Protocol C5041006 (APD334-202 or APD334-202EU)
SUBSTUDY 4 – Long-Term Extension (SS4-E)

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP STUDY TO ASSESS THE EFFICACY AND SAFETY OF ORAL ETRASIMOD AS INDUCTION AND MAINTENANCE THERAPY FOR MODERATELY TO SEVERELY ACTIVE CROHN'S DISEASE

Statistical Analysis Plan
(SAP)

Version: **1.0**

Date: 03 July 2025

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

No table of figures entries found.

APPENDICES

1. VERSION HISTORY

This is the initial version.

2. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analyses of the data collected in Study C5041006 (APD334-202 or APD334-202EU) for Substudy 4 long-term extension (SS4-E). This SAP is based on the protocol (Global Amendment 4.0, dated 31 January 2024, further referred to as protocol).

2.1. Modifications to the Analysis Plan Described in the Protocol

Pfizer has decided to terminate SS4-E on 29 October 2024 after the readout of the dose ranging Phase 2b Substudy 1 (SS1-P2b), which indicated that etrasimod does not have sufficient induction treatment benefit in patients with moderately to severely active CD. This decision was related to efficacy and not due to any safety concerns regarding etrasimod or requests from regulatory authorities.

SS4-E is long term safety study, and there is no primary efficacy endpoint in this study. No estimand is defined. Consequently, only secondary efficacy endpoints, selected exploratory efficacy endpoints and safety endpoints will be summarized using descriptive statistics to meet reporting requirements. Summaries will be presented based on observed data. Efficacy endpoints will be summarized based on observed data for the Full Analysis Set (FAS) as defined in Section 4 and will not be summarized based on the modified FAS (mFAS).

2.2. Study Objectives, Endpoints, and Estimand

Primary (Safety) objective: To characterize the safety and tolerability of etrasimod during the Long-term Extension in subjects with moderately to severely active CD. No estimand will be defined for the Long-term Extension study.

Secondary objective: To evaluate the long-term efficacy of etrasimod in subjects with moderately to severely active CD.

Exploratory Objective: To evaluate the effects of etrasimod as long-term therapy on health-related quality of life outcomes in subjects with moderately to severely active CD.

Endpoints are defined in Section 3.

2.3. Study Design

SS4-E is a Long-term extension (LTE) substudy that will evaluate the long-term safety and efficacy of etrasimod in subjects with moderately to severely active CD. Subjects from SS3-M and from SSA-P2 who complete at least 52 and 66 weeks of treatment, respectively, will be eligible to enter this SS4-E study with a treatment period of up to 208 weeks and a 4-Week Follow-Up Period.

Subjects who enroll in SS4-E from SS3-M will continue on the etrasimod dose (2 mg or 3 mg) they received at the M-38 Visit of SS3-M and subjects who enroll in SS4-E from SSA-P2 will continue on the etrasimod dose (2 mg or 3 mg) they received at the Week 66 Visit of SSA-P2. Subjects on placebo at SS4-E baseline will be randomized (1:1) to receive etrasimod 2 mg or 3 mg. All subjects enrolled in SS4-E receive etrasimod but are blinded to the actual dose being administered.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

3.1.1. Safety Endpoint(s)

AEs will be coded using MedDRA. The most up to date MedDRA version at the time of analysis will be used. Treatment-emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of study treatment (SS4-E). See APPENDIX 2 for handling of partial dates for AEs for the purpose of assigning treatment-emergent flags. In the case where it is not possible to define an AE as treatment-emergent or not, the AE will be classified as treatment-emergent.

Severity

Severity is classified as Grade 1: Mild, Grade 2: Moderate, Grade 3: Severe, Grade 4: Life-Threatening, Grade 5: Death Related to AE, using the Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE v5.0).

Relationship to Study Treatment

Relationship is classified as “not related”, “unlikely related”, “probably related”, or “related” by the Investigator.

TEAEs that result in permanent discontinuation of study treatment will be recorded as "Drug withdrawal," those leading to treatment interruption will be marked as "Drug interrupted" on the Adverse events eCRF, and TEAEs causing discontinuation from the study will be documented with "Adverse Event" as the primary reason on the End of Study eCRF. Serious adverse events (SAEs) are those events recorded as “Serious” on the Adverse Event eCRF. If the seriousness is missing, the AE will be considered as “Serious”. TEAEs leading to Death are those events which are recorded with an outcome as “Fatal” on the Adverse Events eCRF.

TEAEs of Special Interest

Categories of Targeted Medical Events (TMEs) and a list of preferred terms associated with these TME categories were developed based on the mechanism of action of etrasimod, prior experience with other agents acting via a similar mechanism, and disease-specific clinical judgment. The list of

selected preferred terms associated with these TME categories will be reviewed by Pfizer clinicians to identify which events reflect AESI.

TEAEs of special interest will be summarized by category, subcategory, and PT by descending frequency by treatment group. Categories and subcategories of TEAEs of special interest are the following:

- Cardiovascular Events
  - Bradycardia
  - AV conduction delay
  - Hypertension
- Macular Edema
- Pulmonary Disorders
  - Airflow obstruction (FEV_1, FVC)
  - Decreased gas exchange (DLCO)
- Infections
  - Severe infections
  - Opportunistic infections (SMQ Narrow Scope, including PML)
  - Herpes simplex and herpes zoster
- Liver Injury
  - Liver transaminases elevation
  - Bilirubin elevation
- Posterior Reversible Encephalopathy Syndrome (PRES)
- Malignancies

Laboratory Data

Hematology, serum chemistry and coagulation are analyzed and reported by central laboratory and sometimes by local laboratory. Results out of reference range are flagged by the performing laboratory (e.g., low, high).

Presentations will use SI Units. Quantitative laboratory measurements reported as "< X" or "> X", where X may be the lower limit of quantification (LLQ) or the upper limit of quantification (ULQ), respectively, will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings. If local and central laboratory assessments are available from the same day, central laboratory assessments will be used in the summary.

3.1.2. Other Safety Endpoint(s)

3.1.2.1. ECG Evaluations

Electrocardiograms (ECGs) are recorded on a 12-lead ECG machine and read centrally. The following ECG parameters are reported for this study:

- HR (bpm)

- PR interval (msec)
- RR interval (msec)
- QRS interval (msec)
- QTcF interval (msec)

3.1.2.2. ECG Markedly Abnormal Criteria

Markedly abnormal quantitative ECG measurements will be identified in accordance with the following predefined markedly abnormal criteria:

- Absolute values in QTcF:
  - ≥ 450 msec (male) or ≥ 470 msec (female) in QTcF
- Change from SS4-E baseline in QTcF:
  - > 30 msec increase from SS4-E baseline
  - > 60 msec increase from SS4-E baseline
- Absolute Values in PR:
  - PR > 230 msec

3.1.2.3. Vital Signs

The following vital signs measurements (and unit) are reported for this study:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Heart rate (bpm)
- Respiratory rate (resp/min)
- Temperature (°C)
- Weight (kg)
- Height (cm) [Baseline-SS4-E]

Vital Signs Specific Derivations

- Temperature (°C) = (5/9) (Temperature (°F) – 32)

Vital Signs Markedly Abnormal Criteria

Markedly abnormal quantitative vital signs measurements will be identified in accordance with the following predefined markedly abnormal criteria:

Variable	Unit	Low	High
SBP	mmHg	≤ 90 mmHg	> 150 mmHg
DBP	mmHg	≤ 50 mmHg	> 90 mmHg

Variable	Unit	Low	High
Heart rate	bpm	< 40 bpm < 50 bpm < 50 bpm and decrease from predose (baseline) of > 10 bpm at 4 hour postdose on Day 1 (SS4-E) or Day 2	> 100 bpm

3.1.2.4. Physical Examination

Not applicable.

3.1.2.5. Tuberculosis Screening/Questionnaire and Chest X-Ray

Not applicable.

3.1.2.6. Other Safety Summaries

Pulmonary Function Tests (PFTs), all Ophthalmoscopy and Optical Coherence Tomography (OCT), will be reported in listings.

3.2. Secondary Endpoint(s)

- Clinical remission CDAI: Clinical remission CDAI is defined as CDAI < 150.
- Clinical remission PRO2 is defined as: PRO2 < 8.
- Clinical response CDAI: Clinical remission CDAI ≥ 100-point decrease from parent study baseline (SSA or SS1).

The CDAI consists of 8 variables. Two of these, the abdominal pain (AP) and general well-being, are subjective and related to the disease, and each is weighted according to its ability to be predictive of disease activity. Stool frequency, hematocrit, use of anti-diarrheal medications, gender, body weight, height, assessment for EIMs of CD, and presence/absence of an abdominal mass and fever are also needed for the CDAI calculation. The total score ranges from zero to over 600. Details regarding the CDAI derivation can be found in APPENDIX 1.2.

The PRO2 is a patient-reported outcome measure based on stool frequency (SF, loose/watery stool for the loose/watery score is defined as type 6 ["fluffy pieces with ragged edges, a mushy stool"] or type 7 ["watery, no solid pieces, entirely liquid"] on the Bristol Stool Form Scale) and abdominal pain (AP, average rating graded from 0 [none] to 3 [severe] each day for 7 days) components of the CDAI. The CDAI weighting factors for the SF and AP variables will be used to calculate PRO2. PRO2 scoring details and weighting factors can be found in APPENDIX 1.2.

3.3. Other Endpoints

3.3.1. Endoscopy

- Endoscopic response: Endoscopic response is defined as endoscopic remission or ≥ 50% decrease from parent study baseline (SSA or SS1) in SES CD

The SES-CD is an endoscopic grading system that consists of a composite score based on 4 components: the size of mucosal ulcers, the extent of the ulcerated surface, the endoscopic extension, and the presence of stenosis. Each of the four SES-CD components are assessed in the five segments of the ileum and colon: ileum, right, transverse, left, and rectum. The SES-CD is the sum of the individual scores of each of the components across the five segments. SES-CD scoring details can be found in APPENDIX 1.2.

All endoscopy biopsy assessment results will be listed.

3.3.2. Biomarkers

The biomarker endpoints fecal calprotectin (FCP), high-sensitivity C-reactive protein (hs-CRP), absolute lymphocyte counts (ALC) will be summarized by visit and presented in tabular form.

3.3.3. Other summaries

3.3.3.1. CDAI/ PRO2

- Change from SS4-E baseline in CDAI score by visit up to the end of treatment.
- Change from SS4-E baseline in PRO2 score by visit up to the end of treatment.

3.3.3.2. Fistulas, Hospitalizations, and Surgery

- No reports will be generated.

3.4. Baseline Variables

Unless otherwise specified, the baseline is defined as the last non-missing measurement taken up to the date of first dose in the SS4-E substudy (including unscheduled assessments). The baseline may also be derived from data collected during the parent study, if applicable. If measurements include time, the date/time will be used to define baseline. Otherwise, only dates will be compared. In the case where the last non-missing predose measurement and the date of first dose coincide and time is not collected, if the measurement was planned in the protocol to be done prior to the date of first dose, that measurement will be considered in defining baseline. For Quality-of-life assessments (IBDQ, EQ-5D-5L, WPAI-CD, and SF-36), assessments collected on Day 1 (SS4-E) with the same assessment date as the date of first dose, will be considered baseline, regardless of time of collection.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

Analysis Set	Description
Safety Set	The Safety Set will include all enrolled subjects who received at least one dose of study drug in SS4-E.
Full Analysis Set (FAS)	The FAS will include all enrolled subjects who have received at least one dose of study drug in SS4-E.
Modified Full Analysis Set (mFAS)	The mFAS will include all enrolled subjects who have received at least one dose of study drug and have a SS4-E baseline measurement and at least one post baseline measurement. The mFAS is endpoint specific, therefore subjects included in the analysis set for one endpoint may differ from another endpoint, based on the SS4-E baseline and post-baseline data.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

No formal hypothesis testing will be performed in this study.

5.2. General Methods

In general, efficacy endpoints will be summarized based on observed data for the Full Analysis Set (FAS) as defined in Section 4. mFAS will not be used due to the study termination. Analysis of safety endpoints will be performed based on safety set.

5.2.1. Analyses for Binary Endpoints

All efficacy analyses will be performed using descriptive methods. The binary data will be summarized using the frequency count (n) and percentage (%). The corresponding 95% confidence intervals will be provided based on the Clopper-Pearson method. The frequencies will be presented with no decimal place, percentage up to 1 decimal place. If data are not available, a missing category will be presented. The denominator for percentages will be based on the number of patients appropriate for the purpose of the analysis.

5.2.2. Analyses for Continuous Endpoints

The continuous data will be summarized using the number of observations (n), arithmetic mean (mean), standard deviation (SD), confidence interval (CI) for mean estimate, median, minimum value (min), and maximum value (max). The number of observations (n) will be presented with no decimal place, mean and median will be presented up to one decimal place from the original value, SD up to two decimal places from the original value and (min, max) as an original value. Continuous variables will be described by absolute value and as a change from SS4-E baseline per analysis time point, if applicable.

5.2.3. Analysis of safety endpoints

Safety endpoints (section 3.1.1 and 3.1.2) will be summarized descriptively by treatment group through appropriate data tabulations by number of events, patient with event counts and percentage of patients with events, and exposure adjusted incidence rate. Patient listings may be produced for the safety endpoints accordingly.

Summary for continuous lab measurements will follow the summary as described in Section 5.2.2.

5.3. Methods to Manage Missing Data

Missing adverse event (AE) relationship to study drug and AE seriousness will be imputed as described in Section 3.1.1. Partial or missing AE start dates, Concomitant Medication (CM) start/end dates and Crohn's disease diagnosis dates will be imputed as described in APPENDIX 2. The Crohn's disease diagnosis date will be imputed to calculate the duration of disease only. No other missing safety data will be imputed.
No imputation will be performed for efficacy data. Analysis will be performed on observed data.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Safety Analysis Endpoint(s)

All safety analyses will be performed on the safety set. The safety analysis results will be summarized descriptively following Section 5.2.3

All TEAEs
All TEAEs and SAEs will be summarized by system organ class (SOC) and preferred term (PT). This summary table and all other TEAE summaries by SOC and PT will be presented by descending frequency in the etrasimod group. All AEs (TEAEs and non-TEAEs, SAEs) will be listed.
In addition, summaries by maximum severity, (as reported on the eCRF, not grouped) will be presented.

If a participant reports a TEAE more than once within a SOC/ PT, the AE with the worst-case severity, the worst-case relationship will be used in this summary.

Overall Summary of Adverse Events
TEAEs will be summarized (an overview not broken down by SOC or PT; and by SOC and PT) by number and frequency of participants and by number of AEs:

- Any TEAE
- Any related TEAE*
- Any serious TEAEs

- Any non-serious TEAEs (only overall summary)
- Any related serious TEAEs*(only overall summary)
- TEAEs leading to death.
- TEAEs leading to study drug discontinuation.
- TEAEs leading to study discontinuation.
- TEAEs by maximum severity

  TEAEs of Special Interest

* 'Related' TEAEs refers to TEAEs related or probably related to study drug.

6.1.1.1. Laboratory Data

Laboratory data will be summarized following Section 3.1.1 and the general methods described in Section 5.2.3.

The following summaries will be provided for laboratory data:

- Change and percent change from baseline by visit (for selected hematology parameters, selected serum chemistry parameters and coagulation).
- Abnormal values according to laboratory reference ranges by visit will be presented in listing.
- Incidence of lymphocytes < 0.2 x 10^9/L, < 0.5 x 10^9/L, or neutrophils < 0.5 x 10^9/L, < 1 x 10^9/L anytime during the study
- eDISH plots for the following laboratory assessments (using values after the first administration of study treatment):
  - Maximum Aspartate Transaminase (AST) vs Same-Day Total Bilirubin
  - Maximum Alanine Aminotransferase (ALT) vs Same-Day Total Bilirubin

If both central and local assessments of total bilirubin are available on the same day, the central result will take precedence over the local result in the eDISH plot. If the maximum AST/ALT/ALP assessment occurs at two different dates, the assessment with the higher accompanying Bilirubin value will be used. Two versions of the eDISH plots will be presented, with one showing values as multiples of upper limit of normal, and the other one showing values as multiples of upper limit of normal, or participant's SS4-E baseline, whichever is higher.

- Incidence of hepatic enzyme elevations at SS4-E baseline and post-baseline by normal SS4-E baseline, and overall
  - > 1, ≥ 2, ≥ 3, ≥ 5 x ULN elevation in ALT
  - > 1, ≥ 2, ≥ 3, ≥ 5 x ULN elevation in AST
  - > 1, ≥ 2, ≥ 3, ≥ 5 x ULN elevation in total bilirubin
  - > 1, ≥2, ≥3, ≥ 5 x ULN elevation in ALP
  - ≥ 3 x ULN elevation in either ALT or AST and ≥ 1.5 x ULN elevation in total bilirubin
  - ≥ 3 x ULN elevation in either ALT or AST and ≥ 2 x ULN elevation in total bilirubin
  - ≥ 3 x ULN elevation in either ALT or AST and ≥ 1.5 x ULN elevation in ALP

- ≥ 3 x ULN elevation in either ALT or AST and ≥ 2 x ULN elevation in total bilirubin and < 2 x ULN elevation in ALP

- Confirmed Incidence of hepatic enzyme elevations at post-baseline by normal SS4-E baseline, abnormal SS4-E baseline, and overall. A confirmed case is defined as ≥2 consecutive test values meet the criteria.
  - > 1, ≥ 2, ≥ 3, ≥ 5 x ULN elevation in ALT
  - > 1, ≥ 2, ≥ 3, ≥ 5 x ULN elevation in AST
  - > 1, ≥ 2, ≥ 3, ≥ 5 x ULN elevation in total bilirubin
  - > 1, ≥ 2, ≥3, ≥ 5 x ULN elevation in ALP

Participant's laboratory assessments, central or local, at all timepoints in chronological order will be listed. Values outside of the laboratory reference range will be flagged. Values obtained from local laboratory will be flagged. Listing of lymphocytes and neutrophils over time in participants with lymphocytes < 0.5 x 10^9/L or neutrophils < 1 x 10^9/L will also be provided.

6.1.2. Other Safety Endpoints

6.1.2.1. Electrocardiograms

ECGs will be summarized following section 3.1.2.1 and 5.2.

The following summaries will be provided for ECG data:

- Incidence of markedly abnormal values by visit

All ECG results, including first dose cardiac monitoring, will be listed. Participants not satisfying the discharge criteria for first dose cardiac monitoring will also be listed (Table 18 in the Protocol). A listing of all ECG assessments over time in participants meeting markedly abnormal criteria will also be provided. For each participant, only ECG parameters ever meeting markedly abnormal criteria will be included.

6.1.2.2. Vital Signs

Vital signs will be summarized by treatment group following Section 5.2.

The following summaries will be provided for vital signs data:

- Value and change from SS4-E baseline by visit (including Day 1 (SS4-E))
- Incidence of markedly abnormal values by visit

All vital signs, including first dose cardiac monitoring, will be listed. Participants not satisfying the discharge criteria for first dose cardiac monitoring will also be listed (Table 18 in the Protocol). A listing of all vital signs assessments over time in participants meeting markedly abnormal criteria will also be provided. For each participant, only vital sign parameters ever meeting markedly abnormal criteria will be included.

6.2. Secondary Endpoint(s)

The binary secondary end points listed below will be summarized as described in Section 5.2.1 for observed data in the full analysis set population by the study treatment groups (Etrasimod 3 mg vs Etrasimod 2 mg).

- Proportion of subjects with clinical remission CDAI by visit up to the end of treatment.
- Proportion of subjects with clinical remission PRO2 by visit up to the end of treatment.

6.3. Other Endpoints

6.3.1. Biomarkers

The following summaries will be provided for biomarkers data:

- Change and percentage change from SS4-E baseline in ALC by visit up to the end if the treatment.
- Change and percentage change from SS4-E baseline in FCP concentration by visit up to the end of the treatment.
- Change and percentage change from SS4-E baseline in hs-CRP concentration by visit up to the end of the treatment.

6.3.2. Other summaries

Below continuous endpoints (mentioned in section 3.3) will be summarized as described in Section 5.2.2 for observed data in the full analysis set population by the study treatment groups (Etrasimod 3 mg vs Etrasimod 2 mg).

- Change from SS4-E baseline in CDAI score by visit up to the end of treatment.
- Change from SS4-E baseline in PRO2 score by visit up to the end of treatment.

The Endoscopic response by visit up to the end of treatment will be summarized as described in Section 5.2.1 for observed data in the full analysis set population.

Other endpoints mentioned in section 3.3 will be presented in listing.

- Crohn's Disease Patient-Reported Outcomes (CD-PRO) results will be listed.
- Change from SS4-E baseline in IBDQ, SF-36, CD-PRO/SS, FACIT-F, WPAI-CD, and EQ-5D-5L by visit up to the end of treatment.
- Proportion of subjects with improvement in the CD-PRO/SS Bowel and Abdominal Function domain scores by visit up to the end of treatment.
- Change from SS4-E baseline in IBDQ Bowel Symptom domain score by visit up to the end of treatment.
- Change from SS4-E baseline in IBDQ fatigue item score by visit up to the end of treatment.

6.4. Subgroup Analyses

Not Applicable.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

The following demographic data and baseline characteristics will be summarized for the Safety Set:

- Age on consent (years) – including age groups ≤Median and >Median; <18, ≥18 to <65, and ≥65
- Sex
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- Alcohol consumption (Yes/No)
- Tobacco use (Yes/No)
- Region

The following baseline characteristics related to CD will be summarized (baseline refers to SS4-E study baseline, otherwise parent study baseline (SSA or SS1) is referenced):

- Duration of CD at consent at parent study (years, ≤ 5/ >5, ≤15/ >15)
- Disease localization at baseline parent study (Ileum, Colon, Both)
- Baseline oral corticosteroid use at parent study
- SS4-E baseline oral corticosteroid use
- Baseline 5-ASA compound use at parent study (Yes/No)
- SS4-E baseline AP subscore
- SS4-E baseline SF subscore
- SS4-E baseline CDAI score
- SS4-E baseline SES-CD score
- SS4-E baseline PRO2 score
- SS4-E baseline hs-CRP
- SS4-E baseline FCP
- Prior Biologic Therapy (Yes/No), including the number of prior biologic therapies based on parent study baseline

6.5.2. Study Conduct and Participant Disposition

The number and percent of participants who completed SSA-P2 or SS3-M and how many joined SS4 will be summarized. The number and percent of participants who completed/discontinued the treatment period, the number and percent of participants who completed/discontinued the study, and

reasons for discontinuation will be summarized. The number and percent of participants in each analysis set will be summarized in all randomized (or enrolled) participants.

6.5.3. Study Treatment Exposure

The date of the first study treatment administration will be taken from the Day 1 (SS4-E). The last study treatment administration will be taken from the End of Study eCRF for SS4-E date will be used.

Interruptions, compliance, and dose changes are not included in the duration of exposure calculation. Exposure to study treatment in weeks will be summarized for the Safety Set.

Dose interruptions will be recorded on the Dosing Administration eCRF and overdoses will be recorded on the Overdose eCRF. The frequency and percentage of participants who had at least one dose interruption, who had at least one dose interruption of > 7 days, who had at least one dose interruption of > 14 days, who had one overdose, and who had > 1 overdose will be summarized. Dose interruption summaries will be cumulative (i.e. participants with at least one dose interruption >14 days will be counted in the >7 day summary as well). The reasons for dose interruption will be summarized.

Duration of exposure (weeks) = (date of last study treatment administration – date of first study treatment administration + 1) / 7.

For participants with missing Date of Last Dose on the End of Study eCRF, their date of last study treatment administration will be imputed by the last date of all dosing administration start/stop dates recorded.
Total number of tablets expected, total number of tablets taken, total number of tablets missed, overall compliance to study treatment, frequency, and percentage of participants with overall compliance < 80%, 80 – 120%, and > 120% will be summarized for the Safety Set.

6.5.3.1. Derivations

Compliance to study treatment is based on the Drug Accountability eCRF and will be calculated as the total number of tablets taken (total dispensed – total returned) divided by the number of tablets expected during the treatment period, expressed as a percentage, see calculations below:

$$\frac{([\text{Total N of tablets dispensed in period}] - [\text{Total N of tablets returned in period}])}{2 \times ([\text{Date of last dose in period}] - [\text{Date of first dose in period}] + 1)} \times 100$$

If a bottle is not returned, all dispensed tablets will be assumed to be taken (i.e. number returned will be treated as 0). If a high percentage of bottles are not returned, additional analyses may be done where bottles not returned are excluded from the overall compliance calculation.

Both scheduled and unscheduled study treatment dispensations will be used in the compliance calculation.

6.5.3.2. Exposure adjusted incidence rate (EAIR)

The EAIR will be derived as:

$$EAIR = \frac{n}{(TIME1 + TIME2)}$$

n is the number of events

TIME1 (for subjects with event) which is the sum of the exposure time up to the date of the first event

$$TIME1 = \frac{\text{date of the first event} - \text{date of first study treatment administration} + 1}{365.25}$$

TIME2 which is the sum of the exposure time for subject without the event.

$$TIME2 = \frac{\text{end of study} - \text{date of first study treatment administration} + 1}{365.25}$$

6.5.4. Concomitant Medications and Nondrug Treatments

Medications will be captured on the Concomitant Medications eCRF and coded using the recent version of WHO Drug dictionary (WHODD). See APPENDIX 2 for handling of partial dates for medications. In the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case (i.e. concomitant).

- 'Prior' medications are medications which started prior to the first dose of study treatment and were not ongoing OR ended prior to or on the date of first dose of study treatment.
- 'Concomitant' medications are medications which started prior to, on or after the first dose of study treatment AND ended on or after the date of first dose of study treatment or were ongoing at the end of the study.

Concomitant medications will be summarized by ATC Level 2 and Preferred Drug name for the Safety Set. Prior treatment for CD will also be summarized by treatment. Drug class type, duration and reason for discontinuation will also be presented.

7. INTERIM ANALYSES

7.1. Introduction

Not applicable.

7.2. Interim Analyses and Summaries

Not applicable.

Appendix 1. Data Derivation Details

Appendix 1.1. Definition and Use of Visit Windows in Reporting

Windowing Conventions

The First Dose (SS4-E) Visit is the first visit of SS4-E for all participants. The overall duration of this substudy is up to 212 weeks, inclusive of the 208-week Treatment Period and the 4-Week Follow-Up Period. All scheduled study visits are defined relative to Study Day 1, the first date of the SS4-E visit. No repeat assessments are required if the SS4-E Visit is performed on the same day as the last visit of the parent study or substudy. Scheduled visit windows are defined in Appendix 1 of the protocol.

A windowing convention will be used to determine the analysis visit value for a given measurement and will be applicable for all by-visit summaries and analyses for efficacy and safety data. See Table A1 for specific visit windows.

Table A1: Substudy 4 Visit Windows

Scheduled Study Visit[a] (Protocol Study Day)	Analysis Visit Window [b] (Analysis Study Day)
Baseline	⩽ Day 1
E-1 (± 3D)	Day 2 to 76
E-Week 12 (±7D)	Day 77 to 91 (84)
E-Week 24 (±7D)	Day 92 to 175 (168)
E-Week 36 (±7D)	Day 176 to 259 (252)
E-Week 52 (±7D)	Day 260 to 371 (364)
E-Week 64 (±7D)	Day 372 to 455 (448)
E-Week 76 (±7D)	Day 456 to 539 (532)
E-Week 88 (±7D)	Day 540 to 623 (616)
E-Week 104 (±7D)	Day 624 to 735 (728)

E-Week 116 (±7D)	Day 736 to 819 (812)
E-Week 128 (±7D)	Day 820 to 903 (896)
E-Week 140 (±7D)	Day 904 to 987 (980)
E-Week 156 (±7D)	Day 988 to 1099 (1092)
E-Week 168 (±7D)	Day 1100 to 1183 (1176)
E-Week 180 (±7D)	Day 1184 to 1267 (1260)
E-Week 192 (±7D)	Day 1268 to 1351 (1344)
E-Week 208 (±7D)	Day 1352 to 1463 (1456)
2-Week Follow-Up	Based on visit recorded in CRF
4-Week Follow-Up	

[a] Visits will only be displayed for assessments that were expected to be collected at these visits, according to the Schedule of Assessments, Table 33, outlined in the Protocol.
[b] The upper limit of visit windows cannot exceed the participant's last day.

The last non-missing measurement taken up to the date of first dose (including unscheduled assessments) will be labeled as "Baseline".. The early discontinuation visit will be eligible for allocation to an analysis visit. The Follow-up visits will not be included in the visit windows and will be summarized separately without any window applied. For assessments taken less frequently, the same visit windows apply but only visits where assessments were expected to be collected will be summarized.

If one or more results for a variable are assigned to the same analysis visit, the result with the date closest to the protocol scheduled day will be used in the analysis. If two measurements in the same analysis visit window are equidistant from the protocol scheduled study day, the earliest measurement will be used in the analysis. If multiple assessments are available on the same day, then the average of the assessment will be used in the analysis, except for laboratory and ECG data where the assessment at the earliest time of the same day will be used. If both central and local assessments of the same lab test are available on the same day, the central result will take precedence over the local result.

Reference Start Date and Study Day

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events. Reference start date is defined as the date of first dose in SS4-E (Day 1) and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date then:
  - Study Day = (date of event – reference date) + 1
- If the date of the event is prior to the reference date then:
  - Study Day = (date of event – reference date)

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear missing in the listings.

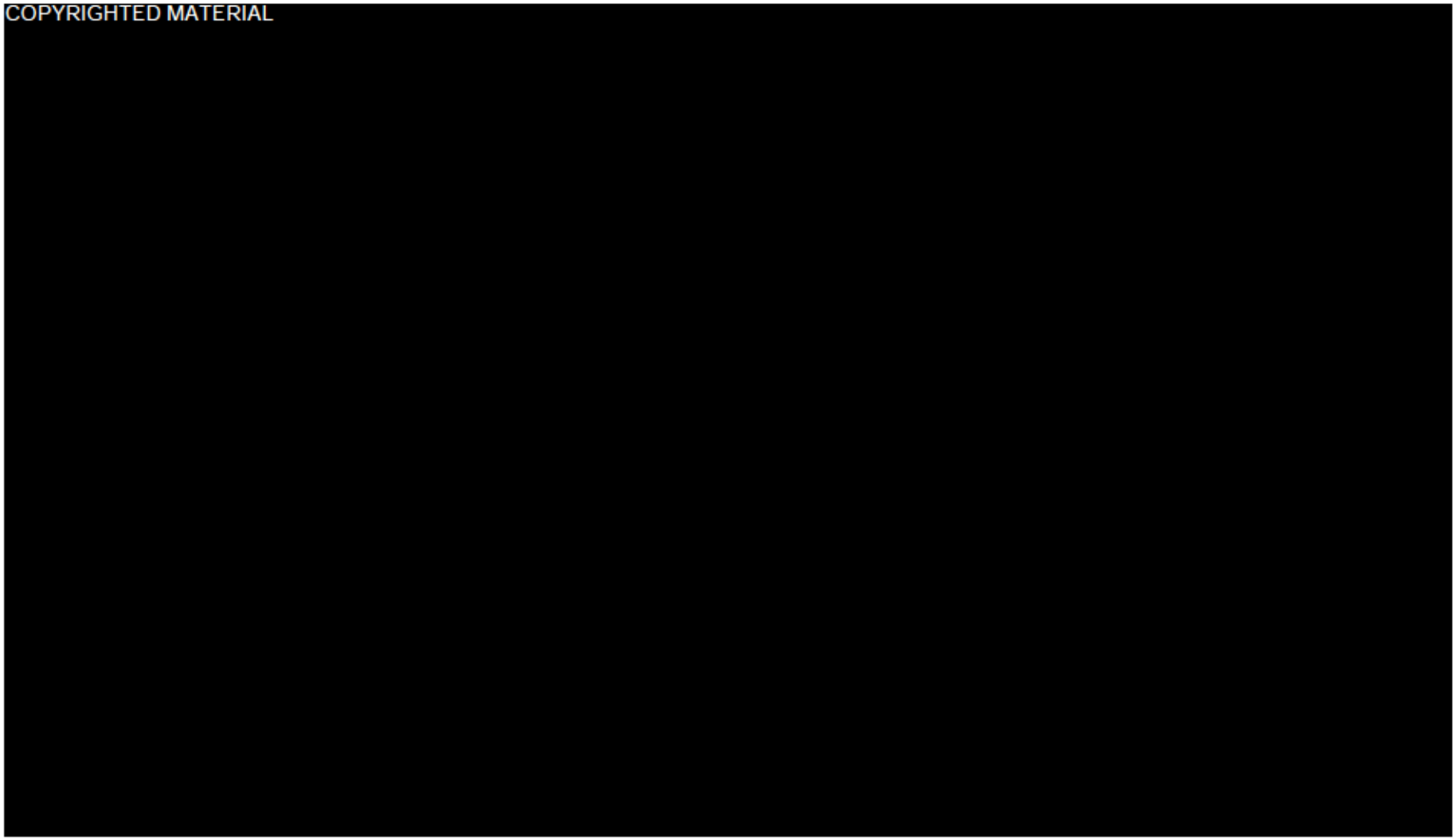
Appendix 1.2. Endpoint Derivations

Basic measurements derivation

- Duration of CD (year) = (Informed consent date – Date of diagnosis + 1) / 365.25
- Weight (kg) = Weight (lb) * 0.4536
- Height (cm) = Height (in) * 2.54
- Height (m) = Height (in) * 0.0254 = Height (cm) * 0.01
- BMI (kg/m^2) = Weight (kg) / Height $(m)^2$

Simple Endoscopic Score in Crohn's Disease

CDAI Variables and Weighting Factors



Appendix 1.3. Definition of Protocol Deviations That Relate to Statistical Analyses/Populations

Important protocol deviations will be summarized for the Safety Set. All protocol deviations will be listed.

- Inclusion Criteria

- Exclusion Criteria
- Concomitant Medication
- Randomization
- Laboratory Assessment
- Study Procedures
- Safety
- Efficacy
- Investigational Product conditions
- Investigational Product administration
- Subject Investigational Product compliance
- Subject Discontinuation
- Visit Schedule
- Administrative
- Blinding
- Patient Reported Outcomes
- PK/PD
- Other Criteria
- Informed Consent

Appendix 2. Data Set Descriptions

Partial Date Conventions

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

AE START DATE	AE STOP DATE	ACTION
Known	Known, Partial or Missing	If AE start date < study drug first dose date, then not TEAE If AE start date ≥ study drug first dose date, then TEAE

AE START DATE	AE STOP DATE	ACTION
Partial, but known components show that it cannot be on or after date of first dose of study drug	Known, Partial or Missing	Not TEAE
Partial, could be on or after date of first dose of study drug	Known	If AE stop date < study drug first dose date, then not TEAE If AE stop date ≥ study drug first dose date, then TEAE
	Partial	Impute AE stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If AE stop date < study drug first dose date, then not TEAE If AE stop date ≥ study drug first dose date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If AE stop date < study drug first dose date, then not TEAE If AE stop date ≥ study drug first dose date, then TEAE
	Partial	Impute AE stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If AE stop date < study drug first dose date, then not TEAE If AE stop date ≥ study drug first dose date, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR AND CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known	Known	If medication stop date < study med first dose date, assign as prior If medication stop date ≥ study med first dose date, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If medication stop date < study med first dose date, assign as prior If medication stop date ≥ study med first dose date, assign as concomitant
	Missing	If medication stop date is missing could never be assumed a prior medication, assign as concomitant
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If medication stop date < study med first dose date, assign as prior If medication stop date ≥ study med first dose date, assign as concomitant
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If medication stop date < study med first dose date, assign as prior If medication stop date ≥ study med first dose date, assign as concomitant

START DATE	STOP DATE	ACTION
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If medication stop date is missing could never be assumed a prior medication, assign as concomitant
Missing	Known	If medication stop date < study med first dose date, assign as prior Else assign as concomitant
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If medication stop date < study med first dose date, assign as prior If medication stop date ≥ study med first dose date, assign as concomitant
	Missing	Impute start date to be informed consent date. Assign as concomitant

ALGORITHM FOR CROHN'S DISEASE DIAGNOSIS DATE:

START DATE	ACTION
Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown)

ALGORITHM FOR CONCOMITANT START/STOP DATES:

START/STOP DATE	ACTION
Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) Impute to latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown)
Missing	Impute medication start date to informed consent date. Impute medication end date to last visit date.

Appendix 3. Statistical Methodology Details

For quantitative measurements:

- Change from SS4-E baseline = Test Value at Visit X – SS4-E baseline Value
- Percent change from SS4-E baseline = ((Test Value at Visit X – SS4-E baseline Value) / SS4-E baseline Value) * 100
- Proportion at Visit X = Number of participants satisfying criteria at Visit X / Total number of participants at Visit X
- IQR = Q3 (75th Percentile) – Q1 (25th Percentile)

Appendix 4. List of Abbreviations

Abbreviation	Term
AE	adverse event
ATC	Anatomic Therapeutic Chemical
BP	blood pressure
CI	confidence interval
CRF	Case Report Form
EAIR	exposure adjusted incidence rate

Abbreviation	Term
ECG	electrocardiogram
FAS	full analysis set
FCP	fecal calprotectin
HCT	hematocrit
hs-CRP	high-sensitivity C-reactive protein
IQR	interquartile range
LOR	loss-of-response
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified full analysis set
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PRO	patient-reported outcome
PT	preferred term
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SS4-E	substudy 4 long-term extension
TA	therapeutic area
ULN	upper limit of normal
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary