CLINICAL STUDY PROTOCOL

Protocol title:	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
Brief title:	Etrasimod Dose-Ranging Versus Placebo as Induction Therapy in Moderately to Severely Active Ulcerative Colitis
Protocol number:	APD334-203(C5041007)
Version:	Amendment 1.0, 12 January 2023
Study drug:	Etrasimod (APD334)
Indication:	Ulcerative colitis
Phase:	2
Sponsor name:	**Arena Pharmaceuticals** Inc., a wholly owned subsidiary of Pfizer Inc.

Confidentiality Statement

PROTOCOL HISTORY

Document	Amendment Type	Date
Amendment 1.0	Global	12 January 2023
Original Protocol	Not applicable	09 February 2021

PROTOCOL SYNOPSIS

Sponsor: Arena Pharmaceuticals Inc.
Name of investigational study drug: Etrasimod (APD334)
Protocol number: APD334-203
Protocol title: 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
Phase: 2
Region: Japan
Objectives: Primary: 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. Secondary: 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. Safety: 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. Other: Other objectives include evaluation of etrasimod pharmacokinetics (PK) and the effect of etrasimod on health-related patient-reported outcomes and biomarkers.
Study Design: This is a multicenter, randomized, double-blind, placebo-controlled, dose-ranging 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. The target participant population will include those who have had an inadequate response to, loss of response to, or intolerance to the following: 1. Conventional therapy, and are naïve to biologic or Janus kinase (JAK) inhibitor therapy 2. Biologics or JAK inhibitors (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 a modified Mayo score (MMS) of 4 to 9, which includes an endoscopic score (ES) ≥ 2 and rectal bleeding (RB) score ≥ 1. 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) naive to biologic or JAK inhibitor therapy at study entry (yes or no), (b) baseline corticosteroid use (yes or no), and (c) baseline disease activity (MMS: 4 to 6 or 7 to 9).

At the end of the 12-Week Induction Treatment Period, participants will undergo the Week 12 study assessments. 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 do not participate in the OLE study will have 2-Week and 4-Week Follow-Up visits after the last treatment administration.

Number of Participants (planned):

A total of 96 participants are planned to be randomized in the study, with 32 participants expected in each of the 3 treatment groups.

Eligibility criteria:

Inclusion criteria:

Participants must meet ALL of the following inclusion criteria to be eligible for enrollment into the study:

1. Japanese ancestry (ie, both parents and 4 grandparents are/were of Japanese descent)
2. 18 to 80 years of age, inclusive, at the time of consent
3. Ability to provide written informed consent and to be compliant with the schedule of protocol assessments

Disease-specific inclusion criteria:

4. Diagnosed with UC ≥ 3 months prior to screening. The diagnosis of UC must be confirmed by endoscopic and histologic evidence. The endoscopy and histology report should be present in the source documents; however, if not available, the screening endoscopy and histology may serve as such.
5. Active UC confirmed by endoscopy with ≥ 10 cm rectal involvement
6. Moderately to severely active UC defined as MMS of 4 to 9, including an ES ≥ 2 and RB subscore ≥ 1
7. Received a surveillance colonoscopy (performed according to local standard) within 12 months before baseline to rule out dysplasia in participants with pancolitis > 8 years duration or participants with left-sided colitis > 12 years duration. Participants without a surveillance colonoscopy within the prior 12 months will have a colonoscopy at screening (ie, in place of screening proctosigmoidoscopy). Any adenomatous polyps must be removed according to routine practice prior to their first dose of study treatment.

Prior treatment:

8. Demonstrated an inadequate response to, loss of response to, or intolerance to at least 1 of the following therapies as defined below:

Conventional therapy

a. Oral 5-aminosalicylic acid (5-ASA) compounds

b. Systemic (oral or IV) Corticosteroids

c. Thiopurines (eg, azathioprine [AZA], or 6-mercaptopurine [6-MP])

- Biologics or JAK inhibitors therapy

a. Anti-tumor necrosis factor alpha (TNFα) antibodies (eg, infliximab, adalimumab, golimumab, or biosimilars)

b. Anti-integrin antibodies (eg, vedolizumab, carotegrast methyl)

c. Anti-interleukin 12/23 antibodies (eg, ustekinumab)

d. JAK inhibitors (eg, tofacitinib)

- Note: To be considered inadequate response, loss of response, and intolerance after treatment with a biologic or JAK inhibitor, the participant **should have received a dosing regimen consistent with the local product labeling, local guidelines for the treatment of UC and/or institutional standard of care.**

Concomitant treatments:

9. Participants are permitted to be receiving a therapeutic dose of the following drugs:
    - Oral 5-ASA compounds provided the dose has been stable for ≥ 2 weeks immediately prior to randomization
    - Oral corticosteroid therapy (prednisone at a stable dose ≤ 20 mg/day or equivalent steroid) provided the dose has been stable for the 4 weeks immediately prior to the screening endoscopy assessment
    - Thiopurines such as oral AZA or 6-MP must be discontinued ≥ 2 weeks prior to randomization
    - Probiotics (eg, *Saccharomyces boulardii*) provided the dose has been stable for the 2 weeks immediately prior to randomization

    If oral 5-ASA or corticosteroids have been recently discontinued, they must have been stopped for at least 2 weeks prior to the endoscopy used for the baseline MMS.

Other general inclusion criteria:

10. Adequate hematological function defined by white blood cell count ≥ 3.5×10^9/L with absolute neutrophil count (ANC) ≥ 1.5×10^9/L, lymphocyte count ≥ 0.8×10^9/L, platelet count ≥ 100×10^9/L, and hemoglobin ≥ 8 g/dL
11. Adequate hepatic function defined by a total bilirubin level ≤ 1.5 × the upper limit of normal (ULN) range and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤ 2.0 × ULN. Participants with an isolated total bilirubin and normal AST and ALT diagnosed with Gilbert's syndrome may participate
12. Adequate renal function defined by an estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2 by the Chronic Kidney Disease Epidemiology Collaboration equation at screening
13. Females must meet either a or b of the following criteria and males must meet criterion c to qualify for the study:
    a. A female who is not of childbearing potential must meet 1 of the following:
        – Postmenopausal, defined as no menses for 12 months without an alternative medical cause
        – Permanent sterilization procedure, such as hysterectomy, bilateral salpingectomy, or bilateral oophorectomy

b. Non-pregnant female of childbearing potential must agree to using a highly effective contraception method during treatment and for 30 days following treatment that can achieve a failure rate of less than 1% per year when used consistently and correctly. The following are considered highly effective birth control methods:

- Combined (estrogen and progestogen containing) oral hormonal contraception associated with inhibition of ovulation
- Progestogen-only oral hormonal contraception associated with inhibition of ovulation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner, provided that partner is the sole sexual partner of the women of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success
- Sexual abstinence (complete sexual abstinence defined as refraining from heterosexual intercourse for the entire period of risk associated with study treatments). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not acceptable.

c. A male participant with a pregnant or non-pregnant female of childbearing potential partner must agree to using condoms during treatment and for 30 days following treatment.

Exclusion criteria:

Participants who meet any of the following exclusion criteria will not be eligible for enrollment into the study:

Exclusions related to general health:

1. Severe extensive colitis as evidenced by:
   - Physician judgment that the participant is likely to require hospitalization for medical care or surgical intervention of any kind for UC (eg, colectomy) within 12 weeks following randomization
   - Current evidence of fulminant colitis, toxic megacolon or recent history (within last 6 months) of toxic megacolon, or bowel perforation
   - Previous total or partial colectomy
2. Diagnosis of Crohn's disease (CD) or indeterminate colitis or the presence or history of a fistula consistent with CD
3. Diagnosis of isolated proctitis (defined as proctitis with < 10 cm rectal involvement), microscopic colitis, ischemic colitis, or infectious colitis
4. Hospitalization for exacerbation of UC requiring intravenous (IV) steroids within 12 weeks of screening (a single dose of intravenous (IV) steroids given is acceptable)

5. Positive assay or stool culture for pathogens (ova and parasite examination, bacteria) or positive test for *Clostridioides difficile* toxin at screening (If *C. difficile* is positive, the participant may be treated and retested ≥ 4 weeks after completing treatment.)
6. Pregnancy, lactation, or a positive serum beta-human chorionic gonadotropin (β-hCG) measured during screening
7. Clinically relevant neurological, endocrine, metabolic (including, but not limited to, hypo- and hyperkalemia), psychiatric, cognitive impairment, alcohol/drug abuse/dependence, or other major systemic disease making implementation of the protocol or interpretation of the study difficult or would put the participant at risk
8. Have any of the following conditions or receiving treatments that may affect cardiovascular function:
    - Myocardial infarction, unstable angina, stroke/transient ischemic attack, decompensated heart failure requiring hospitalization or Class III/IV heart failure ≤ 6 months prior to or during the screening period
    - History or presence of second-degree or third-degree atrioventricular (AV) block, sick sinus syndrome, or periods of asystole for > 3 seconds without a functional pacemaker
    - History or presence of recurrent symptomatic bradycardia or recurrent cardiogenic syncope
    - Screening or Week 0/Day 1 pre-randomization vital signs (taken in the sitting position) with a heart rate (HR) < 50 bpm OR systolic blood pressure (BP) < 90 mm Hg OR diastolic BP < 55 mm Hg. Vital signs may be repeated up to 3 times during a visit to confirm abnormal readings
    - Screening or Week 0/Day 1 pre-randomization electrocardiogram (ECG) with PR interval > 200 ms or Fridericia's corrected QT interval (QTcF) ≥ 450 ms in men or ≥ 470 ms in women
    - Start, stop, change or planned change in dosage of any anti-arrhythmic drugs (Class I to IV) ≤1 week before screening or within 1 week before or after randomization
9. Forced expiratory volume at 1 second (FEV_1) or forced vital capacity (FVC) < 70% of predicted values and FEV_1/FVC ratio < 0.70 at screening
10. Uncontrolled diabetes as determined by hemoglobin A1c (HbA1c) > 9% at screening, or participants with diabetes with significant comorbid conditions such as retinopathy
11. History of macular edema or retinopathy
12. History of active tuberculosis (TB), history of untreated or inadequately treated latent TB infection, active or latent TB infection at screening. The following are EXCEPTIONS to this exclusion criterion:
    - Participants with latent TB, who have been ruled out for active TB, have completed an appropriate course of TB prophylaxis treatment per national/local medical guidelines or WHO guidelines, have a chest radiograph without changes suggestive of active TB infection, and have not had recent close contact with a person with active TB are eligible to enroll in the study. It is the responsibility of the Investigator to verify the adequacy of previous TB treatment and provide appropriate documentation of treatment compliance
    - Participants diagnosed with latent TB at screening, ruled out for active TB and received at least 4 weeks of an appropriate TB prophylaxis regimen may be rescreened for enrollment. Participants will complete their prophylactic regimen during the trial

13. A clinically significant active infection (eg, serious and/or atypical) ≤ 28 days prior to randomization, required IV medication ≤ 14 days prior to randomization, or that may worsen (in the opinion of the Investigator) if the participant is treated with a drug having immunosuppressant effects (ie, etrasimod). Fungal infection of nail beds is allowed.
14. Have human immunodeficiency virus (HIV)/acquired immune deficiency syndrome or test positive for HIV antibodies at screening
15. Have acute or chronic hepatitis B infection or test positive for hepatitis B virus (HBV) at screening (positive for hepatitis B surface antigen [HBsAg]), or
    - negative for HBsAg and positive for hepatitis B core antibody [HBcAb] and negative for hepatitis B surface antibody [HBsAb] in conjunction with detectable HBV DNA, or
    - negative for HBsAg and negative for HBcAb and positive for HBsAb in conjunction with detectable HBV DNA, or
    - negative for HBsAg and positive for HBcAb and positive for HBsAb in conjunction with detectable HBV DNA
16. Have current hepatitis C infection or test positive for hepatitis C virus (HCV) at screening as defined by positive for hepatitis C antibody and detectable HCV RNA
17. History of an opportunistic infection (eg, *Pneumocystis jirovecii*, cryptococcal meningitis, progressive multifocal leukoencephalopathy [PML]) or a history of disseminated herpes simplex or disseminated herpes zoster
18. History of or currently active primary or secondary immunodeficiency
19. History of cancer within the last 5 years, including solid tumors and hematological malignancies (except basal cell and in situ squamous cell carcinomas of the skin that have been excised and resolved) or colonic mucosal dysplasia
20. History of lymphoproliferative disorder, lymphoma, leukemia, myeloproliferative disorder, or multiple myeloma

<u>*Exclusions related to medications*</u>:

21. Hypersensitivity to etrasimod or any of the excipients or placebo compounds
22. Prior treatment with sphingosine 1-phosphate (S1P) receptor modulators
23. Treatment with a biologic agent ≤ 8 weeks or a small-molecule agent ≤ 5 elimination half-lives and detectable drug level prior to randomization
24. Treatment with an investigational therapy ≤ 3 months prior to randomization
25. Prior treatment with ≥ 3 advanced therapies (eg, biologics or JAK inhibitors) approved or recommended for treatment of UC
26. Treatment with topical rectal 5-ASA, short-chain fatty acid enemas, or steroids ≤ 2 weeks prior to or during screening
27. Treatment with topical rectal traditional medicine (eg, Chinese medicine), herb enemas, or suppositories ≤ 2 weeks prior to randomization
28. Treatment with methotrexate ≤ 8 weeks prior to or during screening or cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil (MMF) ≤ 16 weeks prior to and during screening
29. Receipt of a live vaccine ≤ 4 weeks prior to randomization
30. Previous treatment with natalizumab

31. Previous treatment with lymphocyte-depleting therapies (eg, alemtuzumab, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation, daclizumab)
32. Previous treatment with D-penicillamine, thalidomide, dimethyl fumarate, or pyrimidine synthesis inhibitors
33. Treatment with IV immune globulin or plasmapheresis ≤ 3 months prior to randomization
34. Use of moderate or strong inhibitors or inducers that inhibit or induce at least 2 of the following: cytochrome P450 (CYP) 2C8, CYP2C9 and CYP3A4 (eg, fluconazole, rifampin, enzalutamide) within 4 weeks prior to randomization

Test product, dose, and mode of administration:

Etrasimod, 1 and 2 mg tablets, by mouth, once daily

Study duration:

The overall duration of this study is expected to be approximately 2 years.

Reference therapy, dose, and mode of administration:

Placebo tablets, by mouth, once daily

Efficacy Assessments:

The MMS and its component subscores will be used to assess efficacy. The MMS is a composite of 3 assessments, each rated from 0 to 3: Stool frequency (SF), RB, and ES. The ES will be determined by central reading.

Definitions:

- Clinical remission: Defined as an 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 defined as 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

Primary efficacy endpoint:

- Proportion of participants achieving clinical remission at Week 12

Secondary efficacy endpoints:

- The proportion of participants achieving endoscopic improvement at Week 12
- The proportion of participants achieving symptomatic remission at Week 12
- The proportion of participants with mucosal healing at Week 12
- The proportion of participants achieving clinical response at Week 12
- The proportion of participants achieving endoscopic normalization at Week 12

Pharmacokinetic assessments:

Plasma concentrations of etrasimod will be assessed from samples collected predose and 4 hours postdose (after 12-lead ECG) on Week 0/Day 1, and predose (trough) at Weeks 2, 4, 8, and 12, and at 2--Week and 4--Week Follow--Up visits. A PK sample should also be drawn, if possible, at the time of any serious adverse event (SAE) or adverse event leading to study treatment discontinuation.

Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, or to assess other actions of etrasimod with plasma constituents.

Safety Assessments:

Safety will be assessed using monitoring of adverse events, clinical laboratory findings, 12-lead ECGs, physical examinations, vital signs, pulmonary function tests, ophthalmoscopy, and optical coherence tomography.

Safety endpoints:

- Incidence and severity of adverse events
- Incidence and severity of laboratory abnormalities, and change from baseline in laboratory values (to include hematology, serum chemistry, coagulation, and urinalysis)
- Incidence of clinically significant vital sign abnormalities and changes from baseline

Other assessments:

Biomarker endpoints:

- Change from baseline in level of fecal calprotectin at Weeks 2, 4, 8, and 12
- Change from baseline in level of high-sensitivity C reactive protein at Weeks 2, 4, 8, and 12
- Change and percentage change from baseline in lymphocyte counts at Weeks 2, 4, 8, and 12

Health-related Patient-Reported Outcome endpoints:

- Scores and change from baseline at Week 12 for the following:
  - Ulcerative Colitis Patient-Reported Outcomes Signs and Symptoms (UC-PRO/SS), if available
  - Medical Outcomes Study 36-Item Short Form Health Survey, version 2 physical and mental component and domain scores (SF-36)
- Proportion of participants with UC -related hospitalizations
- Proportion of participants requiring UC -related surgeries, including colectomy

Statistical methods:

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.

Efficacy analysis

The analysis of all proportion-based efficacy endpoints will be carried out using the Cochran-Mantel-Haenszel (CMH) method, stratified by (a) naïve to biologic or JAK inhibitor therapy at study entry (yes or no), (b) baseline corticosteroid use (yes or no), and (c) baseline disease activity (MMS: 4 to 6 or 7 to 9). Results will be expressed as the number of participants in remission, remission percentages, difference in remission percentages, odds ratio, and associated 95% confidence intervals and p-values. The stratified CMH analysis will be performed for each etrasimod dose (1 and 2 mg) versus placebo separately. The Cochran-Armitage trend test will also be carried out for all primary and secondary proportion-based efficacy endpoints.

Testing Strategy

There are multiple null hypotheses for the comparison of etrasimod and placebo in the primary and secondary efficacy endpoints. The family-wise Type I error rate will be controlled at a fixed α level at 0.05 (2-sided) using the following testing procedure.

A hierarchical testing procedure will be used to control family-wise Type I error rate at α level 0.05 (2-sided). The comparison of etrasimod 2 mg versus placebo for the primary endpoint (Family 1; F1) is the main gatekeeper. The study is considered positive if F1 is rejected at the α level. Only if this test is significant will etrasimod 2 mg be compared with placebo for all the secondary endpoints (Family 2; F2). The truncated Hochberg method (Dmitrienko 2011, FDA 2017) will be applied to F2 at α level.

If none of the null hypotheses in F2 is rejected, then testing will stop with all nominal p-values reported for subsequent comparisons of etrasimod 1 mg versus placebo. Otherwise, etrasimod 1 mg be compared with placebo for the primary endpoint (Family 3; F3) with the unused α from testing F2. Only if this test is significant will etrasimod 1 mg be compared with placebo for all the secondary endpoints (Family 4; F4). The conventional Hochberg method (FDA 2017) will be applied to F4 with the same unused α for F3.

Pharmacokinetic analysis

A descriptive summary of observed plasma concentration will be displayed by time and by treatment group.

Safety analysis

All safety data will be listed and summarized by treatment group. All treatment-emergent adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities and tabulated by System Organ Class and Preferred Term. Incidence of adverse events, SAEs, and adverse events leading to discontinuation will be summarized and presented in descending order of frequency. Associated laboratory parameters such as hepatic enzymes, renal function, and hematology values will be grouped and presented together. Individual participant values will be listed and values outside of the standard reference range will be flagged. Shift tables and analyses of changes from baseline will be produced.

Full details of efficacy, safety, and PK analyses will be provided in the Statistical Analysis Plan.

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Abbreviation	Definition
5-ASA	5-aminosalicylic acid
ADL	activities of daily living
ADR	adverse drug reaction
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APD334	etrasimod
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AV	atrioventricular
AZA	azathioprine
β-hCG	beta-human chorionic gonadotropin
BP	blood pressure
bpm	beats per minute
CBC	complete blood count
CD	Crohn's disease
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CI	confidence interval
C_{max}	maximum observed plasma or serum concentration
CMH	Cochran-Mantel-Haenszel
CMP	clinical monitoring plan
COVID-19	coronavirus disease 2019
CRO	contract research organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLCO	diffusing capacity of the lungs for carbon monoxide
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECC	emergency contact card

Abbreviation	Definition
ECG	electrocardiogram
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDC	electronic data capture
EDP	exposure during pregnancy
eDiary	electronic diary
EIMs	extraintestinal manifestations
ES	endoscopic score
ET	Early Termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEV_1	forced expiratory volume at 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
HbA1c	hemoglobin A1c
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
hs-CRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICCC	In-Country Caretaker for Clinical Trial
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IGRA	interferon-gamma release assay
IND	Investigational New Drug
IOIBD	International Organization for the Study of Inflammatory Bowel Diseases

Abbreviation	Definition
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
IWRS	Interactive Web Response System
JAK	Janus kinase
6-MP	6-mercaptopurine
MAR	missing at random
MCS	Mayo Clinic score
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified Full Analysis Set
MMF	mycophenolate mofetil
MMS	modified Mayo score
MQI	medically qualified individual
NF	National Formulary
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drugs
OCT	optical coherence tomography
OLE	open-label extension
PD	protocol deviation
PD	pharmacodynamic(s)
PFT	pulmonary function test
PGA	Physicians Global Assessment
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PPD	purified protein derivative
QTcF	Fridericia's corrected QT interval
RB	rectal bleeding
RNA	ribonucleic acid
S1P	sphingosine 1-phosphate
$S1P_{1,4,5}$	sphingosine 1-phosphate receptor subtypes 1, 4, and 5
SAE	serious adverse event

Abbreviation	Definition
SAP	Statistical Analysis Plan
SARS CoV 2	Severe acute respiratory syndrome coronavirus 2
SF	stool frequency
SF-36	Medical Outcomes Study 36-Item Short Form Health Survey
SOP	standard operating procedures
TB	tuberculosis
TBNK	T cell, B cell, natural killer cell
TEAE	treatment-emergent adverse event
TMF	Trial Master File
TMS	Total Mayo Score
TNF	tumor necrosis factor
TNFα	tumor necrosis factor alpha
TST	tuberculin skin test
UC	ulcerative colitis
UC-PRO/SS	Ulcerative Colitis Patient-Reported Outcomes Signs and Symptoms
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

1.1. Ulcerative Colitis

Inflammatory bowel disease (IBD) describes conditions with chronic or recurring immune response and inflammation of the gastrointestinal tract. There are 2 major types of IBD: Crohn's disease (CD) and ulcerative colitis (UC). These are chronic recurrent, remittent, or progressive inflammatory conditions that may affect the entire gastrointestinal tract (CD) and the colonic mucosa (UC), and are associated with an increased risk for colon cancer (Kaser 2010).

Ulcerative colitis is characterized by diffuse mucosal inflammation limited to the colon and involves the rectum in approximately 95% of cases and may extend proximally in a symmetrical, circumferential, and uninterrupted pattern to involve parts or all of the large intestine (Kornbluth 2010). Symptoms for UC can vary, depending on the location and severity of inflammation, but some of the most common are diarrhea, abdominal cramps, and rectal bleeding. The hallmark clinical symptom is bloody diarrhea often with prominent symptoms of rectal urgency and tenesmus (Kornbluth 2010).

Treatment for patients with UC is generally for symptomatic care (relief of symptoms) and mucosal healing and includes 5 major classes of medications: 5-aminosalicylic acid (5-ASA), antibiotics, corticosteroids, immunomodulators, biologic therapies (eg, tumor necrosis factor [TNF] inhibitors and anti-integrins) and most recently Janus kinase (JAK) inhibitor therapy. These drugs may be prescribed in a "step-up" approach, with escalation of the medical regimen until a response is achieved, or a "step-down" manner, with initiation of treatment with biologics and immunomodulators (Rowe 2020).

An unmet medical need exists for the development of targeted therapies for the treatment of UC with easily administered and stable oral drugs, particularly as most patients treated with biologics experience inadequate responses. Moreover, many patients who receive biologics lose responsiveness over time, even though their initial response may have been positive (Ungar 2016).

1.2. Etrasimod

Etrasimod (APD334) is an orally administered, selective, synthetic sphingosine 1-phosphate (S1P) receptor subtypes 1, 4, 5 ($S1P_{1,4,5}$) modulator that is being developed to treat immune-mediated inflammatory disorders, including UC.

The $S1P_1$ is a cell surface expressed protein that has been shown to regulate lymphocyte migration out of lymphoid tissues (Brinkmann 2010). Synthetic small-molecule $S1P_1$ agonists have been observed to act as functional antagonists by inducing sustained receptor internalization, thus inhibiting lymphocyte migration out of lymphoid tissues and lowering the amount of peripheral blood lymphocytes available to be recruited to sites of inflammation. Modulation of the S1P/S1P receptor axis is thought to be a potential therapeutic approach to the management of immune-mediated inflammatory disorders (Nielsen 2017); as such, etrasimod is expected to potentially provide therapeutic benefit to patients with UC. A Phase 2 study with etrasimod in participants with moderately to severely active UC demonstrated consistent and clinically meaningful improvements in endpoint measures reflecting cardinal symptoms of UC and objective findings of endoscopic improvement.

In 2 recently completed Phase 3 studies (APD334-301 and APD334-302), treatment with etrasimod 2 mg resulted in statistically significant and clinically meaningful improvements based on clinical,

endoscopic, symptomatic, and endo-histologic endpoints in adults with moderately to severely active UC. No new safety findings were observed with etrasimod 2 mg treatment for up to 52 weeks (Sandborn 2022). An Open-Label Extension (OLE) study (APD334-303) to evaluate the long-term efficacy and safety of etrasimod in participants with moderately to severely active UC is currently ongoing.

Refer to the current edition of the Investigator's Brochure (IB) for a complete summary of the clinical and nonclinical data relevant to the investigational product and its study in human participants.

1.3. Benefit/Risk Assessment

Considering the significant unmet need for safe and effective, orally administered treatments for UC, etrasimod may potentially provide therapeutic benefit via S1P receptor modulation.

Adverse events that have been reported with S1P receptor modulators include bradycardia at the first dose or atrioventricular (AV) block, macular edema, hypertension, headache, cough, dyspnea, back pain, influenza, and diarrhea.

Safety and tolerability of etrasimod has been evaluated in Phase 1 studies with healthy adult participants at single doses up to 5 mg and repeat doses up to 4 mg once daily. Repeated doses of 2 mg have been evaluated in Phase 2 studies of participants with moderately to severely active UC (refer to the current edition of the IB). Etrasimod was found to be safe and well tolerated in these studies, with no clinically significant safety concerns with respect to vital signs, electrocardiograms (ECGs), pulmonary function tests (PFTs), ophthalmoscopy, or clinical laboratory tests. Etrasimod produced a dose-dependent sustained decrease in total lymphocyte count, which is expected given etrasimod's mechanism of action. Lymphocyte counts were within normal limits by 7 days after the last dose.

A Japanese/Caucasian ethnobridging pharmacokinetic (PK) and pharmacodynamic (PD) study (Study APD334-109) was conducted that demonstrated etrasimod 1 mg and 2 mg once-daily dosing regimens were safe and generally well tolerated by both Japanese and Caucasian participants. In that study, single and multiple dose etrasimod (1 mg and 2 mg) mean exposure (maximum observed plasma or serum concentration [C_{max}] and area under the plasma concentration-time curve [AUC]) were slightly to moderately higher in Japanese participants compared to Caucasian participants, but this was attributable to differences in body weight rather than ethnicity. No differences were observed in absolute lymphocyte counts (ALCs) between Japanese and Caucasian participants following multiple dose administration of etrasimod and levels returned to near baseline during the 7-day washout period. Additionally, there were no clinically relevant first-dose heart rate (HR) differences.

Detailed information regarding the known and expected benefits and risks and reasonably expected adverse events of etrasimod can be found in the IB, which serves as the single reference safety document for this study.

Based on the mechanism of action of etrasimod and prior experience with other agents acting via a similar mechanism, monitoring for specific safety parameters are planned for this study, which include: Auscultation of the lungs as part of the physical exam; PFT, exclusion of participants with macular edema or retinopathy, with assessment of optical coherence tomography (OCT) occurring throughout the study; and exclusion of participants with certain cardiac risks, with assessment of vital signs in the period following dosing.

- Auscultation of lungs will be conducted as part of the physical examination.

- Prospective participants with a history of macular edema or retinopathy will be excluded from the study. All randomized participants will be assessed by OCT at study entry, periodically throughout the treatment period, and as clinically indicated any time during the study.
- Participants with certain cardiac risks will also be excluded from the study. Randomized participants will be monitored in a period following dosing, and vital signs will be assessed for determination of the participant's health before discharge. Participants requiring follow-up monitoring will be evaluated in the clinic until cardiac variances return to acceptable levels.

Based on the preclinical and clinical data that has been generated from etrasimod studies and the precautions outlined above, the favorable benefit/risk assessment justifies the further clinical development of etrasimod in participants with moderately to severely active UC and the current Phase 2 study.

The current study is a Phase 2, dose-ranging, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of etrasimod in Japanese participants with moderately to severely active UC. At the completion of the study (completion of Week 12 assessments), participants will have the opportunity to enroll into open-label extension (OLE) Study APD334-303 that will provide additional information on the long-term efficacy and safety of etrasimod. The results from this study will be used to support the regulatory approval of etrasimod for the treatment of patients with UC in Japan.

2. STUDY OBJECTIVES

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 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 patient-reported outcomes and biomarkers.

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

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 (Figure 1). 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 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).

The target participant population will include those who have had an inadequate response to, loss of response to, or intolerance to the following:

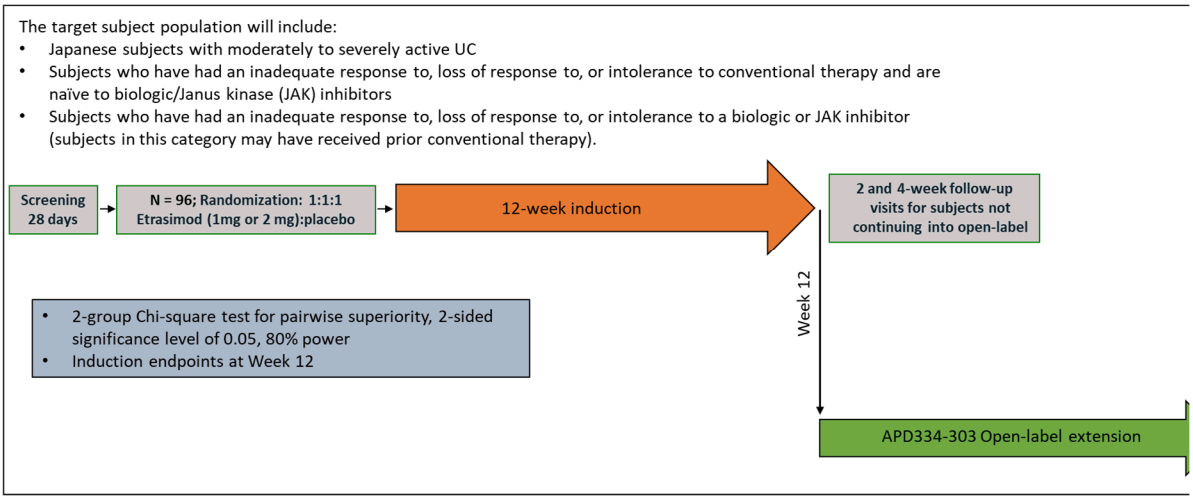
- Conventional therapy, and are naïve to biologic or JAK inhibitor therapy
- Biologics or JAK inhibitors (participants in this category may have received prior conventional therapy)

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 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 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 (Table 6).

Figure 1: Study Design



JAK, Janus kinase; UC, ulcerative colitis

3.2. Rationale for Study Design

Ulcerative colitis, along with CD, are currently the most prevalent intractable diseases in Japan. The clinical characteristics of UC in Japanese, and other East Asian ethnicities are similar in presentation to those in Caucasian patients. While Caucasian and Asian populations appear to have some shared genetic risk factors, others are distinct (Okabayashi 2020). As with all therapeutics, differences in ethnic factors (intrinsic factors as well as extrinsic factors such as local clinical practice and socioeconomic condition) may affect drug efficacy and safety (PMDA 2012). This dose-ranging study is designed to evaluate the efficacy and safety of etrasimod in Japanese participants with moderately to severely active UC.

The etrasimod doses of 1 mg and 2 mg once daily are based on findings of previous Phase 1 and Phase 2 studies, and in particular data from the Phase 1 APD334-109 Japanese/Caucasian ethnobridging PK and PD study and the Phase 2 APD334-003 placebo-controlled study (Sandborn 2020). The APD334-109 study (described in Section 1.3) demonstrated that there were no significant differences in PK and PD of etrasimod in healthy Japanese and Caucasian participants; however, it was not designed to describe potential differences in Japanese and Caucasian UC patients. In the global APD334-003 study, UC participants received etrasimod 1 mg, 2 mg, or placebo. Participants in the etrasimod 2 mg group experienced a statistically significant improvement in the primary endpoint, the mean difference from placebo at Week 12 in the adapted Mayo score (least squares mean [standard error] difference: −0.99 [0.42]; p = 0.0091) compared with placebo. The etrasimod 2 mg group also experienced significant improvement in all secondary endpoints compared with the placebo group at Week 12, including improvement in the Total Mayo Score (TMS [Appendix 3]; estimated least squares mean [standard error] difference from placebo: −1.27 [0.55]; p = 0.0100), and higher percentage of participants with endoscopic improvement (41.8%, difference from placebo: 24.4%, p = 0.003).

Treatment-emergent adverse events (TEAEs) in the 1 mg, 2 mg, and placebo groups were reported for 59.6%, 56.0%, and 50.0% of participants, respectively; treatment-related TEAEs were reported for 7.7%, 10.0%, and 5.6% of participants, respectively; serious adverse events (SAEs) were reported for 5.8%, 0%, and 11.1% of participants, respectively; and TEAEs leading to discontinuation of study

treatment were reported for 5.8%, 8.0%, and 0% of participants, respectively. No participants died during the study. Overall, the 2 mg dose demonstrated a favorable safety profile and was chosen as the dose for the current Phase 3 program.

Participants may continue existing nonbiologic therapy for UC (eg, 5-ASA, corticosteroids) per the concomitant medication and stable dose criteria. As preexisting background therapy is allowed, a placebo comparator is justified. The 12-Week Induction Treatment Period in the current study is based on the safety and efficacy findings of the Phase 2 APD334-003 placebo-controlled study. The 2-Week and 4-Week Follow-Up visits will provide off-treatment safety information.

The primary endpoint of clinical remission at Week 12 as assessed using the MMS is standard, widely used, and in accordance with the nonbinding US FDA Guidance for Industry, *Ulcerative Colitis: Clinical Trials Endpoints* (FDA 2016). Other endpoints for the study are widely used and considered reliable measures of efficacy and safety. The assessment of exposure in this study will provide further insight to the PK and PD of etrasimod in Japanese UC participants and facilitate bridging analyses efficacy and safety with the global data.

As detailed in Section 10.2, the study is powered to the primary endpoint for demonstrating a statistically significant difference in achieving clinical remission between etrasimod therapy and placebo at Week 12. The 1:1:1 randomization scheme will maximize the number of participants receiving a potentially beneficial therapy.

3.3. Study Duration

The study consists of a 28-day Screening Period, a 12-Week Induction Treatment Period, and a 4-Week Follow-Up Period. The study duration is expected to be approximately 2 years.

The End of Study Date is the date when the last participant completes his/her last study visit.

3.4. Independent Data Monitoring Committee

This study will not use an E-DMC.

4. SELECTION OF STUDY POPULATION

The study population consists of Japanese men and women (hereafter referred to as men and women), 18 to 80 years of age, inclusive, with moderately to severely active UC.

4.1. Inclusion Criteria

Participants must meet ALL of the following inclusion criteria to be eligible for enrollment into the study:

1. Japanese ancestry (ie, both parents and 4 grandparents are/were of Japanese descent)
2. 18 to 80 years of age, inclusive, at the time of consent
3. Ability to provide written informed consent and to be compliant with the schedule of protocol assessments

Disease-specific inclusion criteria:

4. Diagnosed with UC ≥ 3 months prior to screening. The diagnosis of UC must be confirmed by endoscopic and histologic evidence. The endoscopy and histology report should be present in the

source documents; however, if not available, the screening endoscopy and histology may serve as such.

5. Active UC confirmed by endoscopy with ≥ 10 cm rectal involvement
6. Moderately to severely active UC defined as MMS of 4 to 9, including an ES ≥ 2 and RB subscore ≥ 1
7. Received a surveillance colonoscopy (performed according to local standard) within 12 months before baseline to rule out dysplasia in participants with pancolitis > 8 years duration or participants with left-sided colitis > 12 years duration. Participants without a surveillance colonoscopy within the prior 12 months will have a colonoscopy at screening (ie, in place of screening proctosigmoidoscopy). Any adenomatous polyps must be removed according to routine practice prior to their first dose of study treatment.

Prior treatment:

8. Demonstrated an inadequate response to, loss of response to, or intolerance to at least 1 of the following therapies as defined below:

- Conventional therapy
    a. Oral 5-ASA compounds
    b. Systemic (oral or IV) Corticosteroids
    c. Thiopurines (eg, AZA, or 6-MP)
- Biologics or JAK inhibitors
    a. Anti-TNFα antibodies (eg, infliximab, adalimumab, golimumab or biosimilars)
    b. Anti-integrin antibodies (eg, vedolizumab, carotegrast methyl)
    c. Anti-interleukin-12/23 antibodies (eg, ustekinumab)
    d. JAK inhibitors (eg, tofacitinib)

Inadequate response, loss of response, and intolerance are defined as:

- Inadequate response: Signs and symptoms of persistently active disease despite a history of completing a dosing regimen
- Loss of response: Recurrence of symptoms of active disease during treatment following prior clinical benefit (discontinuation despite clinical benefit does not qualify as having failed or being intolerant to UC biologic therapy)
- Intolerance: Including, but not limited to, infusion- or injection-related reaction, demyelination, congestive heart failure, infection, or any other related adverse event that led to a reduction in dose or discontinuation of the medication

Note: To be considered inadequate response, loss of response, and intolerance after treatment with a biologic or JAK inhibitor, the participant should have received a dosing regimen consistent with the local product labeling, local guidelines for the treatment of UC and/or institutional standard of care.

Concomitant treatments:

9. Participants are permitted to be receiving a therapeutic dose of the following drugs:Oral 5-ASA compounds provided the dose has been stable for ≥ 2 weeks immediately prior to randomization
    - Oral corticosteroid therapy (prednisone at a stable dose ≤ 20 mg/day or equivalent steroid) provided the dose has been stable for the 4 weeks immediately prior to the screening endoscopy assessment
    - Thiopurines such as oral AZA or 6-MP must be discontinued ≥ 2 weeks prior to randomization
    - Probiotics (eg, *Saccharomyces boulardii*) provided the dose has been stable for the 2 weeks immediately prior to randomization

    If oral 5-ASA or corticosteroids have been recently discontinued, they must have been stopped for at least 2 weeks prior to the endoscopy used for the baseline MMS.

Other general inclusion criteria:

10. Adequate hematological function defined by white blood cell count ≥ 3.5×10^9/L with ANC ≥ 1.5×10^9/L, lymphocyte count ≥ 0.8×10^9/L, platelet count ≥ 100×10^9/L, and hemoglobin ≥ 8 g/dL
11. Adequate hepatic function defined by a total bilirubin level ≤ 1.5 × the upper limit of normal (ULN) range and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤ 2.0 × ULN. Participants with an isolated total bilirubin and normal AST and ALT diagnosed with Gilbert's syndrome may participate
12. Adequate renal function defined by an estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2 by the Chronic Kidney Disease Epidemiology Collaboration equation at screening
13. Females must meet either a or b of the following criteria and males must meet criterion c to qualify for the study:
    a. A female who is not of childbearing potential must meet 1 of the following:
        – Postmenopausal, defined as no menses for 12 months without an alternative medical cause
        – Permanent sterilization procedure, such as hysterectomy, bilateral salpingectomy, or bilateral oophorectomy
    b. Non-pregnant female of childbearing potential must agree to using a highly effective contraception method during treatment and for 30 days following treatment that can achieve a failure rate of less than 1% per year when used consistently and correctly. The following are considered highly effective birth control methods:
        – Combined (estrogen and progestogen containing) oral hormonal contraception associated with inhibition of ovulation
        – Progestogen-only oral hormonal contraception associated with inhibition of ovulation
        – Intrauterine device (IUD)
        – Intrauterine hormone-releasing system

- Bilateral tubal occlusion
- Vasectomized partner, provided that partner is the sole sexual partner of the women of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success
- Sexual abstinence (complete sexual abstinence defined as refraining from heterosexual intercourse for the entire period of risk associated with study treatments). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not acceptable.

c. A male participant with a pregnant or non-pregnant female of childbearing potential partner must agree to using condoms during treatment and for 30 days following treatment.

4.2. Exclusion Criteria

Participants who meet any of the following exclusion criteria will not be eligible for enrollment into the study:

Exclusions related to general health:

1. Severe extensive colitis as evidenced by:
   - Physician judgment that the participant is likely to require hospitalization for medical care or surgical intervention of any kind for UC (eg, colectomy) within 12 weeks following randomization
   - Current evidence of fulminant colitis, toxic megacolon or recent history (within last 6 months) of toxic megacolon, or bowel perforation
   - Previous total or partial colectomy
2. Diagnosis of CD or indeterminate colitis or the presence or history of a fistula consistent with CD
3. Diagnosis of isolated proctitis (defined as proctitis with < 10 cm rectal involvement), microscopic colitis, ischemic colitis, or infectious colitis
4. Hospitalization for exacerbation of UC requiring IV steroids within 12 weeks of screening (a single dose of IV steroids given is acceptable)
5. Positive assay or stool culture for pathogens (ova and parasite examination, bacteria) or positive test for *Clostridioides difficile* toxin at screening (If *C. difficile* is positive, the participant may be treated and retested ≥ 4 weeks after completing treatment.)
6. Pregnancy, lactation, or a positive serum beta-human chorionic gonadotropin (β-hCG) measured during screening
7. Clinically relevant neurological, endocrine, metabolic (including, but not limited to, hypo- and hyperkalemia), psychiatric, cognitive impairment, alcohol/drug abuse/dependence, or other major

systemic disease making implementation of the protocol or interpretation of the study difficult or would put the participant at risk

8. Have any of the following conditions or receiving treatments that may affect cardiovascular function:
    - Myocardial infarction, unstable angina, stroke/transient ischemic attack, decompensated heart failure requiring hospitalization or Class III/IV heart failure ≤ 6 months prior to or during the screening period
    - History or presence of second-degree or third-degree AV block, sick sinus syndrome, or periods of asystole for > 3 seconds without a functional pacemaker
    - History or presence of recurrent symptomatic bradycardia or recurrent cardiogenic syncope
    - Screening or Week 0/Day 1 pre-randomization vital signs (taken in the sitting position) with a HR < 50 bpm OR systolic blood pressure (BP) < 90 mm Hg OR diastolic BP < 55 mm Hg. Vital signs may be repeated up to 3 times during a visit to confirm abnormal readings
    - Screening or Week 0/Day 1 pre-randomization ECG with PR interval > 200 ms or Fridericia's corrected QT interval (QTcF) ≥ 450 ms in men or ≥ 470 ms in women
    - Start, stop, change or planned change in dosage of any anti-arrhythmic drugs (Class I to IV) ≤ 1 week before screening or within 1 week before or after randomization
9. Forced expiratory volume at 1 second (FEV_1) or forced vital capacity (FVC) < 70% of predicted values and FEV_1/FVC ratio < 0.70 at screening
10. Uncontrolled diabetes as determined by hemoglobin A1c (HbA1c) > 9% at screening, or participants with diabetes with significant comorbid conditions such as retinopathy
11. History of macular edema or retinopathy
12. History of active tuberculosis (TB), history of untreated or inadequately treated latent TB infection, active or latent TB infection at screening (refer to Appendix 2 for details on TB screening requirements and interpretation of test results). The following are EXCEPTIONS to this exclusion criterion:
    - Participants with latent TB, who have been ruled out for active TB, have completed an appropriate course of TB prophylaxis treatment per national/local medical guidelines or WHO guidelines, have a chest radiograph without changes suggestive of active TB infection, and have not had recent close contact with a person with active TB are eligible to enroll in the study. It is the responsibility of the Investigator to verify the adequacy of previous TB treatment and provide appropriate documentation of treatment compliance
    - Participants diagnosed with latent TB at screening, ruled out for active TB and received at least 4 weeks of an appropriate TB prophylaxis regimen may be rescreened for enrollment. Participants will complete their prophylactic regimen during the trial
13. A clinically significant active infection (eg, serious and/or atypical) ≤ 28 days prior to randomization, required IV medication ≤ 14 days prior to randomization, or that may worsen (in

the opinion of the Investigator) if the participant is treated with a drug having immunosuppressant effects (ie, etrasimod). Fungal infection of nail beds is allowed.

14. Have human immunodeficiency virus (HIV)/acquired immune deficiency syndrome or test positive for HIV antibodies at screening
15. Have acute or chronic hepatitis B infection or test positive for hepatitis B virus (HBV) at screening (positive for hepatitis B surface antigen [HBsAg]), or
    - negative for HBsAg and positive for hepatitis B core antibody [HBcAb] and negative for hepatitis B surface antibody [HBsAb] in conjunction with detectable HBV DNA, or
    - negative for HBsAg and negative for HBcAb and positive for HBsAb in conjunction with detectable HBV DNA, or
    - negative for HBsAg and positive for HBcAb and positive for HBsAb in conjunction with detectable HBV DNA
16. Have current hepatitis C infection or test positive for hepatitis C virus (HCV) at screening as defined by positive for hepatitis C antibody and detectable HCV RNA
17. History of an opportunistic infection (eg, *Pneumocystis jirovecii*, cryptococcal meningitis, progressive multifocal leukoencephalopathy [PML]) or a history of disseminated herpes simplex or disseminated herpes zoster
18. History of or currently active primary or secondary immunodeficiency
19. History of cancer within the last 5 years, including solid tumors and hematological malignancies (except basal cell and in situ squamous cell carcinomas of the skin that have been excised and resolved) or colonic mucosal dysplasia
20. History of lymphoproliferative disorder, lymphoma, leukemia, myeloproliferative disorder, or multiple myeloma

Exclusions related to medications:

21. Hypersensitivity to etrasimod or any of the excipients or placebo compounds
22. Prior treatment with S1P receptor modulators
23. Treatment with a biologic agent ≤ 8 weeks or a small-molecule agent ≤ 5 elimination half-lives and detectable drug level prior to randomization
24. Treatment with an investigational therapy ≤ 3 months prior to randomization
25. Prior treatment with ≥ 3 advanced therapies (eg, biologics or JAK inhibitors) approved or recommended for treatment of UC
26. Treatment with topical rectal 5-ASA, short-chain fatty acid enemas, or steroids ≤ 2 weeks prior to or during screening
27. Treatment with topical rectal traditional medicine (eg, Chinese medicine), herb enemas, or suppositories ≤ 2 weeks prior to randomization
28. Treatment with methotrexate ≤ 8 weeks prior to or during screening or cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil (MMF) ≤ 16 weeks prior to and during screening

29. Receipt of a live vaccine ≤ 4 weeks prior to randomization
30. Previous treatment with natalizumab
31. Previous treatment with lymphocyte-depleting therapies (eg, alemtuzumab, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation, daclizumab)
32. Previous treatment with D-penicillamine, thalidomide, dimethyl fumarate, or pyrimidine synthesis inhibitors
33. Treatment with IV immune globulin or plasmapheresis ≤ 3 months prior to randomization
34. Use of moderate or strong inhibitors or inducers that inhibit or induce at least 2 of the following: cytochrome P450 (CYP) 2C8, CYP2C9 and CYP3A4 (eg, fluconazole, rifampin, enzalutamide) within 4 weeks prior to randomization

5. REMOVAL OF PARTICIPANTS FROM STUDY TREATMENT OR ASSESSMENT

5.1. Discontinuation from Study Treatment

A participant's double-blind treatment may be discontinued for any of the following reasons:

- Adverse event that in the judgement of the Investigator and/or Medical Monitor indicate the participant should not continue study treatment
- Participant noncompliance with the protocol or study treatment that is considered significant by the Medical Monitor
- Investigator decision
- Withdrawal by participant
- Lack of efficacy
- Lost to follow-up
- Study termination by Sponsor
- Other, non-adverse event

A participant's double-blind treatment must be discontinued for any of the following reasons:

- Decline in PFT values (FEV_1 and/or FVC) below 50% of the predicted values
- Confirmed diagnosis of clinically significant macular edema
- Confirmed diagnosis of active TB
- Participants who have a cardiovascular treatment-related symptomatic event (eg, chest pain, dizziness, palpitations, lightheadedness, shortness of breath, or syncope) associated with reduction of the HR or associated with clinically relevant ECG changes at any time during the 4-hour monitoring period on Day 1 or Day 2 (as applicable) (Section 9.4.2.1)
- Participants who have not met the discharge criteria (Table 3) on Day 1 after ≥ 4 hours of extended monitoring, or Day 2 by 4 hours postdose
- Pregnancy (Section 9.9.9)

- Suspected drug induced liver injury as defined by the 2009 FDA Guidance for Industry (FDA 2009)
  - ALT or AST > 8 × ULN
  - ALT or AST > 5 × ULN for > 2 weeks
  - ALT or AST > 3 × ULN and (total bilirubin > 2 × ULN or international normalized ratio > 1.5)
  - ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

Because transient fluctuations of ALT or AST are common, and progression to severe drug induced- liver injury or acute liver failure is uncommon, automatic discontinuation of study treatment upon finding a greater than 3 × ULN elevation of ALT or AST may be unnecessary. If a drug induced-liver injury is identified, refer to Section 16.6 for guidance.

Participants who discontinue treatment prematurely, regardless of the reason, should be instructed to return for an ET visit within 7 days of the last administration of study treatment (Table 6) and complete all of the ET assessments. If a participant discontinues due to pregnancy, they are not required to complete the endoscopy. If the ET visit is within 4 weeks of the last sigmoidoscopy and biopsy, these procedures do not need to be repeated.

If the ET visit is ≥ 2 weeks after the last administration of study treatment, the 2-Week Follow-Up visit is not required; however, the 4-Week Follow-Up visit should be scheduled and completed. If the ET visit is ≥ 4 weeks of the last dose of study treatment, the 4-Week Follow-Up visit is not required unless the ALC is not within normal limits.

If treatment discontinuation is considered an adverse event, refer to Section 9.9.8.3. for AE/SAE reporting guidance.

5.2. Discontinuation from the Study

Participants may be discontinued from the study at any time for any of the following reasons:

- Withdrawal by participant
- Deviation/noncompliance with the study protocol that in the judgement of the Investigator and/or Medical Monitor the participant should not continue study treatment
- Study termination by Sponsor
- Lost to follow-up
- Death
- Other

A participant may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. If a participant withdraws consent, no further evaluation should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent. The Investigator should make a reasonable attempt to document the specific reason why consent was withdrawn.

In the event that a participant fails to attend any follow-up visits, all reasonable efforts will be made to contact the participant to ensure that he/she is in satisfactory health. All contacts and contact attempts must be documented in the participant's file.

5.3. Participants Lost to Follow-Up Prior to Last Scheduled Visit

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required on-site, offsite, virtual or hybrid visit (Section 9.6):

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and if necessary, a certified letter to the participant's last know mailing address or local equivalent methods). These contact attempts should be documented in the participant's file.

Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

5.4. Premature Termination of the Study

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to participants
- Participant enrollment is unsatisfactory
- Upon request of health authorities

The Sponsor will notify Investigators if the study is placed on hold or if the Sponsor decides to discontinue the study or development program. Health authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the termination of the study in accordance with applicable regulations.

The Sponsor has the right to replace a study site at any time. Reasons for replacing a study site may include, but are not limited to:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the ICH guideline for GCP

6. STUDY TREATMENTS

6.1. Treatments Administered

Participants will be randomly assigned to 1 of 3 treatment groups (1 mg or 2 mg etrasimod or placebo) in a 1:1:1 ratio. Study treatment is outlined in Table 1.

Table 1: Study Treatments

Study treatment name:	Etrasimod	Placebo
Dosage formulation:	1 mg tablet or 2 mg tablet	Matching tablet
Unit dose strength/dosage level:	1 tablet once daily	1 tablet once daily
Route of administration:	By mouth	By mouth
Packaging and labeling:	Study treatment will be provided in 40 cc, induction-sealed, high-density polyethylene bottles with child-resistant screw caps. Each bottle will be labeled as required per country requirement. These bottles should be stored at 15 to 25°C (59 to 77°F).	Study treatment will be provided in 40 cc, induction-sealed, high-density polyethylene bottles with child-resistant screw caps. Each bottle will be labeled as required per country requirement. These bottles should be stored at 15 to 25°C (59 to 77°F).

6.2. Investigational Study Treatment

The active pharmaceutical ingredient in etrasimod tablets is APD334 L-arginine (the arginine salt of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)acetic acid), which is an off-white to light-brown solid with an aqueous solubility of approximately 1.38 mg/mL at pH = 8.9 and 30°C. APD334 L-arginine is manufactured, packaged, tested, and released in compliance with cGMP.

The drug product is a blue, round, biconvex, plain, immediate-release, film-coated tablet. Etrasimod tablets are supplied in the dosage strength (based on etrasimod free acid content) of 1 mg and 2 mg.

The placebo tablet formulation is composed of excipients (microcrystalline cellulose NF, Ph. Eur.; mannitol USP, Ph. Eur.; sodium starch glycolate NF, Ph. Eur.; magnesium stearate NF, Ph. Eur.; and Opadry® II Blue 85F90951). Placebo tablets are identical in appearance to the active-drug tablets as described above.

6.3. Dosage and Administration

One tablet is to be taken each day (with water, either with or without food). Tablets should be taken at approximately the same time each day, preferably in the morning. On study visit days, participants should wait and take their dose after blood draws for PK and after all predose assessments and procedures have been completed. The time of PK sample collection and last dosing prior to the PK sample should be documented in the electronic case report form (eCRF).

6.3.1. Instructions for Missed Dose(s)

Participants should be instructed that if they forget to take a dose, they can take the dose within 8 hours of the normal dosing time; otherwise, they should take their next dose at the regular time on

the following day. If the participant vomits the tablet, he/she should be instructed not to take another tablet on the same day, but to take the next dose at the regular time on the following day. Missed doses should be recorded in the participant's electronic diary (eDiary). Participants should be instructed to contact the Investigator if they miss more than 2 consecutive doses.

Participants must be educated to contact the Investigator to discuss treatment re-initiation if they do not take the study treatment for ≥2 consecutive days within the first week of treatment or for ≥7 consecutive days after the first week of treatment.≥ The participant must take the next dose of study treatment at the study site, and the in-clinic cardiac monitoring as outlined in Section 9.4.2.1 should be performed.

6.3.2. Dose Interruptions

If the Investigator deems it necessary to withhold study treatment, temporary withholding is permitted for up to 6 days without obtaining prior approval from the Medical Monitor. If study treatment interruption ≥ 7 days is required for a medical reason, the Investigator must contact the Medical Monitor.

The first-dose monitoring as outlined in Section 9.4.2.1 should be performed any time a participant misses study treatment as follows:

- ≥ 2 consecutive days within the first week of treatment, or
- ≥ 7 consecutive days after the first week of treatment

6.4. Method of Assigning Participants to Treatment

Participants will be centrally assigned to randomized study treatment using an Interactive Web Response System (IWRS). Before the study is initiated, the log in information and directions for the IWRS will be provided to each study site.

Participants will be randomized to study treatment via stratified randomization. Randomization will be stratified by (a) naïve to biologic or JAK inhibitor therapy at study entry (yes or no), (b) baseline corticosteroid use (yes or no), and (c) baseline disease activity (MMS: 4 to 6 or 7 to 9).

Each participant will be dispensed blinded study treatment at study visits (Table 6).

6.5. Blinding

This is a double-blind study with limited access to the randomization code. The study treatment and placebo tablets and bottles are identical in physical appearance. The treatment each participant receives will not be disclosed to the Investigator, study site staff, participants, sponsor personnel involved with the conduct of the study (with the exception of the clinical supply staff and designated safety staff), or study vendors. The IWRS will hold treatment codes and bottle numbers for study treatment.

Treatment assignments should remain blinded unless that knowledge is necessary to determine participant emergency medical care. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted to provide appropriate medical care. Participant safety must always be the first consideration in making such a determination. The IWRS is programmed with blind-breaking instructions to guide the Investigator on how to obtain treatment assignment in the event of an emergency unblinding. The Investigator is requested to contact the Medical Monitor promptly in case of any treatment

unblinding. If a participant's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason the blind was broken must be recorded in the source documentation and eCRF, as applicable.

For Suspected, Unexpected, Serious Adverse Reactions, the Sponsor's Pharmacovigilance designee responsible for managing SAEs will access the IWRS to obtain the participant's treatment assignment for the purpose of regulatory reporting.

If a participant's treatment assignment is unblinded for any reason, they will be discontinued from the study.

6.6. Treatment Compliance

It is the Investigator's responsibility to ensure that participants are correctly instructed on how to take their study treatment and that each participant is compliant with their assigned regimen. The study treatment should be dispensed by the Investigator, or by a qualified individual under the Investigator's supervision. Participants will record the time of their dose each day in the participant eDiary. An up-to-date treatment inventory/dispensing record must be maintained as described in Section 8.4.

Overall treatment compliance will be calculated at the end of study treatment and tabletcounts < 80% or > 120% of the expected value at the end of treatment should be documented as a protocol deviation. If there is a discrepancy between the tablet count and the participant's compliance per the eDiary between visits, or if overall treatment compliance is <80% or >120% between visits,it should be discussed with the participant to improve compliance and the discussion should be noted in the source documents.

6.7. Concomitant Therapy

All over-the-counter and prescribed concomitant medications, blood products, procedures, vitamins, and holistic products, administered during the Screening Period and during the study through the safety reporting period must be recorded in the eCRF, as appropriate.

6.7.1. Required Concomitant Therapy

Not applicable.

6.7.2. Allowed Concomitant Therapy

Concomitant medication for medical conditions other than UC are permitted as clinically indicated participant to specific protocol requirements outlined in Section 4.1 and Section 4.2.

6.7.2.1. Permitted Medications for the Treatment of Ulcerative Colitis

Oral 5-ASA, AZA, 6-MP, oral corticosteroids, or medicinal probiotics are allowed at the time of screening and as per the inclusion criteria (Section 4.1); however, these products should not be started during screening or during the treatment period in participants who are not already receiving them. Immunosuppressive agents such as oral AZA or 6-MP must be discontinued ≥ 2 weeks prior to randomization.

Participants receiving 5-ASA or medicinal probiotics should maintain a stable dose throughout the study.

Oral corticosteroid therapy (prednisone at a stable dose ≤ 20 mg/day or equivalent steroid) is allowed to be continued during the 12-Week Induction Treatment Period provided the dose has been stable for the 4 weeks immediately prior to the screening endoscopy assessment.

6.7.2.2. Vaccines

Vaccinations are permitted as clinically indicated except for live vaccines (refer to Section). At this time, there are no data on the effect of etrasimod on vaccination including SARS-CoV-2 (COVID-19) vaccines. The IOIBD has published recommendations that patients with IBD should be vaccinated against SARS-CoV-2; that SARS-CoV-2 vaccines, including messenger RNA, replication-incompetent vector, inactivated and recombinant vaccines are safe to administer to patients with IBD; and thus should not be deferred because a patient with IBD is receiving immune-modifying therapies (Siegel 2021).

If a participant receives a vaccination, the vaccination date and type (eg, SARS-CoV-2) will be captured as described in Section 9.3.5 in the Concomitant Medication eCRF. The vaccine brand, manufacturer, and lot number should be captured in the Concomitant Medication eCRF as available.

6.7.3. Prohibited Concomitant Therapy

The following concomitant medications are prohibited during the study:

Note: Participants who enter the 4-Week Follow-Up Period will no longer need to abstain from the medications that were prohibited during the treatment periods, unless noted otherwise (eg, live attenuated vaccines for 4 weeks after the last dose of study drug). Once a participant has discontinued their study medication and had their Week 12 / ET visit, a participant may have their worsening Ulcerative Colitis flare treated according to the local standard of care. The Investigator may initiate a rescue treatment during the Follow-Up period.

- Treatments for UC other than those listed in Section 6.7.2.1 (either approved or investigational)
- All live vaccines, during study treatment and within 4 weeks after the last dose of study treatment
- Moderate/strong inhibitors or inducers that inhibit or induce at least 2 of the following enzymes: CYP2C8, CYP2C9 and CYP3A4 (eg, fluconazole, rifampin, enzalutamide)
- Start, stop, or change in dosage of any anti-arrhythmic drugs (Class I to IV) within 1 week before or after treatment re-initiation following drug interruption as specified in Section 6.3.2
- Chronic nonsteroidal anti-inflammatory drugs (NSAID) use (Note: Occasional use of NSAIDs and acetaminophen [eg, headache, arthritis, myalgias, or menstrual cramps] and aspirin up to 325 mg/day is permitted)
- Marketed biologic therapies
- Immunosuppressive agents (eg, AZA, 6-MP, tofacitinib)
- Any per rectum therapy including enemas (eg, 5-ASA, corticosteroid, traditional [ie, Chinese] medicine, suppositories), other than that required for endoscopy preparation
- Cyclosporine, tacrolimus, sirolimus, methotrexate, or MMF

- Cholestyramine or other drugs interfering with enterohepatic circulation, unless the treatment has been stable for > 6 months prior to screening
- Any investigational drug other than the study treatment
- Treatment with D-penicillamine, thalidomide, dimethyl fumarate, or pyrimidine synthesis inhibitors
- Treatment with lymphocyte-trafficking inhibitors (natalizumab, fingolimod, siponimod, ozanimod)
- Immunosuppressive agents that deplete lymphocytes (eg, alemtuzumab, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, daclizumab)

The following concomitant procedures are prohibited during the study:

- Major elective surgery
- Immunoadsorption columns
- IV immunoglobulin or plasmapheresis
- Blood donations during the study and for 14 days after the last dose of study treatment.
- Sperm or oocyte donations during the study and for 30 days after the last dose of study treatment

7. PARTICIPANT RESTRICTIONS

Prohibited concomitant therapy is described in Section 6.7.3. Additionally, participants are restricted from the following:

- Poppy seeds: Consumption of poppy seeds within 48 hours prior to drug screening may cause a positive drug screen. Participants who report that they have consumed poppy seeds within 48 hours of the Screening Visit should not be screened. They may return 48 hours after the last poppy seed consumption for screening. Poppy seeds should not be eaten between screening and Week 0/Day 1.
- St John's wort: Participants should be instructed to abstain from consuming herbal remedies containing St John's wort during the study as these may interfere with the metabolism of etrasimod.

8. STUDY TREATMENT MATERIALS AND MANAGEMENT

8.1. Packaging and Labeling

Study treatment will be provided in 40-cc induction-sealed, high-density polyethylene bottles with child-resistant screw caps. Each bottle will be labeled as required per Japan requirements.

8.2. Study Treatment Storage and Handling

Bottles should be stored 15°C to 25°C (59°F to 77°F). In the case where a participant attends a virtual visit (refer to Section 9.6) and requires additional study treatment to continue on the study, study treatment may be dispensed and delivered by an approved courier where permitted by local law and regulation. Alternatively, a future supply of study medications may be dispensed to the participant at

an onsite visit to cover study medications to be dispensed at the next planned virtual visit. Advanced planning and communication will be needed to dispense future supply of study medications at an earlier onsite visit. Shipping guidelines and instruction will be provided separately.

8.3. Study Treatment Preparation

Not applicable

8.4. Study Treatment Accountability

The head of the study site or the investigational product manager has overall responsibility for administering and dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the Investigator. This delegation must be documented in the applicable study delegation of authority form.

At each visit, previously dispensed study treatment tablets will be collected by the Investigator or qualified individual and compliance assessed. The investigational product manager must maintain adequate records documenting the receipt, use, loss, or other disposition of the study treatment. To ensure adequate records, all drug supplies will be accounted for in the drug accountability inventory forms and will be monitored by counting of unused medication from individual bottles returned by the participant at each visit.

8.5. Study Treatment Retention and Disposal

All study treatment will be reconciled by the clinical monitor (or delegate) and then returned or destroyed according to applicable country regulations. Study sites with a pharmacy performing study treatment accountability and destruction before the clinical monitor can conduct reconciliation activities are only permitted to do so with prior approval from the Sponsor. On-site destruction following all local regulations and in accordance with applicable site standard operating procedures (SOPs) is permitted. Prior to any action being taken with study treatment, the Investigator or the investigational product manager will contact the Sponsor (or contract research organization [CRO]) for approval of such action. Final reconciliation will be performed at study completion.

9. STUDY ASSESSMENTS AND PROCEDURES

9.1. General Instructions

- Study procedures and their timing are summarized in the Schedule of Assessments (Table 6). Protocol waivers or exemptions are not allowed.
- Results of all protocol-required procedures will be recorded in the eCRF whenever applicable.
- Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Assessments (Table 6), is essential and required for study conduct.
- Study visits should be scheduled in the morning, whenever possible.

- All laboratory assessments required by the protocol will be performed by a central laboratory unless otherwise stated.
- For onsite and offsite study visits (refer to Section 9.6 and Table 6), participants should take their study treatment after blood draws for PK and after all pre-dose assessments and procedures have been completed.

The Investigator will maintain a screening log and enrollment log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

9.2. Participant Information

9.2.1. Informed Consent

The Investigator, or a person designated by the Investigator, will obtain written informed consent from each participant before any study-specific activity is performed (Section for additional details).

9.3. Screening and Eligibility

Participant eligibility will be assessed based on protocol inclusion and exclusion criteria. All screening evaluations must be completed and reviewed to confirm potential participants meet all eligibility criteria.

Screening procedures must be completed within 28 days prior to receiving the first dose of study treatment (Table 6). The Screening Period may be extended for participants who require additional diagnostic testing/consults to determine status of either latent TB or *C. difficile* infection. If the participant is planned to be randomized > 28 days from the signing of the informed consent form (ICF), the Medical Monitor should be consulted to see if repeated testing is needed. The 28-Day Screening Period may also be extended on a case-by-case basis to accommodate reasonable delays in specific screening assessments (eg, PFTs, OCT) due to testing availability. The Medical Monitor must be consulted prior to extension in each case.

Participants may have an abnormal laboratory assessment, repeated 1 time only. If additional retests are considered, the ability to repeat the laboratory assessment should be discussed with the Medical Monitor and the outcome of the conversation should be documented.

9.3.1. Tuberculosis Screening and Chest X-Ray

All participants will complete TB screening to determine eligibility (refer to Appendix 2). If an Investigator feels the test for latent TB is abnormal, a retest to confirm latent TB status should be discussed and approved by the Medical Monitor.

9.3.2. Rescreening

Participants who fail to meet the eligibility criteria can be rescreened per Investigator discretion. Additional screening attempts beyond the first should be approved by the Medical Monitor prior to rescreening. Each participant must be reconsented prior to each screening attempt.

Participants with a Screening visit or Week 0/Day 1 pre-randomization 12-lead ECG showing a second- or third-degree AV block, periods of asystole > 3 seconds, PR interval > 200 ms, or QTcF ≥ 450 ms (men) or QTcF ≥ 470 ms (women) are not eligible for rescreening.

If a participant requires prophylactic therapy for latent TB, they may be rescreened as outlined in Section 4.2.

If a participant is positive for *C. difficile* at screening, the participant may be treated and retested ≥ 4 weeks after completing treatment.

9.3.3. Demography and Other Participant Characteristics

Demographics including year of birth and sex at birth as described by the participant will be collected at screening.

9.3.4. Social History

At screening, a social history including the amount and duration of tobacco, alcohol, and caffeine usage will be collected.

A standard urine drug screen will be performed. Participants who test positive will be assessed for eligibility in study participation by the Investigator.

9.3.5. Prior and Ongoing Therapies

Prior therapies related to the treatment of UC will be collected during screening. In addition, documentation should also include the prior treatment response as one of the following: Inadequate response to, loss of response to, or intolerance to (refer to Section 4.1, Inclusion Criterion 8, for details).

All medications taken and procedures carried out within 30 days prior to the first dose and all ongoing medications will be recorded at screening. Updates for new medications prior to dosing at the Day 1 visit should be made as needed.

9.3.6. Ulcerative Colitis History/Medical History

In order to determine the participant's eligibility to the study, a complete medical history of each participant will be collected and documented during screening. The history should include, recent blood donations (≤ 30 days prior to the screening period), illnesses, and participation in other investigational drug studies.

In addition, a detailed history of the participant's UC, including date of diagnosis, disease severity, hospitalizations, and extraintestinal manifestations (EIMs), will be collected.

9.3.7. Vital Signs

At screening, vital signs (resting HR, systolic and diastolic BP, body temperature, and respiratory rate) will be measured while sitting.

9.3.8. Pulmonary Function Test

Pulmonary function tests including FEV_1 and FVC measurements will be performed. In addition, diffusing capacity of the lungs for carbon monoxide (DLCO) measurements will be performed where locally available (sites where DLCO is not available should consult the Sponsor or Sponsor's delegate).

9.3.9. Ophthalmoscopy and Optical Coherence Tomography

Ophthalmoscopy and OCT will be performed. A general ophthalmologist can do the examination; although, a retinal specialist would be preferred wherever possible. Participants with a history of macular edema or retinopathy are not eligible for the study (Section 4.2).

9.3.10. Clinical Laboratory Assessments

Screening samples for complete blood count (CBC) with differential, platelet count, lymphocyte counts, T lymphocytes, B lymphocytes, natural killer lymphocytes (TBNK) cell counts, serum chemistry, virology, thyroid panel, coagulation, urinalysis, high-sensitivity C-reactive protein (hs-CRP), TB screen, and stool sample should be obtained and results must be available and reviewed prior to randomization. In the case of new clinical laboratory abnormalities detected prior to randomization, the eligibility of the participant should be reconsidered with the guidance of the Medical Monitor.

9.3.11. Proctosigmoidoscopy/Colonoscopy and Modified Mayo Score Derivation

- Proctosigmoidoscopy/colonoscopy must be performed prior to randomization of treatment to allow central reader review (may take approximately 512 days) and confirmation of eligibility. Preferably, proctosigmoidoscopy/colonoscopy should be performed after other criteria for inclusion (eg, laboratory criteria) have been met.
- **Determination of MMS score to qualify for randomization:**
  - The MMS will be evaluated at Day 1. The subscores for stool frequency (SF) and RB are derived from the participant eDiary entries using the scores from the 3 most recent consecutive days within the 7 days prior to the day of bowel preparation (excluding the day of bowel preparation), averaged and rounded to the nearest integer. The scoring will be calculated electronically. Participants who do not have 3 consecutive days of eDiary data within that 7-day period and who do not have a minimum of 7 days of eDiary data prior to bowel preparation are not eligible for randomization. The MMS must be 4 to 9, including an ES $\geq$ 2 and RB subscore $\geq$ 1, for the participant to be eligible for randomization.
  - For the normal SF, it is essential for the participant to be asked to identify how many stools he or she has in a 24-hour period when in remission from UC. Participants should be instructed that a stool is defined as a trip to the toilet when the participant has either a bowel movement, or passes blood alone, blood and mucus, or mucus only. If the participant does not report that he or she has achieved remission, then the participant should be asked to identify the number of stools he or she had before initial onset of signs and symptoms of UC.

9.4. Randomization/Treatment Period

9.4.1. Week 0/Day 1: Pre-randomization

At the Week 0/Day 1 visit (Table 6), prior to randomization, a 12-lead ECG in the supine position and resting vital signs in the sitting position (HR, systolic and diastolic BP, body temperature, and respiratory rate) will be collected. Caffeine and/or nicotine are not permitted within 30 minutes prior to BP measurements.

Participants with the following must not be randomized and should be considered screen failures:

- Sitting vital sign assessment: HR < 50 bpm OR systolic BP < 90 mm Hg OR diastolic BP < 55 mm Hg
- 12-lead ECG showing a second-degree or third-degree AV block, periods of asystole > 3 seconds, PR interval > 200 ms, or QTcF ≥ 450 ms (men) or QTcF ≥ 470 ms (women).

All predose 12-lead ECGs should be obtained prior to blood sample collection.

Participants who continue to meet all eligibility criteria will be randomized as outlined in Section 6.4.

9.4.2. Treatment Period

After randomization, the 12-Week Treatment Period of the study will begin (Table 6). A study visit window of ± 3 days is permitted at each visit beginning with Week 2/Day 15 (PFT and OCT assessments have a window of ± 7 days). Study visits should be scheduled for the morning.

The subscores for SF and RB are derived from the participant eDiary entries. On visits when MMS is calculated, these subscores are derived using the scores from the 3 most recent consecutive days within the 7 days prior to the day of bowel preparation (excluding the day of bowel preparation), averaged and rounded to the nearest integer. If 3 consecutive days are not available, then the average of the 2 most recent consecutive days within the 7 days will be used.

On visits without endoscopy, the SF and RB subscores are derived using the scores from the 3 most recent consecutive days within the 7 days prior to the date of visit, averaged and rounded to the nearest integer. If 3 consecutive days are not available, then the average of the 2 most recent consecutive days within the 7 days will be used.

It is recommended that procedures are performed in a consistent order and at approximately the same time of day for each visit. Below is the recommended sequence of events (refer to Schedule of Assessments, Table 6):

- Questionnaire administration
- Adverse event review
- Vital signs
- 12lead ECG
- Physical examination
- EIMs
- PFT
- OCT
- Blood sample collection for laboratory tests and predose PK sampling

9.4.2.1. Guidance for Cardiac Monitoring Following Treatment Initiation or Re-Initiation

Pre-randomization (ie, pre-dose/baseline) vital signs (resting HR, systolic and diastolic BP, body temperature, and respiratory rate) will be used as the baseline measurement. The pre-dose HR measurement will be used for comparison to the postdose measurement. It is recommended that participants receive the first dose of study treatment before 12:00 PM (noon).

9.4.2.1.1. First Dose Cardiac Monitoring

In-clinic cardiac monitoring, of at least 4 hours, will occur on Day 1 and will include the following (Table 2):

- Full baseline vital signs (HR, systolic and diastolic BP, body temperature, and respiratory rate) and a 12-lead ECG (taken with the participant in the supine position) will be assessed pre-randomization.
- After the first dose of study treatment on Day 1, participants must remain under observation in the clinic for at least 4 hours.
- At Hours 1, 2, and 3 (± 15 minutes) postdose, the HR and systolic and diastolic BP will be assessed with the participant in the sitting position, with the time recorded. If the participant has an HR < 50 bpm or if cardiovascular symptoms develop, then the participant should remain closely monitored, including 12-lead ECGs as clinically indicated, until the Hour 4 discharge assessment.
- At the Hour 4 (± 15 minutes) discharge assessment, HR and systolic and diastolic BP will be assessed with the participant in the sitting position and a 12-lead ECG (with the participant in the supine position) will be performed. Participants may be discharged from the clinic after the 4-hour assessment if they meet the criteria described in Table 3. Participants not meeting the discharge criteria will require extended monitoring as described below.
- Participants experiencing a clinically relevant treatment-related symptomatic event (eg, chest pain, dizziness, palpitations, or syncope) associated with reduction of the HR or clinically relevant 12-lead ECG changes at any time during the 4-hour monitoring period must be discontinued from treatment (Table 4).

Table 2: Procedures to be Performed During the Monitoring Period

Procedure	Predose	Hours 1, 2, 3 Postdose[a]	Hour 4 Postdose[a]
Blood pressure and heart rate[b]	X	X	X
12-lead ECG	X		X
Assess discharge criteria			X

[a] Measurements may be taken ± 15 minutes of the scheduled time.
[b] Heart rate is based on vital signs.
ECG, electrocardiogram

Table 3: Discharge Criteria After Cardiac Monitoring

Participants will be released from the clinical site after dosing on Day 1 (but no sooner than 4 hours postdose) when they fulfill the following discharge criteria:
• Heart rate ≥ 50 bpm or no more than 10 bpm lower than the predose (baseline) value
• No evidence of second-degree AV block or higher
• No cardiac symptoms (eg, chest pain, dizziness, palpitations, lightheadedness, shortness of breath, or syncope)

Note: Participants should have written instructions on when to return to the clinic and a 24-hour contact phone number to call in the event of any new or worsened cardiovascular symptoms.
AV, atrioventricular; bpm, beats per minute

9.4.2.1.2. Extended Cardiac Monitoring

Participants who do not meet discharge criteria at 4-hours postdose will require extended cardiac monitoring:

- Vital signs will be assessed hourly and 12-lead ECG may be performed, as clinically indicated, until the participant meets the discharge criteria (Table 3).
- The Medical Monitor should be contacted if the participant does not meet the discharge criteria after ≥ 4 hours of extended cardiac monitoring.
- Any participant who requires extended monitoring on Day 1 must return on Day 2 for the second dose and will be re-monitored as on Day 1. These participants will be discontinued from study treatment if they do not meet the discharge criteria at 4 hours after the second dose. Extended cardiac monitoring should be continued until the participant meets the discharge criteria (Table 3).
- Participants experiencing a symptomatic event (eg, chest pain, dizziness, palpitations, lightheadedness, shortness of breath, or syncope) at any time during the 4-hour monitoring period that is not associated with either a reduction in HR or clinically relevant change in 12-lead ECG, may be discharged provided they meet the discharge criteria (Table 3), and as deemed appropriate by the Investigator; however, these participants must return on Day 2 for the second dose and will be re-monitored as on Day 1. These participants must be discontinued from treatment if they do not meet the discharge criteria at 4 hours after the second dose on Day 2 and extended cardiac monitoring should be continued until the participant meets the discharge criteria (Table 3).

9.4.2.1.3. Study Treatment Discontinuation Related to Postdose Cardiac Monitoring

A complete list of reasons for study treatment discontinuation is provided in Section 5.1. Reasons for study treatment discontinuation specific to postdose cardiac monitoring are provided in Table 4. The Medical Monitor should be contacted before discontinuing a participant.

Table 4: Discontinuation of Study Treatment Related to Postdose Cardiac Monitoring

Reasons for Study Treatment Discontinuation Related to Postdose Cardiac Monitoring[a]
• Participants who have a cardiovascular treatment-related symptomatic event (eg, chest pain, dizziness, palpitations, lightheadedness, shortness of breath, or syncope) associated with reduction of the heart rate or associated with clinically relevant 12-lead ECG changes at any time during the 4-hour monitoring period on Day 1 or Day 2 (as applicable).
• Participants who have not met the discharge criteria on Day 1 after ≥ 4 hours of extended monitoring, or Day 2 by 4 hours postdose.

[a] All treatment discontinuations should be discussed with the Medical Monitor.
ECG, electrocardiogram

9.4.2.1.4. Cardiac Monitoring Upon Treatment Re-Initiation Following Dose Interruption

Participants should undergo the same first dose cardiac monitoring procedures as the original treatment initiation when study treatment dosing is re-initiated after interruption for:

- ≥ 2 consecutive days within the first week of treatment
- ≥ 7 consecutive days after the first week of treatment

9.5. Follow-Up Period

For participants not participating in the OLE study, follow-up visits will be performed at 2 and 4 weeks after the last administration of study treatment as indicated in the Schedule of Assessments (Table 6).

If the ET or Study Completion visit is ≥ 2 weeks after the last administration of study treatment, the 2-Week Follow-Up visit is not required; however, the 4-Week Follow-Up visit should be scheduled and completed. If the ET or Study Completion visit is ≥ 4 weeks after the last administration of study treatment, the 4-Week Follow-Up visit is not required.

If the absolute peripheral lymphocyte count is not within normal limits at the 4-Week Follow-Up visit, participants should return for CBC with differential according to local standard of care (captured as subsequent Follow-Up visit or unscheduled visit).

All adverse events should be recorded for 30 days after last administration of study treatment (Section 9.9.8.2.2).

9.6. Virtual/Hybrid Visits

Study visits after Day 1 may be conducted via onsite (in-person at the study site or specialty lab), offsite (home health visit by study staff or designee or mobile visit), virtual or telehealth visit (eg, telephone, video conference), hybrid (a combination of aforementioned visit types) depending on the nature of the study assessment, technological capability, and acceptability with institutional practices and in alignment with local law and regulatory requirements. These may take place different days within the study visit window.

During a virtual assessment, a participant may report an AE that requires a follow-up symptom-focused physical exam or diagnostic test, as determined by the Investigator. In this

scenario, the Investigator may have the participant return to the study site for an unscheduled study visit to perform the assessment.

For study drug accountability, the medication bottle and remaining tablets may be visually inspected and counted on video conferencing. Participants must return the dispensed bottle with the remaining tablets along with any empty bottles to the study site at the next onsite visit. Refer to Section 8 for study treatment management.

Regardless of how a study visit and its associated procedures are conducted, all study procedures should be performed by qualified study site staff or qualified individual as delegated by the Principal Investigator.

Study visits are designated accordingly in the Schedule of Assessments (Table 6).

9.6.1. Telehealth Visits

Telehealth visits may be used to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, videoconferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit (see the SoA; Table 6):

- Review and record study treatment(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 9.9.8 .
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Section 4.1.

Study participants must be reminded to promptly notify site staff about any change in their health status.

9.6.2. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. The following may be performed during a home health visit (see the SoA; Table 6):

- Review and record study treatment(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 9.9.8
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Section 4.1.

- Pregnancy testing and central laboratory assessments (eg, blood, stool, and urine samples are taken)

It is recommended that the investigator discuss temporary or permanent discontinuation of study treatment with the study medical monitor.

Certain assessments and/or procedures will **not** be performed in the home setting (eg, endoscopies, OCT, PFT, cardiac monitoring following treatment initiation or re-initiation, and 12-lead ECG).

9.6.3. Mobile Visits

In the event that an in-person visit is not feasible at the site, the following may be performed by a licensed healthcare professional at an alternate site approved by the investigator (see the SoA; Table 6):

- Pregnancy testing and central laboratory assessments (eg, blood, stool, and urine samples)

9.7. Pharmacokinetics

Blood samples for analysis of etrasimod will be collected at the following timepoints from all participants who received at least 1 dose of study drug (etrasimod or placebo):

- Predose and at 4 hours (± 15 minutes) postdose (after 12-lead ECG) on Week 0/Day 1
- Predose (trough; within 60 minutes prior to dosing) at Weeks 2, 4, 8, and 12, for participants enrolling in the OLE at the Week 12 visit, the PK sample can be collected as part of the OLE.
- At 2-Week and 4-Week Follow-Up visits
- If possible, at the time of any SAE or adverse event leading to study treatment discontinuation

Participants should be instructed to document the time of their last dose prior to the study visit and the time must be recorded in the eCRF. The time of administration of study treatment during the study visit must also be recorded in the source along with the time of each PK sample.

Blood samples will be processed for collection of plasma fractions for determination of the concentrations of etrasimod. For the placebo group, a selected number of samples will be analyzed.

Plasma PK samples may also be used for profiling of drug-binding proteins, bioanalytical method validation purposes, stability assessments, or to assess other actions of etrasimod with plasma constituents.

No urine samples will be collected for PK analysis.

Sample collection, preparation, and shipping will be detailed in a Laboratory Manual.

9.8. Efficacy Assessments

The components of the MMS are used to calculate several of the primary, secondary, and exploratory endpoints. The definitions for MMS components are outlined in Section 10.5.

9.8.1. Modified Mayo Score/Mayo Clinic Score

This study utilizes the MMS, which includes the ES, RB, and SF components of the Mayo Clinic score (MCS; Appendix 3), to assess UC disease activity in support of the primary and secondary

endpoints. The total score range of the MMS is from 0 to 9, with each component ranging from 0 to 3 (0 = normal, 1 = mild, 2 = moderate, 3 = severe).

The MMS requires daily participant-reported RB and SF scores; therefore, the importance of daily recording of RB and SF by participants in their daily eDiary should be stressed by the Investigators.

Endoscopy will be used to visualize the mucosa to enable calculation of the ES.

Endoscopic score (ES): The ES reports the worst appearance of the mucosa on flexible sigmoidoscopy or colonoscopy, on a 4-point scale (Appendix 3). Consistent with regulatory advice, this study excludes friability from the definition of an ES of 1. The ES will be determined by a blinded central reader.

Rectal bleeding (RB): The RB subscore is a participant-reported measure. This item reports the most severe amount of blood passed per rectum in a 24-hour period, on a 4-point scale (Appendix 3). The participant will record this in their daily eDiary. The method for calculating the RB subscore is described in Section 9.4.2.

Stool frequency (SF): The SF subscore is a participant-reported measure. This item reports the number of stools in a 24-hour period, relative to the normal number of stools for that participant in the same period, on a 4-point scale (Appendix 3). A stool is defined as a trip to the toilet when the participant has either a bowel movement, passage of blood alone, passage of blood and mucus, or passage of mucus only. The total number of stools passed in a 24-hour period will be recorded by the participant in their daily eDiary. The reference "normal" SF for that participant will be recorded electronically at the Screening Visit and is the number of stools in a 24-hour period when the participant is in remission. If the participant has never achieved remission, the reported SF before initial onset of signs and symptoms of UC will be used as the reference SF. The method for calculating the SF subscore is described in Section 9.4.2.

Physician's Global Assessment (PGA): The PGA is a physician-reported measure that is a component of the MCS and is used in the calculation of the TMS. The PGA summarizes the Investigator's assessment of the participant's UC disease activity on a 4-point scale (Appendix 3). The Investigator will record the PGA in the site tablet at the specified study visits (Table 6). Consistent with regulatory guidance, the PGA will not be used for primary or secondary efficacy assessment in this study.

9.8.1.1. Endoscopy

A flexible proctosigmoidoscopy, performed with a video endoscope following cleansing preparation (oral or rectal cathartic), will be performed during screening (prior to Day 1/randomization) and at Week 12/ET visit.

To ensure quality data and standardization, the same endoscopist should be used throughout the study wherever possible. Endoscopy images will be obtained during each endoscopy and will be sent for central reading and determination of the Mayo ES. A detailed image review charter from the central reading laboratory will outline the endoscopic procedures, video recordings, and equipment. For each participant, a video recording of the entire endoscopic procedure will be performed using an acceptable storage medium. The endoscopic recordings will be read centrally in a blinded manner for mucosal lesions and endoscopic severity by a qualified gastroenterologist according to the image review charter. The ES will be evaluated by the Investigator and the central reader. The central read

will be used for determination of efficacy endpoints; however, treatment decisions will be made by the treating Investigator.

Repeated flexible proctosigmoidoscopy may be permitted by the Sponsor when the central reader indicates that the video endoscope data were acquired incorrectly or did not meet the minimal required quality standards.

Note: For participants with pancolitis > 8 years duration or participants with left-sided colitis > 12 years without a surveillance colonoscopy within 12 months prior to baseline (refer to Section 4.1, Inclusion Criterion 7), a colonoscopy and biopsies taken in accordance with local standard of care at screening to rule out dysplasia (ie, in place of screening proctosigmoidoscopy) is required. Any adenomatous polyps must be removed prior to their first administration of study treatment.

9.8.1.2. Endoscopic Biopsies

Per inclusion criteria (Section 4.1), a histopathology report supporting the diagnosis of UC must be available in the source documents prior to randomization. Post-randomization detected polyps or suspicious findings during endoscopy will be managed as per local standard of care. If a histopathology report is not available, the screening endoscopy may serve as such with histology evaluated at the local histology laboratory.

Biopsies will be obtained at each endoscopy to support assessment of the histopathology endpoints and, where permitted, for the assessment of exploratory biomarkers. Up to 2 biopsy pairs (ie, total 4) will be collected from the most affected area 10 to 25 cm from the anal verge. Samples should be collected, stored, and shipped as described in the laboratory manual.

The original location (colonic segment) of biopsy specimens acquired at screening must be clearly indicated. Detailed instructions for endoscopic biopsies (eg, number of biopsies, anatomic site, normal or inflamed mucosa) will be provided.

Biopsy samples will be processed by a central laboratory and histopathologic scoring using the Geboes, Robarts, and Nancy histopathology indices (Appendix 4) will be performed by a blinded central histopathology reader (Geboes 2000, Marchal-Bressenot 2017, Mosli 2017).

Biopsy specimen transfer, processing, slide preparation and digitization of slides for histopathologic scoring procedures will be detailed in a histopathology manual. Histopathology results will not be made available to study sites.

9.8.2. Extraintestinal Manifestations

During the specified full physical examinations (Table 6), specific systems (such as eyes, liver, skin, and joints) will be examined for EIMs for UC.

9.8.3. Additional Health-Related Patient-Reported Outcomes

Participant-reported quality of life instruments will be completed electronically and checked for completeness at the study site as indicated in the Schedule of Assessments (Table 6) and will be used in support of the efficacy outcomes.

Ulcerative Colitis Patient-Reported Outcomes Signs and Symptoms (UC-PRO/SS): The UC-PRO/SS is used to gather data on the gastrointestinal signs and symptoms of UC directly from the participant. The UC-PRO/SS is a 9-item questionnaire containing 2 domains: Bowel movement signs

and symptoms (6 items) and abdominal symptoms (3 items). An average score is calculated for each domain; a higher score indicates worse symptoms. The UC-PRO/SS will be administered (Table 6) if and when available.

Medical Outcomes Study 36-Item Short Form Health Survey, Version 2 Physical and Mental Component and Domain Scores (SF-36): The SF-36 is a 36-item, participant-reported survey of participant 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 participant'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.

9.8.4. Efficacy-Related Biomarkers

Samples for biomarker assessments will be collected according to the Schedule of Assessments (Table 6). Blood, tissue, and stool samples will be analyzed by the central or specialty laboratory. Details for collection, processing, and storage will be provided in the Laboratory Manual. Residual samples will be stored and may be used for additional analyses if the participant has granted consent where allowed by the regulatory authorities and local ethics committees.

C-reactive protein (CRP): CRP is an acute phase protein expressed by hepatocytes in response to inflammatory cytokines and will be assessed using a hs-CRP assay. Investigators will be blinded to the hs-CRP results during the treatment and follow-up periods.

Fecal calprotectin: Fecal calprotectin is a complex consisting of calcium-binding proteins. It is expressed by activated neutrophils (and to a lesser extent by macrophages and monocytes) and fecal levels correlate with the number of neutrophils in the gut. It is used as a biomarker of intestinal inflammation. Investigators will be blinded to the fecal calprotectin results during the treatment and follow-up periods.

Lymphocyte counts: Etrasimod is believed to modulate lymphocyte trafficking resulting in a reduction in peripheral lymphocyte count and lymphocyte availability for recruitment to sites of inflammation. During the treatment period, the Investigator will be blinded to the white blood cell (WBC) and differential counts. During the treatment period, WBC differential results will be assessed by an unblinded Medical Monitor (not providing direct medical oversight of study conduct). If either of the following occur, the unblinded Medical Monitor will notify the Investigator with additional instructions.

- ANC < 1000 cells/µL
- ALC < 200 cells/µL

If the ANC is confirmed below the 1000 cells/µL limit, the Investigator will be requested to closely monitor for serious infection and institute appropriate follow-up at his or her discretion.

If the ALC is confirmed below the 200 cells/µL limit, study treatment should be interrupted and should not be reinitiated if the ALC remains below this threshold. In this situation, the unblinded Medical Monitor will notify the Investigator and provide instructions on additional actions that the Investigator may need to take. When there is at least one measurement of ALC < 200 cells/µL, blinded values may be released to treating physicians and Investigators as deemed medically

necessary to monitor infection and/or aid in diagnostic work-up as clinically indicated, and/or as a tool to assess the effectiveness of therapeutic interventions for an infection. Investigators will repeat CBC with differentials weekly until ALC > 500 cells/µL.

Re-initiation of the study treatment can only be considered when ALC > 500 cells/µL.

9.8.4.1. Exploratory Efficacy-Related Biomarkers

Samples for exploratory biomarker assessments will be collected according to the Schedule of Assessments (Table 6). Blood and biopsy samples will be analyzed by a specialty laboratory following completion of the study. Details for collection, processing, and storage will be provided in the Laboratory Manual. Residual samples will be stored and may be used for additional analyses to further understand response to treatment and mechanism of action of etrasimod if the participant has granted consent. These additional analyses (as appropriate) will only be conducted where allowed by the regulatory authorities and local ethics committees.

Immunophenotyping: Intestinal biopsies will be collected during endoscopy for immunophenotyping (eg, T cell subsets, B cells, dendritic cell subsets, natural killer cells) and molecular markers of mucosal healing (eg, junctional proteins such as ZO-1, occludin, claudins) to further assess efficacy and the mechanism of action of etrasimod. Assessments will be made using protein-based methods such as immunofluorescence microscopy or comparable methodology.

Proteomics: Blood will be collected for exploratory proteomic analysis to assess the efficacy and mechanism of action of etrasimod. Proteins will be measured by enzyme-linked immunosorbent assay, proximity-extension assay, or comparable technology.

9.9. Safety

The Investigator or site staff will be responsible for detecting, documenting, and reporting events that meet the definition of an adverse event or SAE (Section 9.9.8.1). Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

9.9.1. Physical Examination

Full and symptom-directed physical examinations will be performed according to the Schedule of Assessments (Table 6).

Full physical examination includes the following assessments:

- General inspection
- Weight/height (height at screening only)
- Skin
- Head/ears/eyes/nose/throat examination
- Neck
- Cardiac examination
- Auscultation of lungs
- Abdominal examination (liver, spleen, and lower abdomen)
- Neurological assessment

- Musculoskeletal assessment to include lower extremity edema evaluation

Symptom-directed (focused) physical examinations should assess clinically significant changes from full physical examinations or any new signs or symptoms.

9.9.2. Vital Signs

Resting vital signs measurements will be performed according to the Schedule of Assessments (Table 6) with the participant in the sitting position. Vital signs will be measured prior to any blood draws that occur at the same study visit.

Blood pressure may be measured manually or by automated device. Proper technique should be utilized during the measurement of BP to include the following:

- The participant's arm should be bare and supported at heart level.
- An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be utilized. Participant's legs should not be crossed during the evaluation.

9.9.3. 12-Lead Electrocardiogram

All 12-lead ECGs will be performed according to Section 9.4.2.1 and the Schedule of Assessments (Table 6), and if clinically indicated at any time during the treatment period per Investigator discretion. All ECGs will be recorded from a 12-lead ECG machine with the participant in the supine position. Every attempt should be made to ensure the participant 12-lead ECG readings are obtained using the same machine throughout the study.

Intervals to be provided on the confirmed read for each safety 12-lead ECG are: RR, PR, QRS, QT, and QTcF. If an ECG shows a new onset QTc interval > 500 ms during the treatment period, a repeated ECG is warranted. If this abnormal finding is confirmed, study treatment must be interrupted. Effective diagnostic and therapeutic strategies should be employed.

Reversible causes of prolonged QTc interval (eg, electrolyte abnormalities or hypomagnesemia), should be corrected as clinically indicated. When evaluating a participant with new onset QTc interval above 500 ms, referral to a cardiologist experienced in treating cardiac conduction disorders should be considered. Re-initiation of study treatment (refer to Section 9.4.2.1) can only be considered after all of the following have occurred:

- The QTcF interval is < 450 ms (men) or < 470 ms (women)
- The QTc prolongation is considered by the Investigator and confirmed by the cardiologist as not related to study treatment and likely caused by other factors
- Individual risk-benefit is favorable (as determined by the Investigator, in agreement with the cardiologist), **AND**
- After discussion with the Medical Monitor.

The Investigator will be responsible for review and interpretation of 12-lead ECGs on site and determining if the 12-lead ECG is normal, abnormal clinically insignificant, or abnormal clinically significant. Findings will be documented in the eCRF.

All 12-lead ECGs performed should be available for collection upon request.

9.9.4. Pulmonary Function Test

Pulmonary function tests will be performed according to the Schedule of Assessments (Table 6) and includes FEV_1 and FVC measurements. All participants will have PFTs performed at Screening, and Week 12, or at the ET visit. PFTs occurring at the ET visit that are within 4 weeks of the last assessment (eg, Week 12) will only be required if clinically indicated. The 2-Week Follow-Up visit PFT assessment is only required if clinically indicated.

Participants reporting respiratory adverse events such as dyspnea during the treatment period may return at an unscheduled visit for assessment per Investigator discretion; additional PFTs may be performed as clinically indicated.

Participants experiencing a decline in PFT values (FEV_1 and/or FVC) below 50% of the predicted values must be discontinued from study treatment and scheduled for a follow-up visit.

When available, DLCO measurements will also be performed. When DLCO is not available, sites should consult the Sponsor or Sponsor's delegate. These tests will be performed at a qualified pulmonary function laboratory or respiratory department. Please refer to the American Thoracic Society/European Respiratory Society guidelines for standardization of spirometry and single breath determination of carbon monoxide uptake in the lung (MacIntyre 2005, Miller 2005a, Miller 2005b).

The safety of trial participants and site staff is paramount, so it is at the Investigator's discretion whether PFT can be safely administered to trial participants during the treatment period. The Investigator should evaluate on a case-by-case basis how best to proceed based on the participant's medical history, the Investigator's clinical judgment, and in consultation with the Medical Monitor. All reasonable efforts should be made to ensure safety and adherence to the protocol. When available, spirometry may be conducted at the clinical site instead of at the pulmonary laboratory. If the decision is made that it is not appropriate to conduct PFTs due to the safety concerns (eg, coronavirus disease 2019 [COVID-19] transmission), then this decision and rationale should be appropriately captured in the participant's source documentation. When available and safe (due to lifting of local restrictions, re-opening of local PFT labs, or improved safety conditions) the tests should be conducted as soon as possible and as close to the timepoints as outlined in the protocol.

9.9.5. Ophthalmoscopy and Optical Coherence Tomography

A complete ophthalmoscopy and OCT will be performed according to the Schedule of Assessments (Table 6). OCTs occurring at the ET visit that are within 4 weeks of the last assessment (eg, Week 12) will only be required if clinically indicated. The 2-Week Follow-Up visit OCT assessment is only required if clinically indicated. A standard visual acuity chart should be used for the visual acuity assessment. The OCT machine used should preferably not be changed during the study to allow for comparison of central foveal thickness measurements within each participant across timepoints.

Screening visit:

At the screening ophthalmology visit, the eye examination will include:

- Ophthalmologic history
- Best corrected visual acuity measurement (using Landolt C chart)
- Ophthalmoscopy (may include contact lens biomicroscopy to examine the macula and optic disc). A dilated fundus exam should be performed in all participants at the

screening visit and as needed at subsequent visits in participants with significant abnormalities identified on the screening exam.

- Measurement of central foveal thickness by OCT (recorded in micrometers; required for all participants regardless of the results of visual acuity or ophthalmoscopy)
- Slit lamp examination should be performed to establish uveitis disease status (yes/no). Uveitis should be characterized and graded using the Standardization of Uveitis Nomenclature criteria. Participants with active uveitis without macular edema at Screening are eligible to enroll in the study
- If there is a suspicion of macular edema by ophthalmoscopy and increased central foveal thickness by OCT, then additional testing should be considered at the discretion of the ophthalmologist (for example, fluorescein angiogram may be performed). Participants with diagnosed macular edema at Screening should be deemed a screening failure and should not be randomized.
- Optional procedures in case of clinically significant abnormalities on ophthalmic exam may include but are not limited to:
  - Retinal photographs
  - Intraocular pressure

Scheduled post-screening visits:

At the scheduled ophthalmology visit, the eye examination will include

- Best corrected visual acuity measurement
- Ophthalmoscopy (may include contact lens biomicroscopy to examine the macula and optic disc)
- Measurement of central foveal thickness by OCT
- For participants with uveitis findings on ophthalmic exam, additional testing should be considered (for example, fluorescein angiogram)

Participants experiencing unexpected ophthalmic symptoms without a known suspected etiology or experiencing a relevant ophthalmic adverse event may need to have repeated ophthalmoscopy and OCT testing performed.

9.9.6. Tuberculosis Screening and Chest X-Ray

All participants will complete TB screening to determine eligibility. A TB screening questionnaire will be completed during the Screening Period by the Investigator or delegated site staff for each participant and applicable information will be entered into the eCRF. For participants who are receiving TB prophylaxis treatment, the TB questionnaire will be completed at every study visit (until TB prophylaxis treatment course is completed).

9.9.7. Clinical Laboratory Tests

Refer to Table 5 for the list of clinical laboratory tests to be performed and the Schedule of Assessments (Table 6) for timing and frequency for each test. All scheduled clinical laboratory tests will be completed by a central lab or a sponsor approved regional lab for analysis unless extenuating

circumstances prevent shipments to a central lab (eg, natural disasters, war, etc.) in which case a qualified local laboratory can perform tests only once permission is granted by the Sponsor (or delegate). If a local laboratory is used for protocol-specified tests (even in parallel), this will be captured as a PD. Laboratory tests for a documented new or ongoing AE are not a PD. Details regarding clinical laboratory sample collection, preparation, and shipment are provided in the Laboratory Manual by the central laboratory.

Clinical safety laboratory tests should be completed predose. The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF (results of the total WBC and ALC will be reviewed and monitored as described in Section 9.8.4). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor should be notified.
- All protocol-required laboratory assessments, as defined in the Schedules of Assessments (Table 6), must be conducted in accordance with the Laboratory Manual.
- If laboratory values from non-protocol -specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, adverse event, SAE, or dose modification), then the results must be recorded in the eCRF.

For guidance on monitoring participants with notable lymphopenia, please refer to Section 9.8.4.

See Section 16.6 for suggested actions and Follow-up assessments in the event of potential DILI.

Table 5: Clinical Laboratory Tests

SCREENING Only **Virology** HIV, HBsAg, HBcAb, HBsAb, HBV DNA, HCV (RIBA) **Stool Sample** Bacterial culture, ova and parasites, *C. difficile* **Drugs of Abuse** Amphetamine, barbiturates, benzodiazepines, cocaine, methadone, methamphetamine, methylenedioxymethamphetamine, opiate, oxycodone, phencyclidine **Others** Hemoglobin A1c, Interferon gamma releasing assay (IGRA) (eg, QuantiFERON or T-SPOT-TB)
PREGNANCY TESTING Serum pregnancy test beta-human chorionic gonadotropin (β-hCG) - Screening Urine β-hCG (only for women of childbearing potential)

Table 5: Clinical Laboratory Tests (Continued)

CLINICAL CHEMISTRY, HEMATOLOGY, AND COAGULATION		
Hematology	**Serum Chemistry**	
Hematocrit	Albumin	Potassium
Hemoglobin	Alkaline phosphatase	Sodium
Mean corpuscular hemoglobin	Alanine aminotransferase	Thyroid-stimulating hormone
Mean corpuscular hemoglobin concentration	Aspartate aminotransferase	Thyroxine free
Mean corpuscular volume	Bicarbonate	Total bilirubin
Platelet count	Blood urea nitrogen	Triiodothyronine free
Red blood cell count	C-reactive protein	Total cholesterol
White blood cell count with differential[a]	Calcium	Total protein
TBNK[a]	Chloride	Triglycerides
Coagulation	Creatinine	Uric acid
Prothrombin time	Creatine kinase	
Activated partial thromboplastin time	Direct bilirubin	
International normalized ratio	Glucose	
	Gamma-glutamyl transferase	
	Lactate dehydrogenase	
	Phosphorus	
URINALYSIS		
Appearance	Nitrite	
Bilirubin	Occult blood	
Color	pH	
Glucose	Protein	
Ketones	Specific gravity	
Microscopic examination of sediment	Urobilinogen	
BIOMARKERS		
Lymphocytes[a,b]		
hs-CRP[b]		
Fecal calprotectin[b]		
Immunophenotyping		
Proteomics		
STOOL SAMPLE[c]		
Ova and parasites, *C. difficile*		

[a] Total WBC, neutrophil, lymphocyte, and TBNK will be available for review prior to randomization. After randomization, the total WBC, neutrophil, lymphocyte, and CD4 T cell counts will be reviewed by an unblinded Medical Monitor who will provide instructions to the site Investigator in the event of significant lymphopenia. Investigators will remain blinded to the results after randomization. Refer to Section 9.8.4 for additional details.

[b] Investigators will remain blinded to the results after randomization.

[c] Stool sample for bacterial culture, ova, and parasite evaluation, and *C. difficile* assay at any point in the study when a participant becomes symptomatic, including worsening or return of disease activity.

β-hCG, beta-human chorionic gonadotropin; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; hs-CRP, high-sensitivity C-reactive protein; IgG, immunoglobulin G; RIBA, recombinant immunoblot assay; TBNK; T lymphocytes, B lymphocytes, natural killer lymphocytes; WBC, white blood cell

9.9.7.1. Screening

9.9.7.1.1. Drugs of Abuse

A standard urine drug screen will be performed (Table 5). Participants who test positive will be assessed for eligibility for study participation by the Investigator.

9.9.7.1.2. Pregnancy Testing

A serum pregnancy test for β-hCG will be performed on women of childbearing potential to determine eligibility. Post-screening urine pregnancy tests (β-hCG) should be performed as indicated in the Schedule of Assessments (Table 6). If at any point there is a case of a positive urine β-hCG test, the participant will have study treatment interrupted and a serum sample submitted to the central laboratory for β-hCG testing. If the serum test confirms positive, the participant will be withdrawn from the study treatment and all the necessary follow-up assessments will be conducted as per Section 9.9.9. If the serum test is negative, the participant may resume study treatment.

Negative pregnancy test results must be documented for all women of childbearing potential prior to dosing at applicable study visits. Women who are surgically sterile or who are postmenopausal are not considered to be of childbearing potential. Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause.

9.9.7.1.3. Virology

Screening HIV antibody, hepatitis B (ie, HBsAg, HBcAb, HBsAb, and HBV DNA), and HCV (recombinant immunoblot assay, if positive HCV RNA should be used to confirm infection).

9.9.7.1.4. Clinical Chemistry, Hematology, Coagulation, and Urinalysis

Clinical chemistry, hematology, coagulation, and urinalysis parameters that will be assessed during the study are identified in Table 5.

Participants will be in a seated or supine position during blood collection. All laboratory samples should be collected prior to the administration of study treatment at applicable visits (refer to Section 9.7 for timing of blood draws for PK).

9.9.8. Adverse Events

9.9.8.1. Definitions

9.9.8.1.1. Adverse Event

An adverse event is any untoward medical occurrence in a participant or clinical investigational participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse events can be any of the following:

- Unfavorable changes in general condition
- Subjective or objective signs/symptoms
- Concomitant disease or accidents
- Clinically relevant adverse changes in laboratory parameters over the course of the study

- Preexisting conditions that worsen in severity, increase in frequency, or have new signs/symptoms

9.9.8.1.2. Serious Adverse Event

An adverse event should be classified as an SAE if it meets one of the following criteria:

Fatal:	Adverse event resulted in death.
Life-threatening:	The adverse event placed the participant at immediate risk of death. This classification does not apply to an adverse event that hypothetically might cause death if it were more severe.
Hospitalization:	The adverse event required or prolonged an existing inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this definition.
Disabling/ incapacitating:	The adverse event resulted in a persistent or significant incapacity or substantial disruption of the participant's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a participant exposed to the molecule or study treatment regimen before conception or during pregnancy.
Medically significant:	The adverse event did not meet any of the above criteria but could have jeopardized the participant and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent.

9.9.8.1.3. Adverse Drug Reaction

An adverse drug reaction (ADR) in the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, is any noxious and unintended response to a medicinal product related to any dose. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (ie, the relationship cannot be ruled out).

9.9.8.1.4. Adverse Events of Special Interest

Based on the mechanism of action of etrasimod and prior experience with other agents acting via a similar mechanism, potential adverse events of special interest may be identified. In addition to appropriate reporting of these events as an adverse event or SAE, supplementary detailed information may be collected.

If there are any signs of PML-related symptoms, the Investigator should withhold study treatment and perform appropriate diagnostic evaluation per local standard of care at the first signs suggestive of PML. Typical symptoms associated with PML are diverse, progress over days to weeks, and may include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. The Investigator must notify the Medical Monitor of such an event.

Guidance for the Assessment of Potential Progressive Multifocal Leukoencephalopathy is provided in Appendix 5.

9.9.8.1.5. Severity

The severity of each adverse event will be assessed at the onset by a nurse/or physician. When recording the outcome of the adverse event the maximum severity of the adverse event experienced will also be recorded. The severity of each adverse event will be graded according to the Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE v5.0):

Grade 1:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2:	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money)
Grade 4:	Life-threatening consequences, urgent intervention indicated.
Grade 5:	Death related to adverse event

9.9.8.1.6. Relationship

The Investigator (or designee) will make a determination of the causal relationship of the adverse event to the study drug using a 4-category system according to the following guidelines:

Not Related: (Unrelated = flag no on the AEM Report form)	The adverse event is definitely caused by the participant's clinical state or the study procedure/conditions.
Unlikely Related: (Unrelated = flag no on the AEM Report form)	The temporal association between the adverse event and the drug is such that the drug is not likely to have any reasonable association with the adverse event.
Probably Related: (Related = flag yes on the AEM Report form)	The adverse event follows a reasonable temporal sequence from administration of the drug and cannot be reasonably explained by the known characteristics of the participant's clinical state, environmental, or toxic factors, or other modes of therapy administered to the participant.
Related: (Related = flag yes on the AEM Report form)	The adverse event follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to the study treatment administration should be considered and investigated. The Investigator should consult the IB and the Product Information of marketed products within the drug class, when applicable. For each adverse event/SAE, the Investigator must document in the medical

notes that he/she has reviewed the adverse event/SAE and has provided an assessment of causality. There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor; however, it is very important that the Investigator always make an initial assessment of causality for every event before the initial transmission of the SAE to the Sponsor. The Investigator may change his/her opinion of causality based on subsequent receipt of information and send an SAE follow-up report with the updated causality assessment. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

9.9.8.2. Eliciting and Recording Adverse Events

9.9.8.2.1. Eliciting Adverse Events

Participants will be instructed that they may report adverse events at any time. An open-ended or nondirected method of questioning should be used at each study visit to elicit the reporting of adverse events.

9.9.8.2.2. Recording Adverse Events

The adverse event reporting period for safety surveillance begins when the participant is initially included in the study (date of first signature of informed consent) and continues up to 30 days after the last administration of study treatment. If an adverse event is not resolved or stabilized by this time, the Sponsor in consultation with the Investigator will decide whether to continue to monitor the adverse event or closeout the event in the database if no further follow-up is necessary.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. Any SAE suspected to be related to the study treatment must be reported whenever it occurs, irrespective of the time elapsed since the last administration of study treatment.

Investigators and study personnel will record all adverse events and SAEs whether received through an unsolicited report by a participant, elicited during participant questioning, discovered during physical examination, laboratory testing, and/or other means by recording them on the eCRF and/or SAE Form, as appropriate. The following information should be recorded on the adverse event eCRF:

- Description including onset and resolution dates
- Whether it met SAE criteria
- Severity
- Relationship to study treatment or other causality
- Outcome

For SAEs, events occurring secondary to the primary event should captured and reported via the established safety reporting mechanism. .

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on the eCRF.
- For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The

procedure should be captured in the narrative as part of the action taken in response to the illness.

9.9.8.2.3. Diagnosis Versus Signs or Symptoms

In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate adverse event.

9.9.8.3. Reporting Adverse Events

All SAEs are subject to reporting requirements.

9.9.8.3.1. Serious Adverse Events

Any adverse event considered serious by the Investigator or that meets serious criteria must be reported to Pfizer Safety on the CT SAE Report Form upon awareness **and under no circumstances should the time to report exceed 24 hours of becoming aware of the event.**

If additional information is required or becomes available for a previously reported SAE, entry into CRF of the new or updated information should be completed and reported to Pfizer Safety on a new CT SAE Report Form **within 24 hours of awareness**.

Elective hospitalization and/or surgery for clearly preexisting conditions (eg, a surgery that has been scheduled prior to the participant's entry into the study) will not be reported as an SAE.

Any SAE that is ongoing when the participant completes the study or discontinues the study will be followed by the Investigator until the event resolved, stabilized, or returned to baseline status.

The Sponsor (via the In-Country Caretaker for Clinical Trial [ICCC]) is responsible for notifying the relevant regulatory authorities of any adverse event assessed by the Reporter (Investigator) or the Sponsor as:

a) Serious, unexpected, and related, or

b) Serious, expected, related and life-threatening or fatal

In addition, the ICCC is responsible for notifying the Investigator(s) of active sites, the head(s) of the active study sites, and, if applicable, the IRBs of all SAEs occurring during the study that are assessed by the Reporter (Investigator) or the Sponsor as related and unexpected.

The Investigator is responsible for notifying the head of the study site of SAEs and significant safety findings that occur at his or her site. The Investigator is also responsible for responding to requests for additional information made by the Sponsor, the head of the study site, or the IRB.

9.9.8.3.2. Serious, Unexpected Adverse Drug Reactions

All ADRs that are both serious and unexpected are subject to expedited reporting to regulatory agencies in accordance with regional or national regulatory requirements. An unexpected ADR is one for which the nature or severity is not consistent with information in the relevant source documents.

Since etrasimod is an investigational medicinal product that has not yet been approved for marketing in any country, the IB in effect during the study will serve as the Reference Safety Information for determining whether an adverse event is expected or unexpected.

9.9.9. Exposure During Pregnancy and Breast Feeding

9.9.10. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study treatment. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure. Examples of environmental exposure may include oral ingestion of, inhalation of, or skin contact with a tablet that is broken/crushed.

Any such exposures to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness irrespective of whether an AE has occurred.

9.9.10.1. Exposure During Pregnancy

If at any point a serum β-hCG pregnancy test is positive, the participant will be withdrawn from the study treatment.

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study treatment and until 30 days after the last dose.

Pregnancy (during maternal or paternal exposure to study treatment) does not meet the definition of an adverse event; however, to fulfill regulatory requirements, any pregnancy and/or pregnancy outcome should be reported to Pfizer Safety via the CT SAE Report Form and the EDP Supplemental Form **within 24 hours of awareness** to collect data on the pregnancy and on the outcome for both the mother and the fetus.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and should be reported as such (following the SAE reporting process) even if outside the SAE reporting period.

An environmental exposure during pregnancy (EDP) occurs if:

- A female non-participant is found to be pregnant while being exposed or having been exposed to study treatment because of environmental exposure.
- A male non-participant who has been exposed to the study intervention then inseminates his female partner prior to or around the time of exposure.

When EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and the EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form are maintained in the investigator site file.

9.9.10.2. Exposure During Breastfeeding

An exposure during breastfeeding (EDB) occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

9.9.10.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form must be maintained in the investigator site file.

9.9.11. Lack of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE**.

9.9.12. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Medication errors not associated with an AE/SAE should be recorded as a protocol deviation.

A medication error with a potentially associated AE/SAE are recorded in the CRF. Medication errors associated with an SAE (per the Investigator's assessment) should be reported to Pfizer Safety within 24 hours on the CT SAE Report Form.

9.10. Procedures for Overdose

The current edition of the IB should be referenced for overdose procedures.

There is no established overdose threshold for this clinical study, nor is there any recommended specific treatment for an overdose but to provide supportive care if clinically indicated. Overdose has the potential to induce further dose-dependent reduction in peripheral lymphocyte count which may increase the risk of infections. Providers should employ effective diagnostic and therapeutic strategies in patients with symptoms of infection.

In the event of a suspected overdose, the Investigator and/or treating physician should:

a. Closely monitor the participant for any adverse event/SAE and laboratory abnormalities and follow the AE reporting process, including contacting the Medical Monitor.

b. Obtain a plasma sample for PK analysis within 7 days from the date of the last dose of study treatment, if possible, and if requested by the Medical Monitor.

c. Document the total quantity of the excess dose, taking into consideration the duration of the overdose in the eCRF and the time frame.

Participants who overdose will be counseled on correct dosing and administration of study treatment. Decisions regarding study discontinuation, dose interruptions, or dose modifications will be made by

the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

10. PLANNED STATISTICAL METHODS

10.1. General Considerations

All individual participant data for all randomized participants will be presented in data listings. All efficacy and safety endpoints will be summarized by treatment group. Full details of statistical considerations and the planned analyses will be described in the study Statistical Analysis Plan (SAP).

10.2. 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.

10.3. Analysis Sets

All analysis sets will be defined in the SAP prior to database lock. The following analysis sets may be used in the statistical analysis:

Full Analysis Set (FAS): The FAS will consist of all randomized participants, who receive at least 1 dose of study treatment. Under this approach, participants will be counted in the treatment group to which they were randomized, regardless of the treatment received during the study.

Per Protocol Set: The Per Protocol Set will consist of all participants in the FAS who adhere to the protocol. This set will be used in sensitivity analyses of the primary and key secondary endpoints to evaluate the influence of major protocol violators and protocol deviators on the primary results. Participants may be excluded from this set if they violate the eligibility criteria or significantly deviate from the study plan. Specific reasons for warranting exclusion from this set will be documented prior to database lock and may include, but are not limited to, study treatment noncompliance, receiving incorrect study treatment, and missing a defined number of visits while still on study. The SAP, which will be finalized prior to database lock, will be the final documentation for the Per Protocol definition.

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. Under this approach, participants will be counted in the treatment group to which they were randomized, regardless of the treatment received during the study. 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.

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

10.4. Missing Data

Participants with a lack of efficacy adverse event related will be considered as having a treatment nonresponse outcome in the analysis of all endpoints, including the primary endpoint. In addition,

participants who initiate an agent not allowed in combination with the study treatment that can affect the efficacy of the study treatment, such as an immunosuppressant or corticosteroid, or who have an increase in dose over baseline levels for treatment of worsening disease symptoms will be considered nonresponders for binary responder-type endpoints thereafter or be handled by per protocol analysis.

Participants discussed above will be considered as having a known outcome at the analysis timepoint (ie, a treatment failure outcome) and not as having missing data. Participants who discontinue the double-blind study for reasons other than a lack of efficacy adverse event related to UC will be considered as having missing data and will be handled in the primary and sensitivity analyses as follows.

A full description of the handling of missing data will be provided in the SAP.

Primary method of handling missing data

In the primary analysis of the primary endpoint and main analyses of all binary responder-type endpoints, missing data, eg, component scores of MMS at the planned assessment timepoint, will be imputed using multiple imputation methodology (Rubin 1987) under the missing at random (MAR) assumption. Binary responder-type endpoints will subsequently be computed from observed and imputed data and analyzed using methods as outlined in Section 10.12.1.

In the main analysis of continuous or score endpoints, such as changes from baseline in MMS subscores, biomarker measures, urgency numeric rating scale (NRS), abdominal pain NRS, and health-related quality of life measures, missing data will be handled using the same multiple imputation methodology above and analyzed by either analysis of covariance or a mixed-effect model with repeated measures. Detailed methods will be provided in the SAP.

Sensitivity analyses for missing data

Sensitivity analyses will be performed as follows.

- All participants with missing data, regardless of reason for missingness, will be considered as nonresponders for binary responder-type endpoints.
- A tipping point analysis will be performed for the primary and key secondary endpoints by considering all possible combinations of the number of responders and non-responders among participants with missing data in each treatment group. The results of analysis for all possible combinations will be summarized graphically, depicting a boundary between combinations that result in a statistically significant treatment effect versus not statistically significant. Clinical plausibility of the combinations on the boundary will be discussed in the clinical study report to evaluate robustness of study conclusions to missing data.
- A mechanism of missingness not at random will be investigated for participants with missing data. These participants, regardless of the randomized treatment group, will be assumed to have a similar distribution of outcomes after discontinuation as participants with available data in the placebo group. This is akin to modeling the missing outcomes as if the participants continued on their background therapy only and accounting for the study effect observed in participants on placebo. This will be implemented using a multiple imputation approach of Copy Reference to impute missing values, eg, component scores of MMS at the planned assessment timepoints.

Complete descriptions of the sensitivity analyses and detailed multiple imputation method and procedures will be provided in the SAP prior to database lock.

10.5. Efficacy Endpoint Definitions

The following definitions will be used to assess efficacy outcomes. Summary scores calculated from the components of the MMS and its component subscores will be used to assess efficacy.:

- 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 ≥ 1point 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: Geboes Index score < 3.1
- Histologic remission: Geboes Index score < 2.0

10.5.1. Calculation of Modified Mayo Score Component Scores

In general, the MMS symptom scores will be computed from the eDiary data within 7 days prior to the target analysis timepoint (ie, Week 12). Complete details of the MMS symptom score computation method are provided in Section 9.3.11 and Section 9.4.2.

10.6. Primary Endpoint

The primary efficacy endpoints will evaluate etrasimod versus placebo in:

- The proportion of participants achieving clinical remission at Week 12

Clinical remission is based on the MMS as defined in Section 10.5.

10.7. Secondary Endpoints

Mucosal healing is based on the MMS and Geboes Index and all other endpoints are based on MMS as defined in Section 10.5.

The secondary efficacy endpoints are:

- The proportion of participants achieving endoscopic improvement at Week 12
- The proportion of participants achieving symptomatic remission at Week 12
- The proportion of participants with mucosal healing at Week 12
- The proportion of participants achieving clinical response at Week 12
- The proportion of participants achieving endoscopic normalization at Week 12

10.8. Exploratory Endpoints

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 EIMs at Week 12 in participants with EIMs at baseline

10.9. Pharmacokinetic Assessments

- Plasma concentrations of etrasimod will be assessed from samples collected prior to dosing and 4 hours (± 15 minutes) postdose (after 12lead ECG) on Week 0/Day 1
- Plasma concentrations of etrasimod will be assessed from samples collected prior to dosing (trough) at Weeks 2, 4, 8, 12, and the 2-Week and 4-Week Follow-Up visits

A descriptive summary of observed plasma concentration will be displayed by time and by treatment group. The Safety Set will be used to analyze plasma levels.

Full details of PK analysis will be provided in the SAP.

10.10. Other Assessments

10.10.1. Biomarker Endpoints

- Change from baseline in level of fecal calprotectin at Weeks 2, 4, 8, and 12
- Change from baseline in level of hs-CRP at Weeks 2, 4, 8, and 12
- Change and percentage change from baseline in lymphocyte counts at Weeks 2, 4, 8, and 12

10.10.2. Health-Related Patient-Reported Outcomes

- Scores and change from baseline to Week 12 in the following:
  - UC-PRO/SS
  - SF-36, version 2, physical and mental component and domain scores
- The proportion of participants with UC-related hospitalizations
- The proportion of participants requiring UC-related surgeries, including colectomy

10.10.3. Subgroup Analyses

The following major subgroup analyses for the primary and key secondary endpoints will be performed in order to explore whether the treatment effects are consistent across different subgroups. The SAP will provide a complete list and definition of the subgroups and analysis methods.

- Sex (male, female)
- Age: > or ≤ median age, ≥ or < 65 years
- Baseline oral corticosteroid usage (yes or no)
- Naïve to biologic or JAK inhibitor therapy at study entry (yes or no)
- Baseline disease activity (MMS: 4 to 6 or 7 to 9)
- Baseline fecal calprotectin > or ≤ median value
- Baseline CRP > or ≤ median value
- Baseline TMS ≤ 8 versus > 8

10.11. Safety Endpoints

- Incidence and severity of adverse events
- Incidence and severity of laboratory abnormalities, and change from baseline in laboratory values (to include hematology, serum chemistry, coagulation, and urinalysis)
- Incidence of clinically significant vital sign abnormalities and changes from baseline

10.12. Testing Strategy

10.12.1. Efficacy Analysis

The primary analysis of the proportion-based efficacy endpoints will be carried out using the Cochran-Mantel-Haenszel (CMH) method, stratified by (a) naïve to biologic or JAK inhibitor therapy at study entry (yes or no), (b) baseline corticosteroid use (yes or no), and (c) baseline

disease activity (MMS: 4 to 6 or 7 to 9). Results will be expressed as the number of participants in remission, remission percentages, difference in remission percentages, odds ratio, and associated 95% confidence intervals (CIs) and p-values. The stratified CMH analysis will be performed for each etrasimod dose (1 and 2 mg) versus placebo separately. The Cochran-Armitage trend test will also be carried out for all primary and secondary proportion-based efficacy endpoints.

There are multiple null hypotheses for the comparison of etrasimod and placebo in the primary and secondary endpoints. The family-wise Type I error rate will be controlled at a fixed α level at 0.05 (2-sided) using the following testing procedure.

A hierarchical testing procedure will be used to control family-wise Type I error rate at α level 0.05 (2-sided). The comparison of etrasimod 2 mg versus placebo for the primary endpoint (Family 1; F1) is the main gatekeeper. The study is considered positive if F1 is rejected at the α level. Only if this test is significant will etrasimod 2 mg be compared with placebo for all the secondary endpoints (Family 2; F2). The truncated Hochberg method (Dmitrienko 2011, FDA 2017) will be applied to F2 at α level.

If none of the null hypotheses in F2 is rejected, then testing will stop with all nominal p-values reported for subsequent comparisons of etrasimod 1 mg versus placebo. Otherwise, etrasimod 1 mg be compared with placebo for the primary endpoint (Family 3; F3) with the unused α from testing F2. Only if this test is significant will etrasimod 1 mg be compared with placebo for all the secondary endpoints (Family 4; F4). The conventional Hochberg method (FDA 2017) will be applied to F4 with the same unused α for F3. Full details of the efficacy analysis and the hierarchical testing procedure above will be documented prior to database lock in the SAP.

10.12.2. Safety Analysis

All safety data will be listed and summarized by treatment group. All TEAEs will be coded using the latest version of MedDRA and tabulated by System Organ Class and Preferred Term. Incidence of adverse events, SAEs, and adverse events leading to discontinuation will be summarized and presented in descending order of frequency. Associated laboratory parameters such as hepatic enzymes, renal function, and hematology values will be grouped and presented together. Individual participant values will be listed and values outside of the standard reference range will be flagged. Shift tables and analyses of changes from baseline will be produced. The change from baseline for each of the vital signs and 12-lead ECG parameters will be summarized. Incidence of abnormal vital signs parameters and outlier ECG results will be tabulated.

10.13. Interim Analysis

Not applicable

11. ETHICAL CONSIDERATIONS

11.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the investigator or designee, and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to implementation of changes made to the study design except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

11.2. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, the Sponsor should be informed immediately.

In addition, the investigator will inform the sponsor immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP guidelines that the investigator becomes aware of.

11.3. Informed Consent

The Investigator will fully inform the subject of all pertinent aspects of the study, including the approval of the study by the IRB/IEC. Before informed consent may be obtained, the Investigator should provide the participant ample time and opportunity to inquire about details of the study and to decide whether to participate.

Prior to a participant's participation in the study, the IRB/IEC-approved ICF must be signed and personally dated by the participant and by the person who conducted the informed consent discussion. If a participant is unable to read, an impartial witness will be present during the entire informed consent discussion.

The written ICF and any other written information to be provided to participants should be revised whenever important new information becomes available that may be relevant to the participant's consent. Any revised written ICF or study materials to be available and/or supplied to participants should receive the IRB/IEC's approval in advance of use. The participant will be informed in a timely

manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information should be documented.

During a participant's participation in the study, the participant will receive an updated version of the IRB/IEC-approved signed and dated consent document, as applicable, and any updates to the IRB/IEC-approved written information provided to participants.

11.4. Confidentiality

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is provided from the Sponsor.

Prior to study participation, the Investigator shall inform the participant that the monitor(s), auditor(s), IRB/IEC, and the regulatory authorities will be granted direct access to the participant's original medical records for verification of clinical study procedures and/or data, and that, by signing a written ICF, the participant is authorizing such access.

In addition, prior to study participation, the participant must be informed that the records identifying the participant will not be made publicly available; if the results of the study are published, the participant's identity will remain confidential.

11.5. Protocol Compliance

The Investigator/institution will conduct the study in compliance with the protocol agreed to by the Sponsor and regulatory authorities (if applicable) and that was approved by the IRB/IEC. The Investigator/institution and the Sponsor should sign the protocol, or if applicable an alternative contract, to confirm agreement.

The Investigator should not implement any deviation from, or changes to, the protocol without agreement by the Sponsor and prior review and documented approval from the IRB/IEC of an amendment, except where necessary to eliminate immediate hazard(s) to participants or when the change involves only logistical or administrative aspects of the study (eg, change in monitor, change of telephone number).

When an important deviation from the protocol is deemed necessary for an individual participant, the Investigator must contact the Medical Monitor for the study. Such contact must be made as soon as possible to permit a review by the Sponsor to determine the impact of the deviation on the participant's participation and/or the assessment of safety or efficacy in the study. Any significant protocol deviations affecting participant eligibility and/or safety must be reported by Investigator or site delegate to the IRB/IEC and regulatory authorities, as applicable, prior to implementation.

The Investigator should document and explain any deviation from the approved protocol.

12. QUALITY CONTROL AND QUALITY ASSURANCE

Quality assurance and quality control systems shall be implemented and maintained with written SOPs to ensure that the study is conducted, and data are generated, documented (recorded), and reported in compliance with the study protocol, GCP, and the applicable regulatory requirement(s). Quality control shall be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

An agreement must be secured from all involved parties to ensure direct access to all study-related sites, source documents, and reports for the purpose of monitoring and auditing by the Sponsor and/or designee and inspection by regulatory authorities.

12.1. Training of Study Site Personnel

Prior to study activities being initiated at the study site, the Sponsor or designee will train study site personnel on the protocol and applicable procedures. Training must be documented.

Note: If new study site personnel are assigned to the study after the initial training, study sites should contact the study monitor to coordinate training. Qualified study personnel may conduct training, as appropriate. Training of new study personnel must also be documented.

12.2. Monitoring

Study site monitoring is conducted to ensure the study is progressing as expected, the rights and well-being of human participants are protected, the reported study data are accurate, complete, and verifiable, and the conduct of the study is in compliance with the currently approved protocol, with GCP and with applicable regulatory requirements and local laws. Protocol deviations identified will be documented.

Details of study site monitoring are documented in the study Clinical Monitoring Plan (CMP) or similar document. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed (eg, targeted and/or risk based), and the distribution of monitoring reports. Monitoring may include a study site selection visit, which may be conducted in person or via communication media (eg, teleconference, online meeting) or may be waived in accordance with policy and procedures being followed for the study, if appropriate. Monitoring will include a study site initiation visit, interim monitoring visit(s), and a study site closeout visit. An interim monitoring visit may be combined with a closeout visit, if applicable.

12.3. Audit

An audit of one or more participating study sites may be performed independently of, and separately from, routine monitoring to evaluate clinical study conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

13. DATA HANDLING AND RECORD KEEPING

13.1. Data Management

13.1.1. Case Report Forms

An eCRF must be completed for each participant screened/enrolled in this study. These forms will be used to transmit information collected during the study to the Sponsor and regulatory authorities, as applicable.

The documentation related to the validation of the eCRFs will be maintained in the Trial Master File (TMF). The TMF will be maintained by the CRO and the Sponsor.

The Investigator will document participant data in his/her own participant files. These participant files will serve as source data for the study. All eCRF data required by this protocol will be recorded by study site personnel. All data entered into the eCRF will be supported by source documentation.

The Investigator or an authorized member of the Investigator's staff will make any necessary corrections to the eCRF. All changed information, including the date and person performing the corrections, will be available via the audit trail, which will be part of the electronic data capture system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness and acceptability by Sponsor personnel (or their representatives). The Sponsor (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The Investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to the eCRFs as evidence thereof.

13.1.2. Source Documents

Per regulatory requirements, the Investigator or designee will maintain accurate and up-to-date study documentation, including source documentation for each participant. Source documents are defined as original documents, data, and records. These may include, but are not limited to, hospital records, clinical and office charts, endoscopy reports, laboratory data/information, participants' eDiaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, ECGs, X-rays, ultrasounds, right heart catheterization reports, echocardiograms. Data collected during this study must be recorded on the appropriate source documents.

The Investigator(s)/institution(s) will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) and will provide direct access to the source data.

13.2. Study Documentation and Records Retention

The Investigator and study staff have the responsibility of maintaining a comprehensive and centralized filing system containing all study-related documentation. These files must be available for inspection by the Sponsor, representatives of the Sponsor, the IRB/IEC, and regulatory authorities (ie, FDA or international regulatory authorities) at any time, and should consist of the following elements:

- Participant files: Containing the completed eCRFs (if applicable), supporting source documentation including medical records, laboratory data, and signed ICFs
- Regulatory files: Containing the protocol with all amendments and Investigator signature pages, copies of all other regulatory documentation, all correspondence between the study site and the IRB/IEC and Sponsor, and drug accountability files, including a complete account of the receipt and disposition of the study treatment

Records are to be available for 2 years after the last marketing application approval, or if the application is not approved or never submitted, 2 years after the appropriate regulatory authorities have been notified of the discontinuation of clinical development of the investigational product. The Sponsor will provide written notification when it is appropriate for the Investigator to discard the study-specific documents referenced above.

During the record retention period, the Investigator or designee must inform the Sponsor or designee (eg, CRO), of the following:

- Location of study documentation
- If the custody of documentation will be transferred or moved to another location
- If the Investigator is unable to retain documentation for the specified period

13.3. Clinical Study Report

Whether the study is completed or prematurely terminated, a clinical study report will be prepared and provided to the regulatory agencies according to applicable regulatory requirement(s).

13.4. Disclosure of Study Results

The Sponsor will post the results of the study in a publicly accessible database in accordance with the applicable laws and regulations.

14. RESPONSIBILITIES

14.1. Investigator Responsibilities

The Investigator must comply with this protocol and the conduct of all study procedures. The Investigator will disclose to the Sponsor sufficient, accurate, financial information to allow the Sponsor to submit accurate disclosure statements to the FDA per 21 Code of Federal Regulations (CFR) Part 54 (Financial Disclosure by Clinical Investigators) or to other regulatory authorities that have similar requirements. The Investigator is responsible for compliance with applicable sections of ICH GCP requirements. The investigator may also be responsible for compliance with 21 CFR Part 312, Subpart D (Responsibilities of Investigators), and other ICH GCP requirements, federal, and local laws, applicable to conducting drug studies.

The Investigator is responsible for ensuring an investigation is conducted according to the signed Investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of participants under the Investigator's care; and for the control of drugs under investigation. An Investigator will, in accordance with the provisions of ICH GCP guidelines and/or 21 CFR Part 50, obtain the informed consent of each human subject to whom the drug is administered.

14.2. Sponsor's Medically Qualified Individual

The contact information for the sponsor's MQI for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to their investigator and the sponsor's MQI for study related medical questions or problems from non-study healthcare professionals, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study treatment identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the participant and their investigator and site staff, and between the investigator and sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number is to be used when the investigator and site staff are unavailable. The Pfizer Call Center number is not for use by the participant directly; if a participant calls that number directly, they will be directed back to the investigator site.

14.3. Sponsor Responsibilities

The Sponsor is responsible for compliance with applicable sections of ICH E6(R2) and 21 CFR Part 312, Subpart D (Responsibilities of Sponsors). The Sponsor is responsible for selecting qualified

Investigators, providing them with the information they need to conduct an investigation properly, and ensuring proper monitoring of the investigation(s). Sponsors are also responsible for ensuring the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the Investigational New Drug (IND) application (or equivalent), maintaining an effective IND (or equivalent) with respect to the investigations, and ensuring the FDA (and/or other regulatory authorities as applicable), other applicable health authorities, and all participating Investigators are promptly informed of significant new adverse effects or risks with respect to the drug.

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16. APPENDICES

16.1. APPENDIX 1: SCHEDULE OF ASSESSMENTS

Table 6: Schedule of Assessments – Screening and Induction Treatment Period

Evaluation	Screening Period	12-Week Treatment Period					2-Week Follow-Up Visit[b] ± 3 Days	4-Week Follow-Up Visit[b] ± 3 Days
	□28 to □ 1	W0/D1	W2/D15[a] ± 3 Days	W4/D29[a] ± 3 Days	W8/D57[a] ± 3 Days	W12/D85 / Early Termination[b] ± 3 Days		
Informed consent	X							
Inclusion/exclusion criteria	X	X						
Demographics	X							
Medical and social history[c]	X							
Ulcerative colitis history	X							
Chest X-ray[d]	X							
Tuberculosis test[e]	X							
Tuberculosis questionnaire[e]	X	X	X	X	X	X	X	X
Virology screen (HIV, HBV, HCV)[f]	X							
Randomization		X						
eDiary instruction[g]	X							
eDiary review		X	X	X	X	X		
MMS[h]		X				X		
Stool frequency and rectal bleeding subscore[i]		X	X	X	X	X		
PGA for total Mayo Clinic score		X				X		
UC-PRO/SS, SF-36		X				X		
Adverse event assessment	X	X	X	X	X	X	X	X

Evaluation	Screening Period	12-Week Treatment Period					2-Week Follow-Up Visit[b] ± 3 Days	4-Week Follow-Up Visit[b] ± 3 Days
	□28 to □ 1	W0/D1	W2/D15[a] ± 3 Days	W4/D29[a] ± 3 Days	W8/D57[a] ± 3 Days	W12/D85 / Early Termination[b] ± 3 Days		
Vital signs[j,k]	X[j]	X[j,k]	X	X	X	X	X	X
12-lead ECG[l,m]	X[l]	X[l,m]				X		
Physical examination[n]	X	X	X	X	X	X	X	X
Extraintestinal manifestations[o]	X					X	X	X
Pulmonary function test[p]	X[q]					X[q]	X[q]	
Ophthalmoscopy with OCT[r]	X					X	X[r]	
Urine drug screen[s]	X							
Pregnancy test[t]	X	X		X	X	X		X
CBC with differential and platelets	X	X	X	X	X	X	X	X
TBNK	X	X	X	X	X	X	X	X
Laboratory tests including hs-CRP[u]	X	X	X	X	X	X	X	
Stool sample/fecal calprotectin[v]	X		X	X	X	X		
Flexible proctosigmoidoscopy/ colonoscopy and biopsy[w]	X					X		
PK assessments[x]		X	X	X	X	X	X[x]	X[x]
Biomarkers blood sample[y]		X				X[z]		
Concomitant medications and procedures[aa]		X	X	X	X	X	X	X
Drug dispensation/accountability[bb]		X	X	X	X	X[bb]		
Study treatment administration[cc]		X – Once daily						

[a] All visits beyond W0/D1 may be virtual/hybrid visits (Section 9.6).

[b] Participants discontinuing prior to Week 12 should have an ET visit within 7 days of the last study treatment administration and before initiation of any new treatments. For participants who complete Week 12 and wish to enter the APD334-303 OLE study, the Week 12 visit will be used to assess eligibility for the APD334-303 OLE study. For participants not participating in the APD334-303 OLE study, a follow-up visit will be performed at 2 weeks and 4 weeks after the last administration of study treatment. If the ET or Study Completion visit is ≥ 2 weeks after the last dose of study treatment, the 2-Week Follow-Up visit is not required; however, the 4-Week Follow-Up visit should be scheduled and completed. If the ET or Study Completion visit is ≥ 4 weeks after the last administration of study treatment, the 4-Week Follow-Up visit is not required. If the absolute peripheral lymphocyte count is not within normal limits at the 4-Week Follow-Up visit, participants should return for CBC with differential according to local standard of care (captured as subsequent Follow-Up visit or unscheduled visit).

[c] Medical history, including prior and ongoing medication use, will be collected during screening and should be updated for any new conditions or medications as needed prior to dosing at the Day 1 visit (Section 9.3.5).

[d] A chest X-ray taken within the previous 6 months from the Screening Visit may also be used.

[e] All participants will complete TB screening to determine eligibility (refer to Appendix 2). The IGRA (eg,QuantiFERON TB Gold In-Tube or T-SPOT-TB) and tuberculin skin test should not be performed in participants previously diagnosed with TB infection. The TB questionnaire will be completed for all participants during the Screening period. For participants who are receiving TB prophylaxis treatment, the TB questionnaire will be completed at every study visit (until TB prophylaxis treatment course is completed).

[f] Participants will be tested for HIV antibodies as well as HBV and HCV infection at screening (Section 9.9.7.1.3).

[g] Participants will begin eDiary entries beginning the first day of screening after eDiary training is completed. The eDiary should be completed daily to capture data including daily SF and RB (the 2 subject-reported outcome measures contributing to the calculation of the MMS), and study treatment administration. The participant eDiary will be reviewed by study site staff at each treatment visit.

[h] The MMS will be calculated electronically at the Day 1 and Week 12/ET visits. The subscores for SF and RB are derived from the participant eDiary entries using the scores from the 3 most recent consecutive days within the 7 days prior to the day of bowel preparation (excluding the day of bowel preparation), averaged and rounded to the nearest integer (Section 9.3.10).

[i] Stool frequency and RB subject-reported outcomes will be recorded daily using participant eDiaries. The RB and SF subscores will be calculated as indicated in Section 9.4.2.

[j] Safety vital signs (resting heart rate and systolic and diastolic BP, body temperature, and respiratory rate) taken with participants in the sitting position will be performed at Screening and prior to randomization on Week 0/Day 1 (baseline). If the participant's heart rate is < 50 bpm, or systolic BP < 90 mm Hg, or diastolic BP < 55 mm Hg, or has symptoms of low HR or low BP, the participant must not be randomized and should be considered a screen failure.

[k] On Day 1, vital sign assessments will be conducted as described in Section 9.4.2.1.

[l] Safety 12-lead ECGs with the participant in the supine position will be obtained prior to blood sample collection at Screening and prior to randomization on Week 0/Day 1 (baseline). Participants with a 12-lead ECG showing a second or third-degree AV block, periods of asystole > 3 seconds, PR interval > 200 ms, QTcF ≥ 450 ms (men) or QTcF ≥ 470 ms (women) must not be randomized and should be considered screen failures.

[m] After dosing on Day 1, a 12-lead ECG with the participant in the supine position will be performed 4 hours (± 15 minutes) postdose as described in Section 9.4.2.1.

[n] Complete physical examination (including assessments of the skin, head, eyes, ears, nose, throat, neck, thyroid, lungs, heart, abdomen, back, lymph nodes, extremities, body weight, and height [height collected at Screening Visit only]) should be performed at screening and the Week 12/ET visit. All other visits during the 12-Week Treatment Period should have a focused (complaints, signs, and symptoms) physical examination.

[o] During the specified full physical examinations (screening and Week 12/ET visits), specific systems (eyes, liver, skin, and joints) will be examined for EIMs.

[p] A PFT will include FEV1 and FVC measurements. When available, DLCO measurements will also be performed (when DLCO is not available, sites should consult the Sponsor or Sponsor's delegate). The 2-Week Follow-Up visit assessment is only required if clinically indicated. Details regarding additional PFTs are provided in Section 9.9.4.

[q] The Screening PFT should be done within the 28-Day Screening period. PFTs should be performed ± 7 days during the study treatment period and posttreatment period (ie, 2-Week Follow-Up visit). PFTs occurring at the ET visit that are within 4 weeks of the last assessment (eg, Week 12), will only be required if clinically indicated. The 2-Week Follow-Up visit assessment is only required if clinically indicated. Details regarding additional PFTs are provided in Section 9.9.4.

[r] The Screening OCT should be performed within the 28-Day Screening Period. Subsequent ophthalmoscopy with OCT should be performed ± 7 days of the study treatment period and posttreatment period (ie, 2-Week Follow-Up visit). OCTs occurring at the ET visit that are within 4 weeks of the last assessment (eg, Week 12) will only be required if clinically indicated. The 2-Week Follow-Up visit assessment is only required if clinically indicated. Details regarding ophthalmoscopy and OCT assessments are provided in Section 9.9.5.

[s] Urine drug screen according to Table 5.
[t] Only for women of childbearing potential. Serum β-hCG test required at screening; urine pregnancy test at all other visits. If at any point there is a positive urine β-hCG test, the participant will have study treatment interrupted and a serum sample submitted to the central laboratory for β-hCG testing (Section 9.9.7.1.2)
[u] Clinical laboratory tests will include serum chemistry, hematology (including coagulation), urinalysis, and hs-CRP. Screening samples should be obtained and results must be available and reviewed prior to randomization. On other study visits, samples should be obtained prior to the daily dosing.
[v] Stool sample is for fecal calprotectin (Screening, Weeks 2, 4, 8, and 12) and bacterial culture, ova and parasite evaluation, and *C. difficile* assay at screening and at any point in the study when a participant becomes symptomatic, including worsening or return of disease activity.
[w] To be read by a blinded central reader. Proctosigmoidoscopy/colonoscopy should be performed prior to randomization to allow central reader review (may take approximately 5 to 12 days) and confirmation of eligibility (Section 9.8.1.1). If the ET visit is within 4 weeks of the last sigmoidoscopy and biopsy, these procedures do not need to be repeated.
[x] Pharmacokinetic blood samples are to be collected predose, 4 hours (± 15 minutes) postdose on Week 0/Day 1 (PK sample to be collected after 12lead ECG), and predose (for trough level, within the 60minute period prior to dosing) on all other indicated days. A PK sample should be taken, if possible, at the time of any SAE or adverse event leading to study treatment discontinuation. In addition, for participants not enrolling into the APD334-303 study, a blood sample for PK should be drawn at the 2-Week and 4-Week Follow-Up visits. For all PK blood draws, the time of the last dose should be documented. For participants enrolling in the OLE at the Week 12 visit, the PK sample can be collected as part of the OLE.
[y] Blood samples for biomarkers should be collected on the indicated days prior to the daily dosing as applicable.
[z] Biomarkers will be collected at Week 12 but will not be collected at ET.
[aa] All concomitant medications and procedures should be collected from Day 1 (predose) through the safety reporting period (Section 6.7).
[bb] Study treatment should be dispensed at Week 12 if the participant continues treatment in APD334-303 OLE. Additionally, participants who consent and are eligible for the APD334-303 OLE study but do not enter the OLE on the same day as the Week 12 visit may also be dispensed study treatment.
[cc] On days with scheduled study visits, participants should wait to take their study treatment until after blood draws for PK and after all pre-dose assessments and procedures have been completed.

AV, atrioventricular; β-hCG, beta-human chorionic gonadotropin; BP, blood pressure; CBC, complete blood count; D, day; DLCO, diffusing capacity of the lungs for carbon monoxide; ECG, electrocardiogram; eDiary, electronic diary; EIM, extraintestinal manifestations; ET, Early Termination; FEV_1, forced expiratory volume at 1 second; FVC, forced vital capacity; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, heart rate; hs-CRP, high-sensitivity C-reactive protein; MMS, modified Mayo score; OCT, optical coherence tomography; OLE, open-label extension; PFT, pulmonary function test; PGA, Physicians Global Assessment; PK, pharmacokinetics; QTcF, Fridericia's corrected QT interval; RB, rectal bleeding; SAE, serious adverse event; SF, stool frequency; SF-36, Medical Outcomes Study 36-Item Short Form Health Survey; TB, tuberculosis; TBNK, T cell, B cell, natural killer cell; UC-PRO/SS, Ulcerative Colitis Patient-Reported Outcomes Signs and Symptoms; W, week

16.2. APPENDIX 2: TUBERCULOSIS SCREENING

All participants must undergo screening for a history of tuberculosis (TB) infection and testing for latent/active TB infection. Their medical history review must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. Participants should be asked about past testing for TB, including chest radiograph results and results of interferon-gamma release assay (IGRA, eg, QuantiFERON-TB Gold In-Tube, T-SPOT TB) or response to tuberculin skin test (TST) and history of Bacillus Calmette-Guérin vaccination.

a. Participants without a history of latent or active TB who have a negative IGRA or TST result at screening are eligible to enroll in the study.

b. A TB questionnaire will be completed for all participants (refer to questionnaire below) during the Screening period.

c. For participants who are receiving TB prophylaxis treatment the TB questionnaire will be completed at every study visit (until TB prophylaxis treatment course is completed). This questionnaire will monitor for any emergent symptoms of active TB and compliance with any TB prophylaxis treatment.

d. The IGRA or TST is NOT required at screening (or annually) for participants with a history of active/latent TB infection.

   – Participants with past or current history of active TB, regardless of treatment history, are excluded from enrollment.

   – Participants with a history of latent TB infection diagnosed prior to screening must have documentation of treatment with at least four weeks of an acceptable TB prophylaxis treatment regimen to qualify for enrollment. It is the responsibility of the investigator to verify the adequacy of previous TB treatment and provide appropriate documentation (Direct Observation Therapy report where available).

e. Acceptable TB prophylaxis treatment regimens for latent TB is defined according to local country guidelines. If no local country guidelines for the treatment of latent TB exist, WHO guidelines must be followed.

f. Participants with a newly identified positive IGRA (one retest is allowed with approval from the Medical Monitor per Section 9.3.2) or TST result at Screening must be considered a Screen Failure, however they are eligible for rescreening once they undergo an evaluation to rule out active TB (chest X-ray to rule out pulmonary TB) and initiate an acceptable TB prophylaxis treatment regimen for latent TB at least 4 weeks prior to rescreening (with a plan to complete the TB treatment course during study participation) before they can be considered for enrollment.

g. An assessment of adequacy of the TB prophylaxis treatment regimen and duration of treatment must be performed by an infectious disease consultant or physician TB expert.

h. IGRA and TST interpretation

   – Participants will be considered to have a negative diagnostic test for TB if at least one of the following circumstances applies:
      – Negative IGRA.
      – Combination of a negative IGRA and negative purified protein derivative (PPD) TST (in countries where IGRA is not considered a validated test).

- A combination of two intermediate/indeterminant IGRAs and a negative PPD TST. An intermediate/indeterminant IGRA test result should be repeated. In the event that the second IGRA test result is also intermediate/indeterminate, the participant may be enrolled without treatment for latent TB if his/her chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the participant has no additional risk factors for TB as determined by a physician TB expert physician.
- If the IGRA is not considered a validated test or is not registered for use in the participant's country, a negative TST result is required to rule out latent TB infection.
- A positive TST reaction is ≥ 10 mm of induration, or ≥ 5 mm of induration for participants receiving equivalent of prednisone > 15 mg/day for any medical conditions.

i. Resources

- For the WHO guidelines for the treatment of latent TB visit: https://apps.who.int/iris/bitstream/handle/10665/44165/9789241547833_eng.pdf;jsessionid=115F807C3008D688F75118AF16EA53F0?sequence=1

Tuberculosis Screening Questionnaire

Etrasimod Program
Tuberculosis Screening Questionnaire
Created by Arena Pharmaceuticals, Inc.
Version 1.0, 17Jan2020

Site #: _____
Subject #: _____

Tuberculosis Screening Questionnaire
Source Document Worksheet

Instructions:

1. **This source document worksheet should be completed by the PI or delegated site staff.**
2. **This source document worksheet should NOT be given to the subject for completion.**
3. **Please complete for ALL subjects during the Screening visit.**
4. **Please complete at every study visits for subjects who are receiving TB prophylaxis treatment (until the TB prophylaxis treatment course is completed) and at designated post-baseline study visits (per protocol schedule of assessments) for subjects who reside in countries with a high burden of TB or multi-drug resistant (MDR) TB as identified by WHO. The current WHO TB high burden country (HBC) and MDR TB HBC lists can be found at the following URL: http://www.stoptb.org/countries/tbdata.asp.**
5. **Enter all applicable information on the corresponding eCRF.**

Was the Tuberculosis Screening questionnaire completed? Yes/No

If yes, please enter completion date (DD/MM/YYYY): _____

If no, specify reason:

Date of completion of TB Screening Questionnaire, if applicable: _____

Study Visit Number: _____

Section 1: Questions to ask the subject

*Time frame: in the past year or since your last study visit.

1. Have you experienced any of the following symptoms?*	
a) A productive cough (coughing up phlegm) for more than 3 weeks	Yes / No
b) Hemoptysis (coughing up blood)	Yes / No
c) Unexplained weight loss	Yes / No
d) Fever, chills, or night sweats for no known reason	Yes / No
e) Persistent shortness of breath (difficulty breathing)	Yes / No
f) Unexplained fatigue	Yes / No
g) Chest pain	Yes / No

Etrasimod Program
Tuberculosis Screening Questionnaire
Created by Arena Pharmaceuticals, Inc.
Version 1.0, 17Jan2020

Site #: _____
Subject #: _____

2. Have you had contact with anyone with active tuberculosis disease?*	Yes / No
3. Have you been diagnosed with latent TB infection?	Yes / No
a) If yes, list medication(s) used to treat latent TB infection and treatment dates (please ensure listed on Concomitant Medication Source Log and eCRF, as applicable). Medication #1:_____ Start date of Medication #1:_____ Expected stop date of Medication #1:_____ Have you missed taking any doses of Medication #1? Dates of Missed Doses:_____ # of Missed Doses:_____ Medication #2: _____ Start date of Medication #2:_____ Expected stop date of Medication #2:_____ Have you missed taking any doses of Medication #2? Dates of Missed Doses:_____ # of Missed Doses:_____ Medication #3: _____ Start date of Medication #3:_____ Expected stop date of Medication #3:_____ Have you missed taking any doses of Medication #3? Dates of Missed Doses:_____ # of Missed Doses:_____ Medication #4:_____ Start date of Medication #4:_____ Expected stop date of Medication #:_____ Have you missed taking any doses of Medication #4? Dates of Missed Doses:_____ # of Missed Doses:_____	Yes / No Yes / No Yes / No Yes / No

Please provide details to any question answered "Yes."
_____
_____

Etrasimod Program
Tuberculosis Screening Questionnaire
Created by Arena Pharmaceuticals, Inc.
Version 1.0, 17Jan2020

Site #: _____
Subject #: _____

Section 2: To be completed by the investigator

I. The participant is on concomitant medication(s) with immunosuppressive effects: Yes / No
If yes, specify medication(s) (name, dosage):
Medication #1:
Medication #2:
Medication #3:
Medication #4:

II. TB QuantiFERON or Tuberculin Skin Test result: _____ Date: _____
Chest x-ray/computer tomography (CT) scan done to rule out pulmonary TB? Yes / No
If yes, date of chest x-ray or CT scan: _____
Any evidence of active pulmonary TB disease on chest x-ray or CT scan? Yes / No
Other assessment completed? Yes/ No
If yes, specify assessment: _____
If yes, date of other assessment: _____
Any evidence of active TB disease on assessment? Yes / No

III. Upon review of the responses and discussion with the participant, I recommend the following:
___Perform screening test for latent TB infection
___ Perform additional assessments to rule out active TB disease
___ Refer to physician TB expert for evaluation and treatment
___ Follow up at the next TB-designated study visit and repeat TB screening questionnaire

16.3. APPENDIX 3: MAYO CLINIC SCORE – SAMPLE

Mayo Scoring System for Assessment of Ulcerative Colitis Activity

Stool frequency[a]

0 = Normal number of stools for this subject
1 = 1 to 2 stools more than normal
2 = 3 to 4 stools more than normal
3 = 5 or more stools more than normal
Subscore: 0 to 3

Rectal bleeding[b]

0 = No blood seen
1 = Streaks of blood with stool less than half the time
2 = Obvious blood with stool most of the time
3 = Blood alone passes
Subscore: 0 to 3

Findings on endoscopy[c]

0 = Normal or inactive disease
1 = Mild disease (erythema, decreased vascular pattern)
2 = Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)
3 = Severe disease (spontaneous bleeding, ulceration)
Subscore: 0 to 3

Physician's Global Assessment[d]

0 = Normal
1 = Mild disease
2 = Moderate disease
3 = Severe disease
Subscore: 0 to 3

The Total Mayo Score (TMS) ranges from 0 to 12, with higher scores indicating more severe disease. The modified Mayo score (MMS) ranges from 0 to 9 and comprises the subscores for stool frequency, rectal bleeding, and endoscopy.

a Each participant serves as his or her own control to establish the degree of abnormality of the stool frequency.

b The daily bleeding score represents the most severe bleeding of the day.

c The endoscopy subscore will be determined by qualified personnel at a central laboratory.

d The Physician's Global Assessment acknowledges the 3 other criteria, the subject's daily recollection of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the subject's performance status.

16.4. APPENDIX 4: HISTOLOGICAL SCORING INDICES

Geboes Grading System

The Geboes Grading System is a stepwise grading system used for the evaluation of microscopic inflammation and histopathologic disease activity in ulcerative colitis (UC). The microscopic appearance of the mucosa is categorized into 6 grades. A decrease of the Geboes Score grading system to Grade zero (0) or one (1) indicates mucosal healing (Geboes 2000).

Nancy Histological Index

The Nancy Histological Index is a validated index for assessing histological disease activity in UC. It is composed of three histological items defining five grades of disease activity: absence of significant histological disease (Grade 0), chronic inflammatory infiltrate with no acute inflammatory infiltrate (Grade 1), mildly active disease (Grade 2), moderately active disease (Grade 3), and severely active disease (Grade 4). The presence of ulceration on the biopsy specimen corresponds to severely active disease (Grade 4). If there is no ulceration, acute inflammatory cells infiltrate (presence of neutrophils) is assessed. Moderate or severe acute inflammatory cells infiltrate corresponds to moderately active disease (Grade 3), while mild acute inflammatory cells infiltrate correspond to mildly active disease (Grade 2). If there is no acute inflammatory cells infiltrate, assessment of chronic inflammatory infiltrate (lymphocytes and plasmacytes) is made. A biopsy specimen showing moderate or marked chronic inflammatory infiltrate corresponds to moderate or marked chronic acute inflammatory infiltrate (Grade 1). A biopsy specimen showing mild or no chronic inflammatory infiltrate corresponds to absence of significant histological disease (Grade 0) (Marchal-Bressenot 2017).

Robarts Histopathology Index

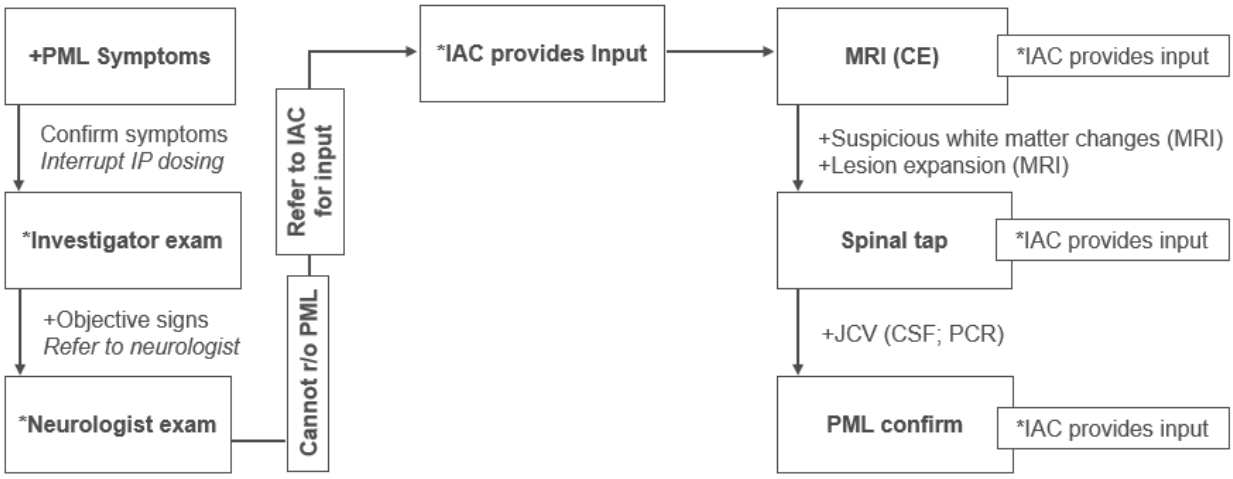
The Robarts Histopathology Index (RHI) is an evaluative index, derived from the Geboes score, that is designed to be reproducible and responsive to clinically meaningful change in disease activity over time. The total RHI score ranges from 0 (no disease activity) to 33 (severe disease activity) and is calculated as follows: RHI = 1×Chronic inflammatory infiltrate + 2×Lamina propria neutrophils + 3×Neutrophilis in epithelium + 5×Erosion or ulceration (Mosli 2017).

16.5. APPENDIX 5: GUIDANCE FOR THE ASSESSMENT OF POTENTIAL PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

If a participant exhibits signs and symptoms suspicious for progressive multifocal leukoencephalopathy (PML), the Investigator must interrupt study treatment and perform a targeted neurologic examination to assess for signs of PML, which are diverse, progress over days to weeks, and may include progressive weakness on one side of the body or clumsiness of limbs or difficulty with walking or writing or fine motor skills, disturbance of vision, changes in thinking, memory and orientation leading to confusion and personality changes, paresthesia/anesthesia (of any domain: peripheral to central), dysarthria (expressive aphasia), and/or agnosia (receptive aphasia). Consultation with a local neurologist may be warranted, as presented in the PML case evaluation algorithm in Figure 2.

The Medical Monitor should be informed of any suspected cases of PML and, if needed, will facilitate investigator/local neurologist consultation with PML medical experts on the independent adjudication committee.

Figure 2: Progressive Multifocal Leukoencephalopathy Case Evaluation Algorithm



Note: IP dosing may resume, and no further evaluation is needed if the Investigator assessment reveals no objective signs of PML, the local neurologist confirms that the patient does not have PML, or the IAC's review of the evidence concludes that PML is ruled out.
CE, contrast-enhanced; CSF, cerebral spinal fluid; IAC, independent adjudication committee; IP, investigational product; JCV, John Cunningham Virus; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PML, progressive multifocal leukoencephalopathy; r/o, rule out

16.6. APPENDIX 6: LIVER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are "adaptors" or are "susceptible."

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to T bili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available (refer to Section 5.1 for guidance on when to discontinue the participant).

- For participants with baseline AST OR ALT OR T bili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values AND ≥3 × ULN; or ≥8 × ULN (whichever is smaller).

    - Preexisting values of T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN or if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and T bili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and T bili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.