STATISTICAL ANALYSIS PLAN

APD334-203 (C5041007)

A Phase 2, Randomized, Double Blind, Placebo Controlled, 12 Week Dose Ranging Study to Assess the Efficacy and Safety of Etrasimod in Japanese Participants with Moderately to Severely Active Ulcerative Colitis

AUTHOR: PPD

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V2.0. (Dated 20Nov2023) for Protocol APD334-203.

	Name	Signature	Date (DDMmmYYYY)
Author:	PPD	Refer to eSignature	November 27, 2023
Position:	PPD		
Company:	IQVIA		

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date (DDMmmYYYY)
Approved By:	PPD	Refer to eSignature	November 28, 2023
Position:	PPD		
Company:	IQVIA		
Approved By:	PPD	Refer to eSignature	November 27, 2023
Position:	PPD		
Company:	Pfizer R&D Japan		

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	28Jul2022	PPD	Not Applicable – First Version
2.0	20Nov2023	PPD	Updated based on Sponsor requirements as below: Updated the derivation of "Time on study" in section 15.1. Section 18.7.2, deleted the analysis of numerical observations of CFT.

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LIST OF ABBREVIATIONS

Abbreviation	Term
5-ASA	5-aminosalicylic acid
AE	adverse event
AESI	adverse events of special interest
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APD334	etrasimod
ANCOVA	analysis of covariance
Arena	Arena Pharmaceuticals, Inc.
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AV	atrioventricular
BLQ	below the limit of quantification
BMI	body mass index
bpm	beats per minute
CI	confidence interval
CM	concomitant medication
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease 2019
CR	copy reference
CRF	case report form
CRP	C-reactive protein
CS	clinically significant
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
$C_{trough,ss}$	average steady-state trough plasma concentration
CV	coefficient of variation
DBP	diastolic blood pressure
DLCO	diffusing capacity of the lungs for carbon monoxide
DMC	Data Monitoring Committee
EAIR	exposure-adjusted incidence rate
ECG	electrocardiogram

eCRF	electronic case report form
eDISH	evaluation of drug-induced serious hepatotoxicity
EIM	extraintestinal manifestation
ES	endoscopic score
FAS	Full Analysis Set
FCP	fecal calprotectin
FCS	fully conditional specification
FDA	Food and Drug Administration
FEF	forced expiratory flow
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GGT	gamma-glutamyl transferase
HR	heart rate
HRQoL	health-related quality of life
hs-CRP	high-sensitivity C-reactive protein
ICF	informed consent form
IRT	Interactive Response Technology
JAK	Janus kinase
LLQ	lower limit of quantification
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full Analysis Set
MMRM	mixed-effect model with repeated measures
MMS	modified Mayo score
NCS	not clinically significant
NHI	Nancy Histological Index
NRI	nonresponder imputation
NRS	numeric rating scale
OCT	optical coherence tomography
OLE	open-label extension
PFT	pulmonary function test
PGA	Physician's Global Assessment
PK	pharmacokinetics
PKS	Pharmacokinetic Set
PMDA	Pharmaceuticals and Medical Devices Agency

PPS	Per Protocol Set
PRES	posterior reversible encephalopathy syndrome
PT	preferred term
RB	rectal bleeding
RHI	Robarts Histopathology Index
SAE	serious adverse event
SS	Safety Set
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SDTM	Study Data Tabulation Model
SE	standard error
SF	stool frequency
SF-36	Medical Outcomes Study 36-Item Short Form Health Survey
SI	International System of Units
SOC	system organ class
ss	steady state
TB	tuberculosis
TEAE	treatment-emergent adverse event
TLC	total lung capacity
TME	targeted medical event
TMS	total Mayo score
TNFα	tumor necrosis factor alpha
UC	ulcerative colitis
UC-PRO/SS	Ulcerative Colitis Patient-Reported Outcomes Signs and Symptoms
ULN	upper limit of normal
ULQ	upper limit of quantitation
WHO	World Health Organization
β-hCG	beta-human chorionic gonadotropin

1. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of efficacy, safety, pharmacokinetic (PK), and efficacy-related biomarker data for Protocol APD334-203. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed (ICH 1998).

This SAP is based on protocol version Amendment 1.0, dated 12 January 2023.

Analyses of exploratory efficacy related biomarkers (Clinical Study Protocol APD334-203 Section 9.8.4.1) data will be specified in a separate biomarker analysis plan.

2. STUDY OBJECTIVES AND ESTIMANDS

2.1. Primary Objective

The primary objective is to assess the efficacy of etrasimod at 2 doses (1 and 2 mg) on clinical remission in Japanese participants with moderately to severely active ulcerative colitis (UC) when administered for 12 weeks.

2.2. Secondary Objective

The secondary objective is to assess the efficacy of etrasimod at 2 doses (1 and 2 mg) on clinical response, symptomatic remission, endoscopic improvements, and mucosal healing in Japanese participants with moderately to severely active UC when administered for 12 weeks.

2.3. Safety Objective

The safety objective is to assess the safety of etrasimod at 2 doses (1 and 2 mg) for 12 weeks in Japanese participants with moderately to severely active UC.

2.4. Other Objectives

Other objectives include evaluation of etrasimod PK and the effect of etrasimod on health-related subject reported outcomes and biomarkers.

2.5. Estimands

The primary and the secondary estimands to support regulatory decisions are described in Table 1 below. The analyses will be performed on the Full Analysis Set (FAS) with baseline MMS 5-9 as defined in Section 5.3. Supplementary analyses for the primary estimand will be performed on the modified Full Analysis Set (mFAS) and the Per Protocol populations, respectively (ICH 2019). Supplementary analyses for secondary estimands will be performed on the mFAS only. Intercurrent events include: 1) discontinue the study for lack of efficacy or adverse event related to UC, 2) initiate a rescue medication for UC, 3) have an increase in dose over Baseline levels in their existing UC medication, or 4) have a rescue non-drug treatment (eg, colectomy, ileostomy, or sigmoidectomy) before the efficacy assessment. Refer to APPENDIX 5 for the definition of rescue therapies (medication and medical procedures).

Table 1: List of Primary and Secondary Estimands

Estimand	Definition	Attributes			
		Population	**Variable/ Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
Primary Estimand	Efficacy of etrasimod on clinical remission at Week 12	Randomized Japanese participants who receive at least 1 dose of study treatment and with Baseline MMS 5 to 9	The proportion of participants with SF subscore = 0 (or = 1 with a ≥ 1-point decrease from Baseline), RB subscore= 0, and ES ≤ 1 (excluding friability) at Week 12	Participants with any of the 4 intercurrent events[a] before the efficacy assessment will be treated as nonresponders.	Difference between each etrasimod dose (1 and 2 mg) and placebo in the endpoint at Week 12
Secondary Estimand 1	Efficacy of etrasimod on endoscopic improvement at Week 12	Randomized Japanese participants who receive at least 1 dose of study treatment and with Baseline MMS 5 to 9	The proportion of participants with ES ≤ 1 (excluding friability) at Week 12.	Same as the intercurrent event handling strategy for the primary estimand	Difference between each etrasimod dose (1 and 2 mg) and placebo in the endpoint at Week 12
Secondary Estimand 2	Efficacy of etrasimod on symptomatic	Randomized Japanese participants who receive at	The proportion of participants with SF subscore = 0 (or = 1 with a ≥ 1-point	Same as the intercurrent event handling strategy	Difference between each etrasimod dose (1 and 2 mg) and placebo in the

Estimand	Definition	Attributes			
		Population	Variable/ Endpoint	Intercurrent event handling strategy	Population-level summary measure
	remission at Week 12	least 1 dose of study treatment and with Baseline MMS 5 to 9	decrease from Baseline) and RB subscore= 0 at Week 12.	for the primary estimand	endpoint at Week 12
Secondary Estimand 3	Efficacy of etrasimod on mucosal healing at Week 12	Randomized Japanese participants who receive at least 1 dose of study treatment and with Baseline MMS 5 to 9	The proportion of participants with ES ≤ 1 (excluding friability) with histologic remission measured by a Geboes Index score < 2.0 at Week 12.	Same as the intercurrent event handling strategy for the primary estimand	Difference between each etrasimod dose (1 and 2 mg) and placebo in the endpoint at Week 12
Secondary Estimand 4	Efficacy of etrasimod on clinical response at Week 12	Randomized Japanese participants who receive at least 1 dose of study treatment and with Baseline MMS 5 to 9	The proportion of participants with a ≥ 2-point and ≥ 30% decrease from baseline in MMS, and a ≥ 1-point decrease from baseline in RB subscore or an absolute RB subscore ≤ 1 at week 12.	Same as the intercurrent event handling strategy for the primary estimand	Difference between each etrasimod dose (1 and 2 mg) and placebo in the endpoint at Week 12
Secondary Estimand 5	Efficacy of etrasimod on endoscopic normalization at Week 12	Randomized Japanese participants who receive at least 1 dose of study treatment and with Baseline MMS 5 to 9	The proportion of participants with ES=0 at week 12.	Same as the intercurrent event handling strategy for the primary estimand	Difference between each etrasimod dose (1 and 2 mg) and placebo in the endpoint at Week 12

[a] Intercurrent events include: 1) discontinue the study for lack of efficacy or adverse event related to UC, 2) initiate a rescue medication for UC, 3) have an increase in dose over Baseline levels in their existing UC medication, or 4) have a rescue non-drug treatment (eg, colectomy, ileostomy, or sigmoidectomy) before the efficacy assessment. Refer to APPENDIX 5 for the definition of rescue therapies (medication and medical procedures).
ES, endoscopic score; MMS, modified Mayo score; RB, rectal bleeding; SF, stool frequency; UC, ulcerative colitis.

3. STUDY DESIGN

3.1. General Description

This is a dose ranging, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of etrasimod 1 and 2 mg in Japanese participants with moderately to severely active UC. The study consists of a 28 Day Screening Period, a 12 Week Induction Treatment Period, and a 4 Week Follow Up Period. Eligible participants will be randomized (1:1:1 ratio) to receive either etrasimod (1 mg once daily), etrasimod (2 mg once daily), or matching placebo (once daily) in a double-blind fashion for 12 weeks. Randomization will be stratified by (a) naïve to biologic or Janus kinase (JAK) inhibitor therapy at study entry (yes or no), (b) baseline corticosteroid use (yes or no), and (c) baseline disease activity (modified Mayo score [MMS]: 4 to 6 or 7 to 9).

A total of 96 participants are planned to be enrolled in the study, with 32 participants expected in each of the 3 treatment groups. The target subject population will include those who have had an inadequate response to, loss of response to, or intolerance to the following:

- Conventional therapy, and are naïve to biologic or JAK inhibitor therapy
- Biologic or JAK inhibitor (participants in this category may have received prior conventional therapy)

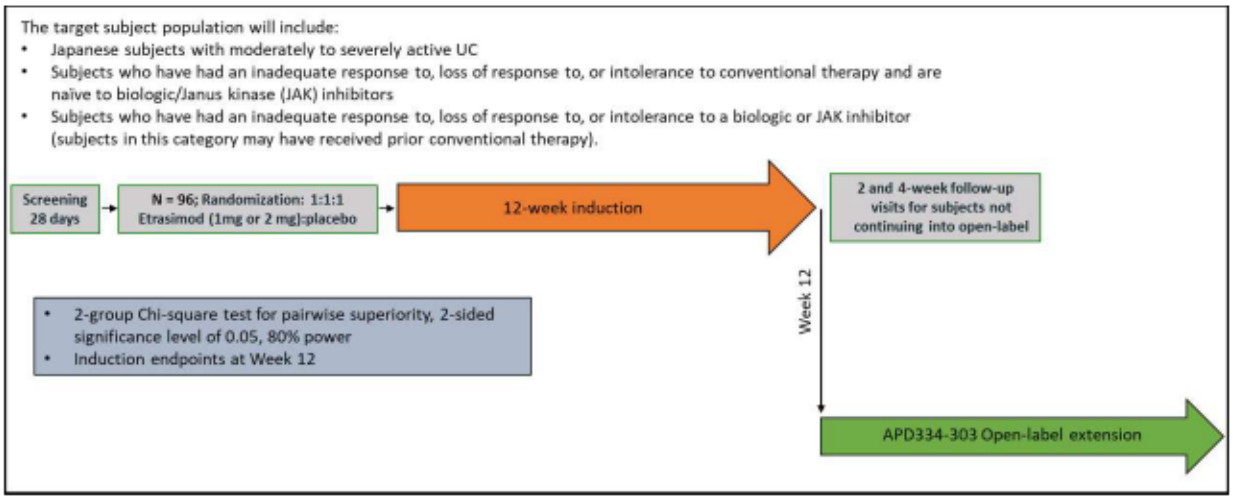
Participant eligibility will be determined during a 4-Week (28-Day) Screening Period. Entry criteria will be based on confirmation of moderately to severely active UC, defined by an MMS of 4 to 9, which includes an ES $\geq$ 2 and rectal bleeding (RB) subscore $\geq$ 1.

At the end of the 12 Week Induction Treatment Period, participants will undergo Week 12 efficacy and safety assessments and be evaluated for clinical response/remission. Participants will then have the option to enter an open label extension (OLE) study (Study APD334-303) following completion of Week 12 study procedures provided they meet all eligibility criteria for the OLE. Participants must complete Week 12 to be eligible for the OLE.

Participants who discontinue from the study and do not participate in the OLE study will have 2 Week and 4 Week Follow Up visits after the last on treatment visit/Early Termination (ET) visit. The study design is outlined in Figure 1 below.

This study will be early discontinued in agreement with Pharmaceuticals and Medical Devices Agency (PMDA).

Figure 1: Study Design



3.2. Schedule of Events

Schedule of events can be found in Appendix 1 of the protocol.

3.3. Changes to Analysis from Protocol

- No statistical test will be conducted due to the number of participants randomized will be decreased.
- No hypothesis will be tested and no adjustment for multiplicity.
- No adjustments for covariates and factors to be include in analysis.
- For primary and secondary efficacy analysis, change the missing data methods from "multiple imputation" to "non-responder imputation". And remove the sensitivity analysis for primary analysis per sponsor requirements.
- CMH test stratified by 3 stratification factors (naïve to biologic/JAK inhibitor therapy at study entry (Yes/No), baseline corticosteroid use (Yes/No), and baseline disease activity (MMS: 4 to 6 or 7 to 9) will not be conducted per sponsor requirements.
- Cochran Armitage test for dose trend is removed.
- For HRQoL endpoints, change the missing data methods from multiple imputation to not impute per sponsor requirements.
- Remove the factors (naïve to biologic or JAK inhibitor therapy at study entry (Yes or No), Baseline

corticosteroid use (Yes or No), Baseline disease activity (MMS: 4 to 6 or 7 to 9)) in MMRM model.

- The primary analysis set for the efficacy endpoints is updated to the Full Analysis Set (FAS) with MMS 5 to 9. Subgroup definition related to MMS is updated accordingly. The FAS with baseline MMS 4 to 9 will be used in supplementary analyses.
- The Per Protocol Set (PPS) will be used in supplementary analysis instead of sensitivity analysis for only primary endpoints.
- The following definitions used to assess efficacy outcomes in Section 16 is changed or added as below:
    - Added definition for histologic improvement (as defined by Robarts Histopathology Index, and Nancy Histologic Index).
    - Added definition for histologic remission (as defined by Robarts Histopathology Index, and Nancy Histologic Index).
    - Added definition for improvement in extraintestinal manifestations (EIMs).
- Not all individual subject data for all randomized participants is presented in data listings, eg, safety data is presented in safety set.

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Final Analysis

4.1. Interim Analysis

There is no planned or unplanned interim analysis for this study.

4.2. Final Analysis

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following Sponsor (Arena Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer Inc., hereafter referred to as Arena) authorization of the SAP, database lock, analysis sets, and unblinding of treatment. After Arena has authorized breaking of the study blind, the final analysis will be performed.

Any, post hoc, exploratory analyses completed to support planned study analyses, which were not identified in this

SAP, will be documented and reported in the clinical study report (CSR). Any results from these unplanned analyses will also be clearly identified in the text of the CSR (ICH, 1995).

5. ANALYSIS SETS

Agreement and authorization of participants included/excluded from each analysis set will be conducted prior to the unblinding of the study.

5.1. Screened Set

The Screened Set will consist of all participants who sign informed consent to participate in the study.

5.2. Randomized Set

The Randomized Set will consist of all participants who are randomized to study treatment.

For analyses and displays based on Randomized Set, participants will be classified according to randomized treatment.

5.3. Full Analysis Set (FAS)

The FAS will consist of all randomized participants who receive at least 1 dose of study treatment. Participants will be summarized by the treatment to which they were randomized, regardless of treatment actually received.

5.4. Per Protocol Set (PPS)

The Per Protocol Set will consist of all participants in the FAS who adhere to the protocol. This set will be used in supplementary analyses of the primary endpoints to evaluate the influence of major protocol violators and protocol deviators on the primary results.

Participants may be excluded from the PPS if they violate the eligibility criteria or significantly deviate from the study plan, including, but not limited to:

- Overall study treatment noncompliance (< 80 or > 120%)

- Receive incorrect study treatment for > 7 days
- Use rescue medication (new or dose increase from the highest dose of background treatment for UC received during Screening) or undergo rescue medical procedure that may affect efficacy endpoint at Week 12
- Miss Week 12 endoscopic score (ES) in prespecified analysis window (per Section 6.4) for reasons other than UC flare or discontinued due to disease worsening or lack of efficacy

Refer to APPENDIX 5 for the definition of rescue therapies (medication and medical procedures). All protocol deviations will be reviewed in addition to the programmable deviations (eg, study treatment noncompliance) to determine if any deviation is significant enough to exclude a subject from the Per Protocol Set. All exclusion flags will be finalized before study unblinding. Participants excluded from Per Protocol Set will be listed along with the reason category above. Participants will be summarized by treatment to which they were randomized, regardless of treatment actually received.

5.5. Modified Full Analysis Set (mFAS)

The mFAS will consist of all randomized participants who receive at least 1 dose of study treatment and have a Baseline and at least 1 post-randomization measurement. Participants will be summarized by treatment to which they were randomized, regardless of treatment actually received. Note that the mFAS can vary with endpoints since some participants may have the needed data for inclusion in the mFAS for some endpoints but others may not.

5.6. Safety Set (SS)

The safety set (SS) will include all randomized participants who receive at least 1 dose of study treatment. Participants will be analyzed according to the treatment received, regardless of randomization. The Safety Set will be used for all safety analyses.

5.7. Pharmacokinetic Set (PKS)

The Pharmacokinetic Set will include all subjects in the Safety Set with at least 1 quantifiable postdose PK measurement of etrasimod which is not impacted by protocol violations or events with potential to affect the PK concentration.

6. GENERAL CONSIDERATIONS

6.1. 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. It will appear in listing where an assessment date or event date appears.

Reference start date is defined as the day of the first dose of study medication (Day 1 is the day of the first dose of study medication).

- If the date of the event is on or after the reference date, then:

Study Day = (date of event – reference start date) + 1

- If the date of the event is prior to the reference date, then:

Study Day = (date of event – reference start date)

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

6.2. Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to the first dose administration (including unscheduled assessments). If measurements include time (except for health-related quality of life [HRQoL] instruments), the date/time will be used to define Baseline. Otherwise, only dates will be compared. For HRQoL instruments, only the date will be used to derive Baseline. In the case where the last non-missing measurement and the date of first dose administration 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.

6.3. Retests, Unscheduled Visits and Early Termination Data

For by visit analyses and summaries, efficacy, safety, HRQoL, and biomarker data (including scheduled, retests, unscheduled, and early termination) will be assigned to visits after the application of the windowing conventions described in Section 6.4. All measurements will be considered in summaries of abnormalities or worst-case values

post-Baseline.

The visit windowing will be applied before missing data are imputed.

Listings will include scheduled, unscheduled, retest, and early termination data.

6.4. Windowing Conventions

All scheduled study visits are defined relative to Study Day 1, the date of first dose administration. Scheduled visit windows are defined in Clinical Study Protocol APD334-203 Appendix 1. 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. Refer to Table 2 for specific visit windows.

For cardiac remonitoring upon treatment reinitiation after Day 2, as evidenced by more than 1 timed measurement in vital signs or electrocardiogram (ECG) parameters on the same collection date of an unscheduled visit, measurements will be mapped to analysis visit of Cardiac Remonitoring 1, Cardiac Remonitoring 2, etc. in the respective analysis dataset. For analysis, each timed measurement will be programmatically assigned to the nearest hourly timepoint (eg, Predose, 1-hour Postdose) based on their relationship to the dosing time on the same day. If the dosing date/time on the same day is missing, the timepoint will remain missing. Once mapped, these timed measurements from cardiac remonitoring visits will not be considered for any other analysis visit.

Windowing will be applied prior to any missing data calculations. The last non-missing measurement taken prior to Day 1 (including unscheduled assessments) will be labeled as "Baseline". Unless stated otherwise, data from all visits including scheduled, unscheduled and ET visits will be eligible for allocation to an analysis visit. The 2-Week and 4-Week Follow-Up visits will not be included in the visit windows and will be summarized separately without any window applied.

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, except for component subscores of MMS or TMS, in which case, the composite score and component subscores from the same date 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 ECG or lab test are available on the same day/analysis visit, the central result will take precedence over the local result.

For the overlapping visit windows at Week 12 and Week 8, a hierarchical algorithm will be applied as following: always map to the Week 12 study visit if the study day falls within the visit window of the Week 12 study visit, then assess the other records for the Week 8 study visit.

Table 2: Visit Windows for Efficacy and Safety Analyses

For All Efficacy (Except Endoscopy/MMS/Histology), Efficacy-Related Biomarkers, Safety Labs and Vital Signs	
Scheduled Study Visit (Protocol Scheduled Day)	**Analysis Visit Window (Study Day)**
Baseline	≤ 1
Week 0 (Day 1)	1
Week 0 (Day 2)[a]	2
Week 2 (Day 15 ± 3)	2 to 22, or 3 to 22[a]
Week 4 (Day 29 ± 3)	23 to 43
Week 8 (Day 57 ± 3)	44 to 71
Week 12 (Day 85 ± 7)	> 71
For Endoscopy/MMS/Histology/All Composite Endpoints That Include an Endoscopy Component and/or RB/SF Component, Physician's Global Assessment, Health-Related Quality of Life, ECGs, OCT, and PFT	
Scheduled Study Visit (Protocol Scheduled Day)	**Analysis Visit Window (Study Day)**
Baseline	≤ 1
Week 0 (Day 1)	1
Week 0 (Day 2)[a]	2
Week 12 (Day 85 ± 7)[b,c]	66 to 113[e] (66 to 141 for assessments impacted by COVID-19 pandemic)[d] or 57 to 113[f] (57 to 141 for assessments impacted by COVID-19 pandemic)[e]

[a] Applicable only for participants who required extended monitoring on Day 2 for vital signs and ECGs
[b] Applicable to all Week 12 efficacy endpoints based on any component of Mayo clinic score, such as clinical remission and symptomatic remission. Protocol visit window for PFT and OCT at Week 12 is Day 85 ± 7(FDA 2020)
[c] Due to overlapping windows at Week 12 and Week 8, a hierarchical algorithm will be used for the mapping. Week 12 will always be mapped first, then assess records for the Week 8 mapping. If scheduled Week 8 and 12 visits are both present in the same visit window, they will be mapped to separate visits (ie, Week 8 and Week 12)
[d] Assessments impacted by the COVID-19 pandemic are reported in the Date of Visit eCRF

[e] Not applicable for OCT/PFT
[f] Applicable for OCT/PFT

COVID-19, Coronavirus disease 2019; ECG, electrocardiogram; eCRF, electronic case report form; MMS, modified Mayo score; OCT, optical coherence tomography; PFT, pulmonary function test; RB, rectal bleeding; SF, stool frequency

6.5. Statistical Tests

No statistical test will be conducted. Point estimate with 95% confidence intervals (CI) will be reported.

6.6. Common Calculations

For quantitative measurements:

- Change from Baseline = Test Value at Visit X – Baseline Value
- Percent change from Baseline = (Test Value at Visit X – Baseline Value) / Baseline Value × 100
- Proportion at Visit X = Number of participants satisfying criteria at Visit X / Total number of participants at Visit X

6.7. General Study Information

A general table with summary of study information will be generated, including the date of first participant signed informed consent form (ICF), the last participant visit date and the database lock date. All analyses will be conducted using SAS® (v9.4 or later, SAS Institute Inc., Cary, NC).

7. DETERMINATION OF SAMPLE SIZE

Based on a Chi square test at 2-sided significance level of 0.05, a total of 96 participants (32 per treatment group) will provide at least 80% power to show pairwise superiority of etrasimod 2 mg to placebo in the primary endpoint assuming 5% remission rate in the placebo group and a 31.5% remission rate in the etrasimod 2 mg group. The assumptions are based on the results from the completed Phase 2 Study APD334-003. Sample size is calculated using the EAST® software.

The actual sample size will be smaller than original planned because this study will be early discontinued in agreement with PMDA consultation.

8. STATISTICAL CONSIDERATIONS

8.1. Multicenter Studies

This study will be conducted by multiple investigators at multiple centers in Japan.

Randomization to treatment groups is stratified by:

- Naïve to biologic or JAK inhibitor therapy at study entry (Yes or No)
- Baseline corticosteroid use (Yes or No)
- Baseline disease activity (MMS: 4 to 6 or 7 to 9)

Data from all sites will be pooled and statistical analyses will not be adjusted for investigational site.

8.2. Adjustments for Covariates and Factors to be Included in Analyses

Not applicable.

8.3. Missing Data

Missing adverse event (AE) relationship to study treatment and AE seriousness will be imputed as described in Section 18.1.1.2 and Section 18.1.3, respectively. Partial or missing AE start dates, concomitant medication (CM) start dates, and hospitalization dates will also be imputed as described in APPENDIX 2. No other missing safety data will be imputed.

Missing efficacy data will be handled as described in Sections 16.1.2, 16.2.2, 16.3.2. In the primary analysis of the primary endpoint and main analyses of all binary responder-type endpoints, all participants with missing data, regardless of reason for missingness, will be considered as non-responders. In the main analysis of continuous or score endpoints, such as biomarker measures and health-related quality of life measures, participants with missing data will be analysed with their observed data only, a mixed-effect model with repeated measures or analysis of covariance (ANCOVA).

8.4. Multiple Comparisons/ Multiplicity

There is no hypothesis to be tested and adjustment for multiplicity.

8.5. Subgroups Analysis

The following subgroups will be assessed for the primary and secondary endpoints using primary method described in Section 16.1.3 on FAS with Baseline MMS 5 to 9:

- Sex (Female or Male)
- Age (≤ or > Median, < or ≥ 65)
- Baseline oral corticosteroid usage (Yes or No)
- Naïve to biologic or JAK inhibitor therapy at study entry (Yes or No)
- Baseline disease activity – Actual MMS (4 to 6, 7 to 9)
- Actual Baseline MMS (5 to 7, 8 to 9)
- Baseline fecal calprotectin (≤ or > Median)
- Baseline high-sensitivity C reactive protein (≤ or > Median)
- Baseline Total Mayo score (≤ or > 8)
- Duration of UC (≤ or > Median)
- Extent of disease (Proctosigmoiditis/Left sided colitis, Pancolitis, Proctitis as reported on the eCRF)
- Proctitis (Yes or No, based on central read)
- Prior UC treatment of oral 5-aminosalicylic acid (5-ASA) only (Yes or No)
- Prior UC treatment failure of oral 5-ASA only (Yes or No)
- Number of prior biologic or JAK inhibitor therapies (1 or > 1)
- Prior UC treatment failure of antitumor necrosis factor alpha (anti-TNFα) (Yes or No)

Additional subgroups may be assessed, if deemed necessary. The medians will be derived based on FAS with baseline MMS 5 to 9 for all subgroups cut at median. It should be noted that the study was not designed to detect treatment differences with high statistical power within subgroups. If any subgroup includes < 5% of all participants, no inferential statistics will be generated.

Actual stratum at baseline will be used for all subgroup analyses.

Forest plots of the overall analysis set and all subgroups will be presented for the primary endpoint. Inference from the model described in Section 16.1.3 will be used and differences in remission percentages along with 95% CIs will be displayed.

9. OUTPUT PRESENTATIONS

APPENDIX 1 shows conventions for presentation of data in outputs.

10. DISPOSITION AND PROTOCOL DEVIATIONS

All participants who provide informed consent will be accounted for in this study.

10.1. Disposition

Inclusion criteria not met and exclusion criteria met will be listed.

Among the randomized participants, the number and percent of participants who completed/discontinued treatment, reasons off treatment, the number and percent of participants who completed/discontinued the study, reasons off study, and the number of participants who continue to APD334-303 will be summarized.

The number and percent of participants in each analysis set will be summarized for all randomized participants. An additional summary of the number of participants screened, the number of screen-failed participants, and reason for screen failure will be presented for all screened participants. A listing of participants whose blind was broken will be provided.

The number of participants whose visit was impacted by the coronavirus disease 2019 (COVID-19) pandemic per eCRF will also be summarized by nominal visit.

Additionally, a summary of missing endoscopy regardless of reason and missing endoscopy due to visit impacted by the COVID-19 pandemic will be presented by visit.

10.2. Protocol Deviations

During site monitoring, protocol deviations are graded as Critical, Major or Minor.

According to ICH E3 and ICH E3(R1), important protocol deviations are a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being (ICH 1995, ICH 2012). For example, important protocol deviations might include enrolling participants in violation of key eligibility criteria designed to ensure a specific subject population

or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the study.

During the review of all reported deviations, important deviations related to study inclusion or exclusion criteria, conduct of the study, patient management or patient assessment will be identified. Where relevant the importance of a potentially important protocol deviations will be assessed in the context of the study's estimands to evaluate potential impact.

All important protocol deviations will be summarized for the FAS in the following categories in descending frequency in the etrasimod 2 mg group.

All protocol deviations will be listed, including whether a deviation was impacted by the COVID-19 pandemic (Yes or No). Protocol deviation categories include but are not limited to the following:

- Informed Consent
- Eligibility and Entry Criteria
- Concomitant Medication
- Laboratory Assessment
- Study Procedures
- Serious Adverse Event
- Randomization
- Visit Schedule
- Investigational Product Compliance
- Efficacy
- Administrative
- Source Document
- Regulatory or Ethics Approvals
- Other

Important protocol deviations will also be summarized by whether they were impacted by the COVID-19 pandemic (Yes or No).

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The following demographic and baseline characteristics will be summarized for the FAS.

- Age on consent (years)
- Sex (Male or Female)
- Woman of childbearing potential (Yes or No)
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)
- Alcohol consumption (Yes or No)
- Caffeine consumption (Yes or No)
- Tobacco use (Yes or No)

The following Baseline characteristics related to UC will be summarized:

- Extent of disease (Proctosigmoiditis/Left-sided colitis, Pancolitis, Proctitis reported on the Ulcerative Colitis History electronic case report form [eCRF], and Proctitis reported from central reader review)
- Baseline MMS
- Baseline rectal bleeding (RB) subscore
- Baseline stool frequency (SF) subscore
- Baseline endoscopic score
- Baseline Physician's Global Assessment (PGA)
- Baseline TMS
- Duration of UC (years)
- Any acute exacerbations within past 12 months (Yes or No), including the number of acute exacerbations among those with any acute exacerbation = Yes
- Colonoscopy within past 12 months (Yes or No)
- Surgery for UC (Yes or No), including the number of surgeries among those with surgery for UC = Yes
- Hospitalizations for UC (Yes or No), including the number of hospitalizations
- Naïve to biologic or JAK inhibitor therapy (Yes or No) – Reported (used for stratification at randomization)
- Naïve to biologic or JAK inhibitor therapy (Yes or No) – Actual (Category of Treatment reported on the Prior Treatment for Ulcerative Colitis eCRF)
- Baseline corticosteroid use (Yes or No) – Reported (used for stratification at randomization)
- Baseline corticosteroid use (Yes or No) – Actual (Category of Treatment reported on the Prior Treatment for Ulcerative Colitis eCRF)

- Baseline MMS group (4 to 6, 7 to 9) – Reported (used for stratification at randomization)
- Baseline MMS group (4 to 6, 7 to 9, and 5 to 9) – Actual (scores reported on the Mayo Clinic Score eCRF)
- Naïve to biologic or JAK inhibitor therapy – Difference between the Reported and the Actual
- Baseline corticosteroid use (Yes or No) – Difference between the Reported and the Actual
- Baseline MMS group (4 to 6, 7 to 9) – Difference between the Reported and the Actual
- Prior failure of oral 5-ASA only (Yes or No)
- Prior failure of anti-TNFα (Yes or No)
- Prior failure of anti-TNFα or vedolizumab (Yes or No)

Prior treatment for UC will be summarized, including category of treatment, reason for discontinuation, and estimated duration (weeks) of corticosteroid use over the last 12 months.

11.1. Derivations

- Duration of UC (year) = (Informed consent date – Date of diagnosis by physician + 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 $(m)^2$

For date of diagnosis by physician, if day is missing, then impute to 1st of the month, if day and month is missing, then impute to 1st January.

12. MEDICAL HISTORY

Medical history will be collected on the medical history eCRF and coded using Medical Dictionary for Regulatory Activities (MedDRA, v24.1 or higher). The version used to code medical history will be displayed in the outputs. All medical history will be summarized for the Safety Set by system organ class (SOC) and preferred term (PT).

13. MEDICATIONS AND NON-DRUG TREATMENT

Medications will be captured on the Concomitant Medications eCRF and coded using the World Health Organization (WHO) Drug dictionary (WHODDE01SEP2021 or higher). Refer to 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 (ie, concomitant).

- 'Prior' medications are medications which started and stopped prior to the 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 Anatomical Therapeutic Chemical (ATC) Level 2 and Preferred Drug name for the Safety Set. Concomitant medications being used for UC will be flagged as such on the Concomitant Medications eCRF and summarized by ATC Level 2 and Preferred Drug name for the Safety Set.

Non-drug treatment will be captured on the Concomitant Non-Drug Treatment eCRF and coded using MedDRA version 24.1 or higher. A listing will be provided for Safety Set.

14. STUDY TREATMENT EXPOSURE

The date of first and last study treatment administration will be taken from the Day 1 On Site Dosing Administration eCRF and the End of Study eCRF, respectively. Interruptions, compliance, and dose changes are not taken into account for duration of exposure. Exposure to study treatment in weeks will be summarized for the Safety Set.

Dose interruptions will be recorded on the Dosing Administration eCRF, and overdose will be recorded on the Overdose eCRF. The frequency and percentage of participants who had at least 1 dose interruption, who had at least 1 dose interruption of > 7 days, who had at least 1 dose interruption of > 14 days, who had 1 overdose, and who had > 1 overdose will be summarized.

14.1. Derivations

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/end dates eCRF recorded.

15. STUDY TREATMENT COMPLIANCE

The time on study (weeks), total subject-years on study, total treatment exposure (weeks), total subject-years of exposure, total number of tablets expected, total number of tablets taken, total number of tablets missed, overall

compliance with study treatment, and frequency and percentage of study treatment exposure category (< 4 weeks, ≥ 4 and < 8 weeks, ≥ 8 and < 12 weeks and ≥ 12 weeks) and participants with overall compliance of < 80% or > 120% will be summarized for the Safety Set.

15.1. Derivations

Compliance with 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, refer to calculations below.

The total number of tablets expected is defined as the number of tablets that a subject is expected to have taken between their first and last study treatment administration and is numerically identical to the subject's overall study treatment exposure, since the medication is to be taken once daily. On any site visit day, the medication is to be held and taken at the site, after all predose assessments have been completed. For example, if a subject took their last dose of study treatment on Day 60 and returned to the site on Day 78 to return the study treatment bottle, then the total number of tablets expected would be 60, not 77.

- Total number of tablets expected = (date of last study treatment administration – date of first study treatment administration + 1) (days) × 1 (tablet / day)

For all bottles not returned, it will be assumed that all dispensed tablets were taken. For each subject, if a high percentage (> 25%) of bottles were not returned by a subject, additional analyses may be done where bottles not returned are excluded from the overall compliance calculation for that subject. In such analysis, the date of last dose or the date of last bottle return, whichever is earlier, will be used as the "date of last dose" in the calculation above.

Both scheduled and unscheduled study treatment dispensations will be used in the compliance calculation. Overall compliance calculations will be performed for the 12-Week Treatment Period and will be used in determining inclusion/exclusion of participants in the respective Per Protocol Set.

Other derivations are shown below:

- Time on study (weeks) is calculated as ("Date of Completion/Termination of Study" on the eCRF Page "End of Study" – informed consent date + 1)/7.
- Total subject-years on study is calculated as the sum of duration of time on study (days) across all subjects divided by 365.25.
- Exposure (weeks) is calculated as (end date of study treatment - start date of study treatment + 1)/7.

- Total subject-years of exposure is calculated as the sum of duration of treatment exposure (days) across all subjects divided by 365.25.
- Tablets missed is calculated as (the number of tablets expected – the number of tablets taken) and can be negative if subject has taken more than expected number of tablets.

16. EFFICACY OUTCOMES

Unless otherwise stated, the primary efficacy analyses will be based on the FAS with Baseline MMS 5 to 9. Primary and secondary efficacy analyses will be repeated for all participants in FAS with Baseline MMS 4 to 9 as supplementary analysis.

The following definitions will be used to assess efficacy outcomes:

- Clinical remission: SF subscore = 0 (or = 1 with a ≥ 1-point decrease from baseline), RB subscore = 0, and ES ≤ 1 (excluding friability)
- Endoscopic improvement: ES ≤ 1 (excluding friability)
- Symptomatic remission: SF subscore = 0 (or = 1 with a ≥ 1-point decrease from baseline) and RB subscore = 0
- Mucosal healing: ES ≤ 1 (excluding friability) with histologic remission measured by a Geboes Index score < 2.0
- Clinical response: A ≥ 2-point and ≥ 30% decrease from baseline in MMS, and a ≥ 1-point decrease from baseline in RB subscore or an absolute RB subscore ≤ 1
- Endoscopic normalization: ES = 0
- Complete symptomatic remission: SF subscore = 0 and RB subscore = 0
- Noninvasive clinical response: A ≥ 30% decrease from baseline in composite RB and SF, and a ≥ 1-point decrease from baseline in RB subscore or an absolute RB subscore ≤ 1
- Symptomatic response: Decrease from baseline ≥ 30% in composite RB and SF subscores
- Clinical remission using TMS: TMS of ≤ 2 points with no individual subscore of > 1 point
- Clinical response using TMS: A ≥ 3-point and ≥ 30% decrease from baseline in TMS, and a ≥ 1-point decrease from baseline in RB subscore or an absolute RB subscore ≤ 1
- Histologic improvement using Geboes Index: Geboes Index score < 3.1
- Histologic remission using Geboes Index: Geboes Index score < 2.0
- Histologic improvement using Robarts Histopathology Index (RHI): ≥ 50% reduction from Baseline in RHI or RHI ≤ 3
- Histologic remission using RHI: RHI ≤ 3, with scores of 0 (zero) for both Geboes Grade 2B (lamina propria

neutrophils) and Grade 3 (neutrophils in epithelium)

- Histologic improvement using Nancy Histologic Index (NHI): ≥ 1 point reduction from Baseline NHI
- Histologic remission using NHI: ≤ 1
- Improvement in extraintestinal manifestations (EIMs): any category improved at post-baseline

16.1. Primary Efficacy

16.1.1. Primary Efficacy Variable & Derivation

The primary efficacy endpoint will compare each etrasimod dose (1 and 2 mg) to placebo for:

- The proportion of participants achieving clinical remission at Week 12

Clinical remission is defined in Section 16. The SF, RB, and ES subscores will be based on the Mayo Clinic score eCRF, but only if a subscore at baseline in eCRF is missing it will be imputed by corresponding data in Interactive Response Technology (IRT). Participants who achieve clinical remission will be referred to as responders. Participants who do not achieve clinical remission will be referred to as nonresponders.

16.1.2. Missing Data Methods for Primary Efficacy Variable

Participants who:1) discontinue the study for lack of efficacy or adverse event related to UC (data collected for Primary Reason off Study from End of study eCRF and Adverse Events eCRF), 2) initiate a rescue medication for UC, 3) have an increase in dose over Baseline levels in their existing UC medication, or 4) have rescue non-drug treatment (eg, colectomy, ileostomy, or sigmoidectomy) during the study as confirmed after blinded review by clinical and medical team members before study unblinding will be considered to have a known (ie, non-missing) outcome of nonresponse and not as having missing data in the analysis of all efficacy endpoints at any subsequent timepoints, including the primary endpoint. The rescue therapies will be identified by the Arena clinical team during blinded data review. Refer to APPENDIX 5 for the definition of rescue therapies (medication and medical procedures). In scenarios 2 and 3 above, if a subject has an efficacy measurement collected after the initiation or dose increase from Baseline of UC medication, the observed data will be censored at the time of initiation or dose increase and they will be considered as having a nonresponse. Subjects in all 4 scenarios above may still be included in the respective Per Protocol Set, provided they do not violate other criteria for Per Protocol Set. For example, they will be excluded from the Per Protocol Set if they initiate a prohibited medication before the Week 12 efficacy assessment that can affect efficacy of the study treatment and the indication is unrelated to UC.

Analysis visits will be mapped as per Section 6.4 before any missing data imputation method is applied.

Participants with a missing efficacy outcome will be included in the primary analysis using single imputation as non-responder.

16.1.3. Primary Analysis of Primary Efficacy Variable

The primary efficacy analysis will be performed for the FAS with Baseline MMS 5 to 9. Results will be expressed as the number and percentage of participants in clinical remission, difference in clinical remission percentages and 95% CI, odds ratio and associated 95% CI.

16.1.4. Supplementary Analysis of Primary Efficacy Variable

The primary analysis as described in Section 16.1.3 using non-responder imputation will be repeated using the mFAS and Per Protocol Set as supplementary analyses in participants with actual Baseline MMS 5 to 9.

The primary analysis as described in Section 16.1.3 will be repeated for the primary endpoint using the FAS with Baseline MMS 4 to 9.

16.2. Secondary Efficacy

There is no statistical hypothetical testing of the secondary endpoints.

Secondary efficacy endpoints are defined in Section 16. In general, the primary analysis and supplementary analyses in mFAS planned for the primary endpoints in Sections 16.1.3 and 16.1.4 will be repeated for each secondary efficacy endpoint (Table 3).

Table 3: Planned Analysis by Endpoint

Endpoint	Primary Analysis	Supplementary Analyses in mFAS	Supplementary Analyses in PPS
Primary endpoints	X	X	X
Secondary endpoints			
Endoscopic improvement	X	X	
Symptomatic remission	X	X	

Endpoint	Primary Analysis	Supplementary Analyses in mFAS	Supplementary Analyses in PPS
Mucosal healing	X	X	
Clinical response	X	X	
Endoscopic normalization	X	X	

Analyses in the table will be repeated for participants in the FAS with Baseline MMS 4 to 9.
mFAS, modified Full Analysis Set.

16.2.1. Secondary Efficacy Variables & Derivations

- Endoscopic improvement at Week 12
- Symptomatic remission at Week 12
- Mucosal healing at Week 12
- Clinical response at Week 12
- Endoscopic normalization at Week 12

16.2.2. Missing Data Methods for Secondary Efficacy Variables

The same missing data methods used for the primary endpoint described in Section 16.1.1 and Section 16.1.2 will be used for the secondary endpoints.

16.2.3. Primary Analysis of Secondary Efficacy Variables

The primary analysis of all the secondary efficacy endpoints will be performed for the FAS with Baseline MMS 5 to 9. For all secondary endpoints, the same analysis that was described in Section 16.1.3 will be performed.

16.2.4. Supplementary Analysis of Secondary Efficacy Varaibles

For all secondary endpoints, the primary analysis as described in Section 16.1.3 using non-responder imputation will be repeated using the mFAS with actual Baseline MMS 5 to 9 as supplementary analyses.

For all the secondary endpoints, primary analyses listed in Table 3 will be repeated in participants using FAS with Baseline MMS 4 to 9.

16.3. Exploratory Efficacy

Exploratory efficacy endpoints are defined in Section 16.

16.3.1. Exploratory Efficacy Variables and Derivations

Exploratory efficacy endpoints are:

- The proportion of participants achieving symptomatic remission at Weeks 2, 4, 8
- The proportion of participants achieving complete symptomatic remission at each study visit (Weeks 2, 4, 8, 12)
- The proportion of participants achieving noninvasive clinical response at each study visit (Weeks 2, 4, 8, 12)
- The proportion of participants achieving symptomatic response at each study visit (Weeks 2, 4, 8, 12)
- The proportion of participants with remission and response using TMS at Week 12
- The proportion of participants with histologic improvement at Week 12 (as defined by the Geboes Index, Robarts Histopathology Index, and Nancy Histologic Index)
- The proportion of participants with histologic remission at Week 12 (as defined by the Geboes Index, Robarts Histopathology Index, and Nancy Histologic Index)
- The proportion of participants with improvement in extraintestinal manifestations (EIMs) at Week 12 in participants with EIMs at baseline

16.3.2. Missing Data Methods for Exploratory Efficacy Variables

All participants with missing data, regardless of reason for missingness, will be considered as non-responders. The intercurrent events that are considered in the primary efficacy analysis will be handled similarly for the exploratory efficacy endpoints, as specified in Section 16.1.2.

16.3.3. Analysis of Exploratory Efficacy Variables

All proportion-based endpoints will be analysed as described in Section 16.1.3 for the mFAS with Baseline MMS 5 to 9. The pairwise Spearman's rank correlation coefficients among the 3 histological scoring indices will also be presented by treatment group.

No multiplicity adjustments will be made.

16.4. Efficacy-Related Biomarkers

Value and change from Baseline in level of fecal calprotectin (FCP), hs-CRP, and lymphocyte counts at protocol-specified visits will be summarized by visit and treatment for the FAS with Baseline MMS 5 to 9. Additionally, percent change from Baseline in lymphocyte counts will also be summarized. Change from Baseline in these biomarkers will also be analysed using a mixed-effect model with repeated measures (MMRM), with factors for treatment, visit, treatment by visit interaction, and a covariate of the corresponding Baseline value. Unstructured covariance will be used. If there is a convergence issue in fitting the unstructured covariance, a heterogeneous Toeplitz, heterogeneous autoregressive (1), autoregressive (1), or compound symmetry covariance structure will be used. The same model will be fit to the percent change from Baseline in lymphocytes. LS means, SEs, and CIs by visit will be reported.

Additionally, the following summaries will be provided for biomarker data:

- Line plots over time for LS mean and SE for the following laboratory assessments:
    - Change from Baseline in lymphocytes
    - Percent change from Baseline in lymphocytes
    - Change from Baseline in hs-CRP
    - Change from Baseline in FCP

The exploratory efficacy-related biomarker analyses for immunophenotyping and proteomics will be described in a separate biomarker analysis plan.

17. HEALTH-RELATED QUALITY OF LIFE (HRQOL) AND HEALTHCARE RESOURCE UTILIZATION ANALYSIS

Subject-reported HRQoL instruments will be electronically captured and used in support of the efficacy outcomes. All HRQoL are administered at Baseline and Week 12. The HRQoL analyses will be performed using the mFAS with Baseline MMS 5 to 9.

All HRQoL endpoints will be analyzed using an ANCOVA for the change from Baseline, with a factor for treatment and a covariate of the corresponding HRQoL Baseline value.

Healthcare resource utilization endpoints, ie, the proportion of concomitant UC-related hospitalizations and the proportion of concomitant UC-related surgeries, including colectomy, will be analyzed as described in Section

16.1.3 for the FAS with Baseline MMS 5 to 9.

17.1. Variables and Derivations

17.1.1. Ulcerative Colitis Patient-Reported Outcomes Signs and Symptoms

The Ulcerative Colitis Patient-Reported Outcomes Signs and Symptoms (UC-PRO/SS) is a 9-item daily diary designed to quantify the effects of treatment on patient-reported signs and symptoms of UC. Two separate weekly average scores will be calculated, one for bowel signs and symptoms score (6 items), and the other for abdominal symptoms (3 items). The higher the score, the worse the symptoms. The UC-PRO/SS scores and change from Baseline at Week 12 will be evaluated. Details about scoring rules can be found in APPENDIX 3.

17.1.2. 36 Item Short Form Health Survey, version 2

The 36-Item Short Form Health Survey (SF-36) is a 36-item, subject-reported survey of subject health. The SF-36 consists of 36 questions measuring 8 health domains: physical functioning, bodily pain, role limitations due to physical problems, role limitations due to emotional problems, general health perceptions, mental health, social function, and vitality. The subject's responses are solicited using Likert scales that vary in length, with 3 to 6 response options per item. The SF-36 will be scored using 2 overall summary scores: physical component summary and mental component summary scores. A higher score indicates better health status.

The Physical Component Summary Score (norm-based), the Mental Component Summary Score (norm-based), 8 domain subscores (0 to 100 based), and the SF-6D health utility index score are derived by Optum and integrated into the SF-36 eCRF. Details about scoring rules and derivations of domain/component scores can be found in APPENDIX 4.

17.1.3. UC-Related Hospitalizations and Surgeries

The UC-related hospitalizations are captured on the Adverse Events eCRF. The UC-related surgeries, including colectomy, are captured on the Concomitant Non-Drug Treatment eCRF. Blinded review of AE preferred terms will be performed to determine UC-related hospitalizations.

17.2. Missing Data Methods

Missing data will not be imputed for HRQoL endpoints.

18. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SS. There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified.

18.1. Adverse Events

AEs will be coded using MedDRA (v24.1 or higher). The version used to code AEs will be displayed in the analyses. Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of study treatment.

Refer to 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.

18.1.1. All TEAEs

All TEAEs will be summarized by SOC and PT. This summary table and all other TEAE summaries by SOC and PT will be presented by descending frequency in the etrasimod total group. All AEs, regardless of treatment emergent status, will be included in an AE listing. Additionally, a listing of other AE details, as collected on the eCRF, will be presented.

Exposure-adjusted incidence rate (EAIR) of TEAEs will be summarized by SOC and PT. Exposure is defined as the sum of either time (year) from first dose to the onset of first such event for those who experienced this AE, or time (year) from first dose to last participation date in the study for those who did not experience this AE. The EAIR is calculated as the number of participants with the AE divided by the total exposure in subject-years.

18.1.1.1. 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, v5.0 (CTCAE v5.0).

All TEAEs will be summarized by SOC, PT, and maximum severity, with SOC and PT presented by descending frequency of etrasimod total group. If a subject reports a TEAE more than once within a SOC/PT, the AE with the worst-case severity will be used in this summary.

TEAEs with a missing severity will be classified as Grade 3: Severe to study treatment for summary tabulation purpose only.

18.1.1.2. Relationship to Study Treatment

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

All related TEAEs will be summarized by SOC and PT. A "related TEAE" for the purpose of this summary is defined as a TEAE with relationship to study treatment of "probably related" or "related".

All TEAEs will be summarized by SOC, PT, and highest relationship (as reported on the eCRF, not grouped), with SOC and PT presented by descending frequency of etrasimod total group. If a subject reports a TEAE more than once within a SOC/PT, the AE with the worst-case relationship to study treatment will be used in this summary.

TEAEs with a missing relationship to study treatment will be regarded as "Related" to study treatment for summary tabulation purpose only.

18.1.2. TEAEs Leading to Discontinuation of Study Treatment

TEAEs leading to discontinuation of study treatment will be identified by action taken with study treatment being recorded as "Drug withdrawal" on the Adverse Events eCRF.

All TEAEs leading to discontinuation of study treatment will be summarized by SOC and PT. A listing of all TEAEs leading to discontinuation of study treatment will also be presented.

Liver-related AEs are defined by either SOC of hepatobiliary disorders or PT of alanine aminotransferase abnormal, alanine aminotransferase increased, aspartate aminotransferase abnormal, aspartate aminotransferase increased, hepatic enzyme abnormal, hepatic enzyme increased, liver function test abnormal, liver function test increased, transaminases abnormal, or transaminases increased.

18.1.3. Serious and Non-Serious TEAEs

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events eCRF.

All serious TEAEs will be summarized by SOC and PT. If the seriousness is missing, the AE will be considered as "Serious" for summary tabulation purpose only. A serious TEAE listing will also be presented. All non-serious TEAEs will be summarized by SOC and PT.

18.1.4. TEAEs Leading to Death

TEAEs leading to Death are those events which are recorded with an outcome as "Fatal" or AE Severity is equal to Grade 5 on the Adverse Events eCRF. All TEAEs leading to death will be listed.

18.1.5. 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. In addition, where standard testing has been implemented to screen for potential AESI (eg, electrocardiograms, spirometry, serum transaminases, etc.), the relevant data will be reviewed to identify potential cases of AESI that investigators may not have identified and to provide quantitative data for AESIs. The proposed candidate terms will be reviewed to identify which events reflect AESI.

Treatment-emergent AESIs 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 (forced expiratory volume in 1 second [FEV_1], forced vital capacity [FVC])
    - Decrease gas exchange (diffusing capacity of the lungs for carbon monoxide [DLCO])
- Infections
    - Severe infections
    - Opportunistic infections (Narrow)

- Herpes simplex and herpes zoster

- Liver Injury
  - Liver transaminases elevation
  - Bilirubin elevation

- Posterior Reversible Encephalopathy Syndrome (PRES)
- Malignancies

18.1.6. Overall Summary of Adverse Event

In addition to the summaries above, an overview of TEAEs will be summarized (not broken down by SOC or PT) by number and percentage of participants and by number of AEs:

- Any TEAEs
- Any related TEAEs*
- Any serious TEAEs
- Any related serious TEAEs*
- TEAEs leading to death
  - Liver related TEAEs leading to death
- TEAEs leading to study treatment discontinuation
  - Related TEAEs leading to study treatment discontinuation*
  - Liver related TEAEs leading to study treatment discontinuation
- TEAEs leading to study treatment interruption (events recorded with an action taken with study treatment as "Drug interrupted" on the Adverse Events eCRF)
  - Related TEAEs leading to study treatment interruption*
- TEAEs by maximum severity
- Related TEAEs by maximum severity*
- TEAEs by maximum relationship to study treatment

* "Related TEAEs" refers to TEAEs "related" or "probably related" to study treatment or are missing relationship.

18.2. Deaths

Information collected about deaths (eg, date of death, primary cause of death) will be presented in a data listing, as described in Section 18.1.4.

18.3. Laboratory Evaluations

No local laboratory assessments will be used in any summaries except for lipid panel and thyroid panel tests. No local laboratory assessments will be used to derive maximum/minimum/worst value. Local laboratory assessments will be listed.

18.3.1. Safety Laboratory Evaluations

Hematology, serum chemistry, coagulation, and urinalysis are analysed and reported by central laboratory and sometimes by local laboratory. Results out of reference range are flagged by the performing laboratory (eg, low, high). A full list of laboratory assessments to be included in the outputs is included in Clinical Study Protocol APD334-203 Table 6.

In general, presentations will use Système international d'Unités (SI units). Quantitative laboratory measurements reported as "< X" or "> X", where X may be the lower limit of quantitation (LLQ) or the upper limit of quantitation (ULQ), respectively, will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, ie, as "< X" or "> X" in the listings. For urinalysis, only pH and specific gravity are considered as quantitative tests. If local and central laboratory assessments are available from the same day, central laboratory assessments will be used in the summary as per Section 6.4.

The following summaries will be provided for laboratory data:

- Value and change from Baseline by visit (for hematology, serum chemistry, quantitative urinalysis [pH and specific gravity], coagulation, and high-sensitivity C-reactive protein [hs-CRP])
- Incidence of abnormal values according to laboratory reference ranges by visit
- Incidence of lymphocytes $< 0.2 \times 10^9$/L, 0.5×10^9/L, or neutrophils $< 0.5 \times 10^9$/L, 1×10^9/L at end of treatment and anytime in the study
- Shift from end of treatment to each follow-up visit in incidence of lymphocytes in normal range and in incidence of lymphocytes of at least 80% percent of Baseline, by visit (2-Week Follow-Up, 4-Week Follow-Up, and Last Follow-Up)

- Shift from Baseline to end of treatment according to laboratory reference range (for quantitative measurements and categorical measurements)
- Evaluation of drug-induced serious hepatotoxicity (eDISH) plots for the following laboratory assessments (using values after the first administration of study treatment):
    - Maximum aspartate aminotransferase (AST) versus same-day total bilirubin
    - Maximum alanine aminotransferase (ALT) versus same-day total bilirubin
    - Maximum gamma-glutamyl transferase (GGT) versus same-day total bilirubin
    - Maximum alkaline phosphatase (ALP) versus same-day total bilirubin

The eDISH plots above will be repeated with adjustment for elevated baseline.

- Incidence of hepatic enzyme elevations by visit
    - > 1 ×, 2 ×, 3 ×, 5 ×, 8 ×, 10 ×, 20 × upper limit of normal (ULN) elevation in ALT
    - > 1 ×, 2 ×, 3 ×, 5 ×, 8 ×, 10 ×, 20 × ULN elevation in AST
    - > 3 ×, 5 ×, 10 ×, 20 × ULN elevation in either ALT or AST
    - > 1 ×, 1.5 ×, 2 ×, 3 × ULN elevation in total bilirubin
    - > 1 ×, 1.5 ×, 2 ×, 3 ×, 5 ×, 8 × ULN elevation in ALP
    - > 1 ×, 2 ×, 3 ×, 5 ×, 8 × ULN elevation in GGT
    - > 3 × ULN elevation in either ALT or AST and > 1.5 × ULN elevation in total bilirubin
    - > 3 × ULN elevation in either ALT or AST and > 2 × ULN elevation in total bilirubin
    - > 3 × ULN elevation in either ALT or AST and > 1.5 × ULN elevation in ALP
    - > 3 × ULN elevation in either ALT or AST in temporal association with treatment-emergent nausea, vomiting, anorexia, abdominal pain, or fatigue identified by PT, where temporal association is defined as ±14 days of onset date from the time of elevation.

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, GGT, or ALP assessment occurs at 2 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 ULN, and the other one showing values as multiples of ULN, or subject's baseline, whichever is higher.

All laboratory tests will be listed. Subject's laboratory assessments at all timepoints will be listed in chronological order. 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 who ever had lymphocytes < 0.5 ×

10^9/L or neutrophils < 1 × 10^9/L will also be provided.

18.3.2. Pregnancy Tests

Urine beta-human chorionic gonadotropin (β-hCG) and/or serum β-hCG pregnancy tests are performed throughout the study in female participants of childbearing potential. All pregnancy test results (positive or negative) will be listed in chronological order.

18.3.3. Other Screening Laboratory Assessments

Screening laboratory assessments for virology, drug screen/toxicology, QuantiFERON Tuberculosis (TB) Gold, stool pathogens, and Clostridioides difficile (formerly known as Clostridium difficile) will be listed. Analyses of exploratory efficacy-related biomarkers data based on samples collected at Screening in participants who provided consent will be described in a separate plan.

18.4. ECG Evaluations

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

- HR (beats per minute [bpm])
- PR interval (ms)
- RR interval (ms)
- QRS interval (ms)
- QT interval (ms)
- QTcF interval (ms)
- Overall interpretation of ECG (Investigator's judgment):
    - Normal
    - Abnormal, Not Clinically Significant (Abnormal not clinically significant [NCS])
    - Abnormal, Clinically Significant (Abnormal CS)
- Overall interpretation of ECG (central reader):
    - Normal

- Abnormal NCS
- Abnormal CS

- AV conduction abnormalities
  - First degree AV block
  - Second degree AV block type 1
  - Second degree AV block type 2
  - Third-degree AV block

The following summaries will be provided for ECG data:

- Value and change from Baseline by visit (for quantitative measurements)
- Incidence of markedly abnormal values (defined in Section 18.4.1) and AV blocks by visit
- Shift in normal/abnormal NCS/abnormal CS in the overall interpretation (by investigator) from Baseline to end of treatment and to the worst-case post-Baseline
- Shift in markedly abnormal categories from Baseline to post-Baseline by visit

Listings of ECG results, including first dose cardiac monitoring, and discharge criteria for first dose cardiac monitoring will be provided.

A listing of all ECG assessments over time in participants meeting markedly abnormal criteria will also be provided. For each subject, only ECG parameters ever meeting markedly abnormal criteria will be included.

18.4.1. ECG Markedly Abnormal Criteria

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

- Absolute values in QT and QTcF:
  - ≥ 450 ms (male) or ≥ 470 ms (female) in QTcF
  - > 500 ms in QT

- Change from Baseline in QT and QTcF:
  - > 30 ms increase from Baseline
  - > 60 ms increase from Baseline

In shift tables, participants will be classified according to the binary category for each parameter and the predefined markedly abnormal criterion (ie, Markedly abnormal versus Not markedly abnormal, with Markedly abnormal defined in the footnote).

18.5. Vital Signs

The following vital signs measurements will be 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) (Screening only)

The following summaries will be provided for vital signs data:

- Value and change from Baseline by visit
- Value and change from predose on Day 1 (as reported on the eCRF) by timepoint
    - Value and change from predose to minimum postdose heart rate on Day 1 will be included in the same table
- Incidence of markedly abnormal values (defined in Table 4) by visit
- Listing of participants meeting markedly abnormal criteria
- Incidence of minimum heart rate on Day 1 by postdose timepoint (1, 2, 3, 4, and > 4 hours postdose, and Day 1 overall) and heart rate interval (≥ 65, 60 to 64, 55 to 59, 50 to 54, 45 to 49, 40 to 44, < 40 bpm)
    - If minimum heart rate is attained at multiple postdose timepoints, only the earliest timepoint will be counted in this incidence summary.
- Time to minimum heart rate on Day 1 by planned hourly timepoint (if minimum heart rate is attained at multiple postdose timepoints, only the earliest timepoint will be counted).
    - Actual time elapsed from first dose to minimum heart rate on Day 1 will also be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum) in the same table.

- Line plots for mean value and mean change from predose on Day 1, up to 4 hours postdose by parameter and timepoint (systolic blood pressure, diastolic blood pressure, and heart rate)
- Line plots for mean value and mean change from Baseline by parameter and visit (systolic blood pressure, diastolic blood pressure, heart rate)

Listings of all vital signs, including first dose cardiac monitoring, and discharge criteria for first dose cardiac monitoring will be provided. A listing of vital signs assessments over time in participants meeting a markedly abnormal criterion will also be provided. For each subject, only the parameters with at least one markedly abnormal criterion satisfied will be included.

For participants with extended monitoring or re-monitoring, a listing of systolic blood pressure, diastolic blood pressure, heart rate values, and change from predose in all parameters on Day 1, Day 2, and any re-monitoring visit will be provided.

18.5.1. Vital Signs Specific Derivations

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

18.5.2. Vital Signs Markedly Abnormal Criteria

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

Table 4: Markedly Abnormal Criteria for Vital Signs

Variable	Unit	Low	High
SBP	mmHg	≤ 90 mmHg	> 150 mmHg
DBP	mmHg	≤ 50 mmHg	> 90 mmHg
Heart rate	bpm	< 40 bpm < 50 bpm < 50 bpm and decrease from predose (Baseline) of > 10 bpm at 4 hours on Day 1 or Day 2 or remonitoring visit	> 100 bpm

bpm, beats per minute; DBP, diastolic blood pressure; SBP, systolic blood pressure.

18.6. Physical Examination

A listing of all physical examination assessments in participants who had at least 1 abnormal physical examination finding will be provided.

18.7. Other Safety Assessments

18.7.1. Pulmonary Function Test

The following pulmonary function test (PFT) measurements (actual and % Predicted) will be reported for this study:

- Forced Expiratory Volume at 1 second (FEV1)
- Forced Vital Capacity (FVC)
- Total Lung Capacity (TLC)
- FEV1/FVC
- Forced Expiratory Flow (FEF) 25-75
- Diffusing Capacity of the Lungs for Carbon Monoxide (DLCO) (if available)

The following summaries will be provided for PFT data:

- Value and change from Baseline by visit
- Incidence of markedly abnormal values by visit (Section 18.7.1.1)

All PFT data will be listed. A listing in participants who ever reported an abnormality in PFT will also be provided, including a flag for whether markedly abnormal criterion is also met.

18.7.1.1. PFT Markedly Abnormal and Potentially Important Criteria

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

- % Predicted $FEV_1 < 50\%$
- % Predicted FVC < 50%
- % Predicted FEV_1/FVC ratio < 50%

Potentially important PFT measurements will also be identified using the criteria below:

- Decrease from Baseline > 20% in FEV_1, ie, percent change from Baseline < -20%
- Decrease from Baseline > 20% in FVC, ie, percent change from Baseline < -20%
- Decrease from Baseline > 20% in DLCO, ie, percent change from Baseline < -20%

18.7.2. Ophthalmoscopy and Optical Coherence Tomography

The following summaries will be provided for ophthalmoscopy and optical coherence tomography (OCT) data:

- Values and change from Baseline in intraocular pressure by visit
- Categorical result in ophthalmoscopy with OCT parameters by visit (the categories are listed on the Ophthalmoscopy with OCT eCRF)

A listing of all ophthalmoscopy and OCT assessments will be provided. A listing of participants who ever reported an abnormality in OCT will also be provided. Additionally, a listing of retinal photograph and eye pressure assessments will be provided for participants who experienced an AE related to eye disorders.

18.7.3. Tuberculosis Screening and Chest X-Ray

Screening tuberculosis results and chest X-rays will be listed. Results of tuberculosis questionnaires will also be listed.

19. PHARMACOKINETIC ANALYSIS

Plasma concentrations of etrasimod will be assessed from samples collected prior to dosing and 4 hours (±15 minutes) post-dose (after 12-lead ECG) on Week 0/Day 1, samples collected prior to dosing (trough; within 60 minutes prior to dosing) at Weeks 2, 4, 8, and 12. Additionally, samples are being collected at 2-Week and 4-Week Safety Follow-up visits (for subjects not enrolling into the OLE study), and if possible, at the time of any SAE or adverse event leading to study treatment discontinuation are being collected. Concentrations below the limit of quantification (BLQ) will be assigned a numerical value of zero for the calculation of descriptive statistics in concentrations (except for geometric mean and geometric %CV) and plotting of concentrations. For geometric mean and geometric %CV, the zero values will be excluded.

The pharmacokineticist will determine the strategy for dealing with data affected by protocol deviations or events which may impact the quality of PK concentration data on a case-by-case basis with input from the Pfizer study physician and Pfizer clinical pharmacologist, as needed. Examples for protocol deviations or events include, but

may not be limited to, vomiting on the day prior to trough sample collection, sample processing errors that lead to inaccurate bioanalytical results, and/or inaccurate dosing prior to PK sampling. In the case of an important protocol deviation or event, the affected PK data collected may be excluded from the summaries, calculation of the average steady state trough plasma concentration (C_{trough}) based on available Week 2 to Week 12 trough concentrations ($C_{trough,ss,W2\text{-}W12}$), exposure-response analysis, and/or population PK analysis, but will still be reported in the study result listings. The time window of 24 hours ±8 hours after the last dose prior to PK sample is required for inclusion in calculating $C_{trough,ss,W2\text{-}W12}$ and summarizing trough.

Unless otherwise specified, PK summaries will use the Pharmacokinetic Set. Exposure-response analysis will use the Safety Set.

Individual subject etrasimod plasma concentrations will be presented in the data listings, including subject ID, treatment received, sex, age, weight, nominal timepoint, actual blood collection date/time, concentration, and time since last dose, and also summarized using descriptive statistics (n, mean, SD, %CV, geometric mean, geometric % CV, median, minimum, and maximum) by nominal timepoint and treatment. Summary table will be repeated by: Sex (male/female), age at consent (<18, 18 to <65, ≥65), Tobacco use (Yes/No), and weight (≤ Median or > Median).

All subjects are expected to achieve steady-state plasma concentration by Week 2. For each subject, the average steady state trough (pre-dose) plasma concentration (C_{trough}) based on Week 2 to Week 12 trough concentrations ($C_{trough,ss,W2\text{-}W12}$) per subject will also be calculated and presented in a data listing and summarized using descriptive statistics by treatment.

Mean (±SD) etrasimod concentration versus nominal time will be plotted by treatment on linear scale. Summary figure will be repeated by: Sex (male/female), age at consent (<18, 18 to <65, ≥65), Tobacco use (Yes/No), and weight (≤ Median or > Median).

Box plots of etrasimod concentrations at Day 1, 4 hour post-dose timepoint (C4hr) and average steady-state C_{trough} (Weeks 2 through 12 [$C_{trough,ss,W2\text{-}W12}$]) will be plotted versus nominal timepoint on ordinal scale, separately by treatment. Box plots figure will be repeated by: Sex (male/female), age at consent (<18, 18 to <65, ≥65), Tobacco use (Yes/No), and weight (≤ Median or > Median).

Individual subject plasma concentrations versus actual time will be plotted since start of treatment on linear scale.

Scatter plots of individual subject average steady-state $C_{trough\ ss,W2\text{-}W12}$ versus Baseline body weight and versus Baseline age as continuous variables will be generated by treatment for the Pharmacokinetic Set, which will also include the Spearman's rank correlation coefficient, p-value, and LOESS trend line.

To explore potential etrasimod plasma exposure-response relationships, the following scatter plots will be generated in the Safety Set, including data from placebo subjects (plotted at 'zero' concentration). Any contributing data from the placebo subjects will be annotated with a different color or symbol. All scatter plots will include the Spearman's rank correlation coefficient, p-value, and LOESS trend line (based on subjects that received active treatment only).

- Individual subject absolute change from Baseline in MMS versus etrasimod steady state C_{trough} at the common visit where both MMS and C_{trough} are measured (Week 12). Figure will be repeated by: Sex (male/female), age at consent (<18, 18 to <65, ≥65), Tobacco use (Yes/No), and weight (≤ Median or > Median).
- Individual subject absolute change from Baseline in MMS versus average steady-state $C_{trough\ ss,W2\text{-}W12}$. Figure will be repeated by: Sex (male/female), age at consent (<18, 18 to <65, ≥65), Tobacco use (Yes/No), and weight (≤ Median or > Median).
- Individual subject lymphocytes versus etrasimod steady-state C_{trough} by Visit (Week 2 to Week 12). Figure will be repeated by: Sex (male/female), and age at consent (<18, 18 to <65, ≥65).
- Individual subject absolute changes from Baseline in lymphocytes versus etrasimod steady-state C_{trough} by Visit (Week 2 to Week 12). Figure will be repeated by: Sex (male/female), and age at consent (<18, 18 to <65, ≥65).
- Individual subject percent changes from Baseline in lymphocytes versus etrasimod steady-state C_{trough} by Visit (Week 2 to Week 12). Figure will be repeated by: Sex (male/female), and age at consent (<18, 18 to <65, ≥65).

Furthermore, the following overlay plots will be generated in the Pharmacokinetic Set within the etrasimod group only:

- Mean (SD) absolute lymphocytes and mean (SD) etrasimod concentration versus nominal timepoint (Weeks 0 through 12). This figure will be repeated by: Sex (male/female), and age at consent (<18, 18 to <65, ≥65).
- Mean (SD) absolute change from Baseline in lymphocytes and mean (SD) etrasimod concentration versus nominal timepoint (Weeks 0 through 12). This figure will be repeated by: Sex (male/female), and age at consent (<18, 18 to <65, ≥65).
- Mean (SD) percent change from Baseline in lymphocytes and mean (SD) etrasimod concentration versus nominal timepoint (Weeks 0 through 12). This figure will be repeated by: Sex (male/female), and age at consent (<18, 18 to <65, ≥65).
- Mean (SD) heart rate and mean (SD) etrasimod concentration versus nominal timepoint (Weeks 0 through 12). This figure will be repeated by: Sex (male/female), and age at consent (<18, 18 to <65, ≥65).
- Mean (SD) absolute change from Baseline in heart rate and mean (SD) etrasimod concentration versus nominal

timepoint (Weeks 0 through12). This figure will be repeated by: Sex (male/female), and age at consent (<18, 18 to <65, ≥65).

20. DATA NOT SUMMARIZED OR PRESENTED

The other variables and/or domains not summarized are:

- Comments

These domains and/or variables will not be summarized but will be available in the clinical study database and Study Data Tabulation Model (SDTM) datasets.

21. REFERENCES

Cao D, He X. Statistical analysis of adverse events in randomized clinical trials using SAS. Cao D, He X. Statistical analysis of adverse events in randomized clinical trials using SAS. PharmaSUG Conference Proceedings; 2011.

FDA. Multiple endpoints in clinical trials. U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry Web site. https://www.fda.gov/media/102657/download. Published 2017. Accessed February 19, 2021.

FDA. FDA guidance on conduct of clinical trials of medical products during COVID-19 public health emergency. U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry, Investigators, and Institutional Review Boards Web site. https://www.fda.gov/media/136238/download. Published 2020. Accessed July 8, 2020.

ICH. Structure and content of clinical study reports, E3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. https://database.ich.org/sites/default/files/E3_Guideline.pdf. Published 1995. Accessed March 10, 2021.

ICH. Statistical principles for clinical trials, E9. International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. https://database.ich.org/sites/default/files/E9_Guideline.pdf. Published 1998. Accessed March 19, 2021.

ICH. Structure and content of clinical study reports questions & answers (R1). https://database.ich.org/sites/default/files/E3_Q%26As_R1_Q%26As.pdf. Published 2012. Accessed Dec 14, 2021.

ICH. Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials, E9(R1). International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf. Published 2019. Accessed March 19, 2021.

Rubin DB. *Multiple imputation for nonresponse in surveys.* New York, NY: John Wiley and Sons; 1987. On file at Arena.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA Output Conventions

Outputs will be presented as shown in the Output shells.

Decimals, Percentages and CI

- If the original data has N decimal places, then the summary statistics should have the following decimal places:
    - Minimum and maximum: N
    - Mean (and LS Means), median: N + 1
    - SD or SE: N + 2
    - CI: 2
- Percentages will be reported to one decimal place. Where counts are zero, percentages will not appear in the output.

Conventions Related to Pharmacokinetic Data

All etrasimod concentrations will be reported and analyzed with the same precision as the source data provided by the bioanalytical laboratory regardless of how many significant figures or decimals the data carry. The derived PK data (etrasimod concentration) will be rounded to carry 3 significant digits and considered the source data for the calculation of descriptive statistics and the statistical analysis source data.

For the reporting of descriptive statistics, the mean, geometric mean, median, SD, % CV, and geometric %CV will be presented with 4 significant digits. The minimum and maximum will be presented with 3 significant digits.

Dates & Times

Depending on data available, dates and times will take the form DDMMMYYYY or DDMMMYYYY:hh:mm.

Spelling Format

English US.

Presentation of Treatment Groups

For outputs, treatment groups will be represented as follows and in the given order:

Treatment Group	For Tables, Graphs and Listings
Etrasimod Total[a]	Etrasimod 2 mg and Etrasimod 1 mg
Etrasimod 2 mg	Etrasimod 2 mg
Etrasimod 1 mg	Etrasimod 1 mg
Placebo	Placebo
Screen Failure	Screen Failure
Not Treated[a]	Not Treated

[a] To be only used for AE tables.

Presentation of Visits and Study Period

For outputs, visits and study periods will be represented as follows and in that order:

Visit Name	Study Period
Screening	Screening
Baseline, Day 1, Day 2, Week 2, Week 4, Week 8, Week 12	Treatment
End of Study/Early Termination	Depend on Analysis Visit assigned, described in Section 6.4
2-Week Follow-Up, 4-Week Follow-Up	Follow-Up

Listings

All listings will be ordered by the following (unless otherwise indicated in the template):

- Randomized treatment group (or treatment received if it is a safety output), first by Etrasimod 2 mg, Etrasimod

1 mg, then Placebo, then Screen Failure)

- Subject number (which is expected to incorporate study site/center)
- Date (where applicable)

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

Incomplete Start Dates for Adverse Events:

In case the start date of an AE is completely missing, or the start date is in the same year as the date of study drug administration (when only year is recorded), or the start date is in the same month and year (if only the day is missing) as the date of first study drug administration, then the start date of the AE will be imputed by the minimum of the date of first study drug administration and the AE end date. In all other cases the missing start day will be imputed by the 1st and the missing start month will be replaced by January.

Algorithm for Treatment Emergence of Adverse Events:

AE Start Date	AE Stop Date	Action
Known	Known, Partial or Missing	If AE start date < study treatment first dose date, then not TEAE If AE start date ≥ study treatment first dose date, then TEAE
Partial, but known components show that it cannot be on or after date of first dose of study treatment	Known, Partial or Missing	Not TEAE
Partial, could be on or after date of first dose of study treatment OR Missing	Known	If AE stop date < study treatment first dose date, then not TEAE If AE stop date ≥ study treatment first dose date, then TEAE
	Partial	Impute AE stop date as latest possible date (ie, last day of month if day unknown or 31st December if day and month are unknown), then: If AE stop date < study treatment first dose date, then not TEAE If AE stop date ≥ study treatment first dose date, then TEAE
	Missing	Assumed TEAE

Algorithm for Prior / Concomitant Medications:

Start Date	Stop Date	Action
Known	Known	If medication stop date < study treatment first dose date, assign as prior If medication stop date ≥ study treatment first dose date, assign as concomitant
	Partial	Impute stop date as latest possible date (ie, last day of month if day unknown or 31st December if day and month are unknown), then: If medication stop date < study treatment first dose date, assign as prior If medication stop date ≥ study treatment 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 (ie, first day of month if day unknown or 1st January if day and month are unknown), then: If medication stop date < study treatment first dose date, assign as prior If medication stop date ≥ study treatment first dose date, assign as concomitant
	Partial	Impute start date as earliest possible date (ie, first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (ie, last day of month if day unknown or 31st December if day and month are unknown), then: If medication stop date < study treatment first dose date, assign as prior If medication stop date ≥ study treatment first dose date, assign as concomitant
	Missing	Impute start date as earliest possible date (ie, 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 treatment first dose date, assign as prior Else assign as concomitant
	Partial	Impute stop date as latest possible date (ie, last day of month if day unknown or 31st December if day and month are unknown), then: If medication stop date < study treatment first dose date, assign as prior If medication stop date ≥ study treatment first dose date, assign as concomitant
	Missing	Assign as concomitant

Algorithm for Starting Date of Hospitalization and Start/Stop Dates of Concomitant Medications:

Start Date	Stop Date	Action
Partial	Partial	Impute start date as earliest possible date (ie, first day of month if day unknown or 1st January if day and month are unknown). Impute stop date to latest possible date (ie, last day of month if day unknown or 31st December if day and month are unknown). No partial stop date imputation for hospitalization.
Missing	Missing	Impute start date as informed consent date. Impute stop date as last visit date when the concomitant medication timepoint is not ongoing. No missing stop date imputation for hospitalization.

APPENDIX 3. UC-PRO/SS SCORING RULES

The Ulcerative Colitis Patient-Reported Outcomes Signs and Symptoms (UC-PRO/SS) is a 9-item daily diary, designed for electronic administration. Patients/respondents are instructed to complete the diary each evening, reflecting back on their experiences "during the past 24 hours." Daily administration is essential in order to capture change in the patient's condition consistent with symptom variability. The UC-PRO/SS takes approximately three minutes to complete.

The UC-PRO/SS yields two separate weekly average scores: Bowel signs and symptoms (6 items) and functional symptoms (3 items). There is no single total score. The weekly scores can be used alone or as part of a profile.

Questions:

1. In the past 24 hours, how many bowel movements did you have?
   - 0=0
   - 1=1-2
   - 2=3-4
   - 3=5-6
   - 4=7-9
   - 5=10-12
   - 6=13-17
   - 7=18 or more
2. In the past 24 hours, how often were your bowel movements mostly or completely liquid?
   - 0=Never
   - 1=Rarely
   - 2=Sometimes
   - 3=Often
   - 4=Always
3. In the past 24 hours, did you have blood in your bowel movements?
   - 0=No
   - 1=Rarely
   - 2=Sometimes
   - 3=Often
   - 4=Always
4. In the past 24 hours, did you have mucus (white material) in your bowel movements?

0=No

1=Rarely

2=Sometimes

3=Often

4=Always

5. In the past 24 hours, did stool, blood, or liquid leak out before you reached a toilet?

0=No

1=Rarely

2=Sometimes

3=Often

4=Always

6. In the past 24 hours, did you pass gas?

0=No

1=Rarely

2=Sometimes

3=Often

4=Very often

7. In the past 24 hours, did you feel the need to have a bowel movement right away?

0=No

1=Mild

2=Moderate

3=Severe

4= Very Severe

8. In the past 24 hours, did you feel pain in your belly?

0=No

1=Mild

2=Moderate

3=Severe

4=Very Severe

9. In the past 24 hours, did you feel bloating in your belly?

0=No

1=Mild

2=Moderate

3=Severe

4=Very Severe

Derivation:

A daily score is the mean of responses to items for each scale: Bowel signs and symptoms (Questions 1-5 and 7), and functional symptoms (Questions 6, 8 and 9). A weekly average score for each scale is then calculated with no imputation using the mean of at least four out of the seven daily scores. If four or more days of data are missing for any week, the weekly average score for each scale is set to missing for that week.

APPENDIX 4. SF-36 SCORING RULES

The Medical Outcomes Study 36 Item Short Form Health Survey (SF-36) is a 36-item self-administered questionnaire which has 8 scales: Physical functioning (10 items), role limitations due to physical problems (4 items), role limitations due to emotional problems (3 items), vitality (4 items), mental health (5 items), social function (2 items), bodily pain (2 items), and general health perceptions (5 items). Each item response is scored from 0 to 100 and items in the same scale are averaged together to create 8 subscores. Scores range from 0 to 100. A higher score indicates a more favorable health state.

The 8 dimensions are defined as:

- Physical functioning: Questions 3 to 12
- Role limitations due to physical problems: Questions 13 to 16
- Role limitations due to emotional problems: Questions 17 to 19
- Vitality: Questions 23, 27, 29, 31
- Mental health: Questions 24 to 26, 28, 30
- Social function: Questions 20, 32
- Bodily pain: Questions 21, 22
- General health perceptions: Questions 1, 33 to 36

APPENDIX 5. CLASSIFICATION OF RESCUE THERAPY

This appendix outlines the algorithm for the Arena clinical team/medical reviewers to classify rescue therapies for ulcerative colitis (UC) in a blinded manner. This will help establish 1) intercurrent events for the efficacy estimands, and 2) whether a subject will be excluded from the Per Protocol Set(s). All rescue therapies identified by the medical reviewers per the algorithm below will be imported in programming. This process will be repeated until database lock and the list of all rescue therapies identified will be finalized before study unblinding.

Only medications and medical procedures reported on the electronic case report forms (eCRFs) can be assessed whether they are rescue therapy for UC. If the exposure happens in the follow-up period (beginning on or after the date of last study treatment administration), then it would not be considered as a rescue therapy.

Biologics with immunomodulatory properties

- Rule:
    - Any exposure after first dose
- List of medications
    - Anti-TNFα antibodies:
        - ADALIMUMAB
        - CERTOLIZUMAB
        - CERTOLIZUMAB PEGOL
        - GOLIMUMAB
        - INFLIXIMAB
    - Other Biologics:
        - USTEKINUMAB
        - VEDOLIZUMAB

Non-biologics with immunomodulatory properties

- Immunosuppressants
    - Rules:
        - After first dose and up to and including Week 8: any increase from baseline for more than 5 days

        - After Week 8: Any dose above baseline
    - List of medications
        - MERCAPTOPURINE
        - AZATHIOPRINE
        - TIOGUANINE
        - METHOTREXATE
        - METHOTREXATE SODIUM

- 5-ASA compounds
    - Rules:
        - After first dose and up to and including Week 8: Any increase from baseline for more than 5 days
        - After Week 8: Any dose above baseline
    - List of medications
        - MESALAZINE
        - BALSALAZIDE
        - BALSALAZIDE DISODIUM DIHYDRATE
        - BALSALAZIDE SODIUM
        - OLSALAZINE SODIUM
        - SULFASALAZINE
        - BECLOMETASONE W/MESALAZINE
    - Routes
        - ORAL
        - RECTAL

- Other small molecule immunomodulatory active agents
    - Rules:
        - After first dose and up to and including Week 8: Any increase from baseline (including new use) for more than 5 days
        - After Week 8: Any dose above baseline
    - List of medications
        - CICLOSPORIN
        - TACROLIMUS

- TOFACITINIB
- TOFACITINIB CITRATE

- Systemic glucocorticoids
  - Systemic glucocorticoids given via oral or rectal routes of administration
    - Rules:
      - After first dose and up to and including Week 8: Any increase from baseline for more than 7 days
      - After Week 8: Any dose above baseline
    - List of medications
      - BETAMETHASONE
      - BETAMETHASONE DIPROPIONATE
      - BETAMETHASONE SODIUM PHOSPHATE
      - DEXAMETHASONE
      - DEXAMETHASONE SODIUM PHOSPHATE
      - DEXAMETHASONE VALERATE
      - METHYLPREDNISOLONE
      - METHYLPREDNISOLONE SODIUM SUCCINATE
      - PREDNISOLONE
      - PREDNISOLONE SODIUM PHOSPHATE
      - PREDNISOLONE METASULFOBENZOATE SODIUM
      - PREDNISONE
      - TRIAMCINOLONE
      - HYDROCORTISONE
      - HYDROCORTISONE ACETATE
      - HYDROCORTISONE BUTYRATE
      - HYDROCORTISONE SODIUM SUCCINATE
    - Routes
      - ORAL
      - RECTAL
  - Systemic glucocorticoids given via parenteral routes of administration
    - Rule:
      - Any exposure after first dose

- List of medications
  - BETAMETHASONE
  - BETAMETHASONE DIPROPIONATE
  - BETAMETHASONE SODIUM PHOSPHATE
  - DEXAMETHASONE
  - DEXAMETHASONE SODIUM PHOSPHATE
  - DEXAMETHASONE VALERATE
  - METHYLPREDNISOLONE
  - METHYLPREDNISOLONE SODIUM SUCCINATE
  - PREDNISOLONE
  - PREDNISOLONE SODIUM PHOSPHATE
  - PREDNISOLONE METASULFOBENZOATE SODIUM
  - PREDNISONE
  - TRIAMCINOLONE
  - HYDROCORTISONE
  - HYDROCORTISONE ACETATE
  - HYDROCORTISONE BUTYRATE
  - HYDROCORTISONE SODIUM SUCCINATE
- Routes
  - INTRAVENOUS
  - INTRAMUSCULAR

- Topical Glucocorticoids
  - Rules
    - After first dose and up to and including Week 8: Any exposure above baseline (or new use) for more than 5 days
    - After Week 8: Any dose above baseline
  - List of medications
    - BUDESONIDE
  - Routes
    - ORAL
    - RECTAL

- Beclomethasone

- Rules
  - After first dose and up to and including Week 8: Any increase above baseline for more than 5 days
  - After Week 8: Any dose above baseline
- List of medications
  - BECLOMETASONE
  - BECLOMETASONE DIPROPIONATE
  - BECLOMETASONE W/MESALAZINE
- Routes
  - ORAL
  - RECTAL

Medical procedures

- Leukocyte apheresis, other apheresis, and plasma exchange
  - Rule:
    - Any exposure after first dose
  - List of medical procedures
    - APHERESIS
    - LEUKAPHERESIS
    - COLECTOMY (partial or total)
    - SIGMOIDECTOMY
    - COLOSTOMY
    - ILEOSTOMY

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Electronic Record and Signature Disclosure: Accepted: 7/30/2023 10:37:20 PM ID: PPD		

Signer Events	Signature	Timestamp
PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 11/27/2023 1:39:37 AM Viewed: 11/27/2023 9:06:59 PM Signed: 11/27/2023 10:07:09 PM
Electronic Record and Signature Disclosure: Accepted: 2/9/2021 8:17:47 PM ID: PPD		
In Person Signer Events	**Signature**	**Timestamp**
Editor Delivery Events	**Status**	**Timestamp**
Agent Delivery Events	**Status**	**Timestamp**
Intermediary Delivery Events	**Status**	**Timestamp**
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**
Envelope Summary Events	**Status**	**Timestamps**
Envelope Sent	Hashed/Encrypted	11/27/2023 1:39:37 AM
Certified Delivered	Security Checked	11/27/2023 9:06:59 PM
Signing Complete	Security Checked	11/27/2023 10:07:09 PM
Completed	Security Checked	11/27/2023 10:07:09 PM
Payment Events	**Status**	**Timestamps**
Electronic Record and Signature Disclosure		

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PDF Reader:	Acrobat® or similar software may be required to view and print PDF files
Screen Resolution:	1024 x 768 Recommended
Enabled Security Settings:	Allow per session cookies
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