1365-2036.2009.04144.x.

# 7 APPENDIX

## 7.1 Modified Mayo Score

Patient Reported Outcomes Questionnaire: mMS was removed due to copyrights.

## 7.2 Evening diary

Patient Reported Outcomes Questionnaire: Evening Diary was removed due to copyrights.

Patient Reported Outcomes Questionnaire: Evening Diary was removed due to copyrights.

Patient Reported Outcomes Questionnaire: Evening Diary was removed due to copyrights.

## 7.3 Missing start and stop dates

For adverse events and prior or concomitant medications, including rescue medications, incomplete (i.e., partly missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a participant, the start date will be imputed first.

### 7.3.1 Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

If the start date is missing, then it will be set to the date of the first study intervention, unless the end date suggests that the start date could be prior to the date of the first study intervention. In that case, set the start date to January 1 of the same year as the end date.

**Missing month and day**
The start date will be set to January 1 of the year of occurrence.

If the start year is the same as the year of the first study intervention, then the start date will be set to the date of first study intervention.

**Missing month only**
If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure.

**Missing day only**
The missing start day will be set to the first day of the month of occurrence if the start month and year is after the month and year of the first study intervention.

If the month and year of the incomplete start date are the same as the month and year of the first dose of the study intervention, the day of the first dose of the study intervention will be assigned to the missing day.

If the month and year of the incomplete start date is before the month and year of the first study intervention, the date of informed consent will be assigned to the incomplete date.

### 7.3.2 Incomplete Stop Date

Because participants will receive their study intervention doses under the direct supervision of study centre personal, the date of dose of study intervention will always be known. The following rules will be applied to impute missing date fields for an incomplete AE, prior, or concomitant medication stop date. If the imputed stop date is before the start date (imputed or non-imputed start date), the imputed stop date will be equal to the start date.

If the end date is missing and the event is not recorded as ongoing, then set the end date as the date of the first study intervention if the start date is prior to the date of the first study intervention. If the start date is on or after the date of first study intervention, set the end date to the date of last visit.

**Missing month and day**

If the year of occurrence is the same as the last study intervention year, then the incomplete date will be set to the date of last study intervention. If the year of the incomplete stop date is the same as the year of the last dose of study treatment, the month and day of the last dose of study treatment will be assigned to the missing fields.

If the year of the incomplete stop date is before the year of the last dose of study treatment, *December 31* of the year of occurrence will be assigned to the missing fields.

The stop date will be set to December 31 of the year of occurrence. If the participant died in the same year, the stop date will be set to the date of death.

**Missing month only**

If only the month is missing, the day will be treated as missing and both the month and the day will be replaced as described in Section 7.3.1.

**Missing day only**

If the month and year of the incomplete stop date are after the month and year of the first study intervention, then the missing end day will be set to the last day of the month of the occurrence.

If the participant died, the end date will be set to the death date.

If the month and year of the incomplete stop date are the same as the month and year of the last dose of study intervention, the day of the last dose of study intervention will be assigned to the missing day.

If either the year of the incomplete stop date is before the year of the date of the last dose of study intervention or if both years are the same, but the month of the incomplete stop date is before the month of the date of the last dose of study intervention, the last day of the month will be assigned to the missing day.

If either the year of the incomplete stop date is after the year of the date of the last dose of study intervention or if both years are the same, but the month of the incomplete stop date is after the month of the date of the last dose of study intervention, the first day of the month will be assigned to the missing day.

# SIGNATURE PAGE

*This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature*

| **Document Name:** d5272c00002-sap-ed-1 | | |
|---|---|---|
| **Document Title:** | D5272C00002 Statistical Analysis Plan Edition 1 | |
| **Document ID:** | Doc ID-004946205 | |
| **Version Label:** | 1.0 CURRENT LATEST APPROVED | |
| **Server Date** (dd-MMM-yyyy HH:mm 'UTC'Z) | **Signed by** | **Meaning of Signature** |
| 17-Oct-2022 15:20 UTC | PPD | Content Approval |
| 17-Oct-2022 16:21 UTC | PPD<br>PPD | Author Approval |

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.