CLINICAL STUDY PROTOCOL

Protocol number:	APD334-301
Protocol title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 52-Week Study to Assess the Efficacy and Safety of Etrasimod in Subjects with Moderately to Severely Active Ulcerative Colitis
Brief title:	ELEVATE UC 52: Etrasimod Versus Placebo for the Treatment of Moderately to Severely Active Ulcerative Colitis
Study drug:	Etrasimod (APD334)
Indication:	Ulcerative colitis
Phase:	3
IND number:	[redacted]
EudraCT number:	2018-003985-15
NCT number:	03945188
Sponsor name:	Arena Pharmaceuticals, Inc. 6154 Nancy Ridge Drive San Diego, CA 92121
Sponsor's Responsible Medical Officer:	[redacted] Senior Vice President, Clinical Development, and Chief Medical Officer
Clinical lead:	[redacted] Senior Director, Clinical Development, Arena Pharmaceuticals, Inc., San Diego, CA [redacted]
SAE reporting:	IQVIA Pharmacovigilance [redacted]
Version:	Amendment 4.0, 22 December 2020
Sponsor approval:	This protocol was approved by the Sponsor's Responsible Medical Officer or delegate. The electronic signature manifest is appended.

PROTOCOL HISTORY

Document	Amendment Type	Date
Amendment 4.0	Global	22 December 2020
Amendment 3.1	Region-Specific	21 February 2020
Amendment 3.0	Global	07 February 2020
Amendment 2.1	Region-specific	21 February 2020
Amendment 2.0	Global	20 December 2019
Amendment 1.1	Region-specific	12 June 2019
Amendment 1	Global	05 March 2019
Original Protocol	Not applicable	19 December 2018

PROTOCOL SYNOPSIS

Sponsor: Arena Pharmaceuticals, Inc.
Name of investigational study drug: Etrasimod (APD334)
Protocol number: APD334-301
Protocol title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 52-Week Study to Assess the Efficacy and Safety of Etrasimod in Subjects with Moderately to Severely Active Ulcerative Colitis
Phase: 3
Regions: North America, South America, Asia Pacific, Europe, Middle East, Africa
Objectives: Primary: The primary objective is to assess the efficacy of etrasimod on clinical remission in subjects with moderately to severely active ulcerative colitis (UC) after 12 and 52 weeks of treatment. Secondary: The secondary objective is to assess the efficacy of etrasimod on clinical response, symptomatic response and remission, endoscopic changes, corticosteroid-free remission, and mucosal healing in subjects with moderately to severely active UC at timepoints up to 52 weeks of treatment. Safety: The safety objective is to assess the long-term safety of etrasimod after daily doses of 2 mg for up to 52 weeks in subjects with moderately to severely active UC. Other: Other objectives include evaluation of etrasimod pharmacokinetics (PK) and the effect of etrasimod on health-related subject-reported outcomes and biomarkers.
Study design: This is a multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of etrasimod 2 mg in subjects with moderately to severely active UC. The study consists of a 28-Day Screening Period, a 12-Week Treatment Period, a 40-Week Treatment Period, and a 2-Week and 4-Week Follow-Up Period. The target subject population will include (approximately 50% of subjects in each of the following categories): 1. Subjects who have had an inadequate response to, loss of response to, or intolerance to conventional therapy and are näive to biologic or Janus kinase (JAK) inhibitor therapy 2. Subjects who have had an inadequate response to, loss of response to, or intolerance to a biologic or JAK inhibitor (subjects in this category may have received prior conventional therapy).

Subject 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 subjects will be randomized (2:1 ratio) to receive either etrasimod (2 mg once daily) or matching placebo (once daily) in a double-blind fashion for up to 52 weeks (12-Week Treatment Period + 40-Week Treatment Period). 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).

End of 12-Week Double-Blind Treatment Period

At the end of the 12-Week Treatment Period, subjects will undergo the Week 12 efficacy and safety assessments and procedures. Subjects whose disease is stable or improving compared with baseline (Week 0/Day 1) will continue with their double-blind treatment and move into the 40-Week Treatment Period.

Subjects must complete Week 12 to be eligible for the OLE. Subjects who do not meet disease worsening criteria, including those demonstrating clinical response/remission at Week 12 will continue into the 40-Week Treatment Period and continue their double-blind treatment. Disease worsening will continue to be monitored by Investigators through the 40-Week Treatment Period (ie, from Weeks 13 to 52). Subjects who either experience disease worsening in the 40-Week Treatment Period or complete all study procedures at Week 52 will have the option to enroll into the OLE study if they meet all eligibility criteria.

Subjects may be eligible to enroll in the OLE provided their ES is ≥ 2 and they meet one of the following entry criteria:

- RB subscore ≥ 2 at 2 timepoints at least 7 days and no more than 14 days apart
- RB + SF subscores ≥ 4 at 2 timepoints at least 7 days and no more than 14 days apart
- RB subscore ≥ 2 or RB + SF subscores ≥ 4 (in any order) at 2 timepoints at least 7 days and no more than 14 days apart

For subjects discontinuing prior to Week 52, an endoscopic evaluation is required to confirm eligibility for the OLE. An endoscopy should be performed upon the appearance of UC symptoms but no more than 14 days after the second timepoint for symptom criteria above. A proctosigmoidoscopy does not need to be repeated if performed within the last 4 weeks.

Subjects who do not participate in the OLE study will have 2-Week and 4-Week Follow-Up visits after their last treatment administration

End of 40-Week Double-Blind Treatment Period (Week 52)

At the end of the 40-Week Treatment Period (ie, Week 52) and following completion of all study procedures, subjects will have the option to enter into the OLE study (APD334-303) provided they meet all eligibility criteria.

Subjects who do not participate in the OLE study will have 2-Week and 4-Week Follow-Up visits after their last treatment administration

Number of subjects (planned):

Approximately 420 subjects are planned to be enrolled into this study.

Eligibility criteria:

Inclusion criteria:

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

1. Men or women 16 to 80 years of age, inclusive, at the time of assent/consent. Enrollment of subjects < 18 years should be conducted only if acceptable according to local laws and regulations
2. Ability to provide written informed consent or assent (parent or legal guardian must provide consent for a subject < 18 years of age who has assented to participate in the study or as required per local regulations) and to be compliant with the schedule of protocol assessments

Disease-specific inclusion criteria:

3. 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
4. Active UC confirmed by endoscopy with ≥ 10 cm rectal involvement. Subjects with proctitis only at baseline who meet the other eligibility criteria for inclusion, including the endoscopic and rectal bleeding criteria for moderate to severe disease, will be capped at 15% of the total subjects enrolled
5. Moderately to severely active UC defined as MMS of 4 to 9, including an ES of ≥ 2 and RB score ≥ 1
6. Received a surveillance colonoscopy (performed according to local standard) within 12 months before baseline to rule out dysplasia in subjects with pancolitis > 8 years duration or subjects with left-sided colitis > 12 years duration. Subjects 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:

7. 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. Corticosteroids
c. Thiopurines

Biologic therapy or JAK inhibitor therapy

a. Antitumor necrosis factor alpha (TNFα) antibodies (eg, infliximab, adalimumab, golimumab, or biosimilars)
b. Anti-integrin antibodies (eg, vedolizumab)

c. Anti-interleukin 12/23 antibodies (eg, ustekinumab)
d. JAK inhibitors (eg, tofacitinib)

Note: The medication used to qualify the subject for entry into this category must be approved for the treatment of UC in the country of use and the subject must have received an adequate course of therapy based on local guidelines for that therapy.

Concomitant treatments:

8. Subjects 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, budesonide at a stable dose ≤ 9 mg/day, or equivalent steroid) provided the dose has been stable for the 4 weeks immediately prior to the screening endoscopy assessment (Note: Subjects on existing oral corticosteroid therapy will be tapered during the 40-Week Treatment Period.)
   - Immunosuppressive agents such as oral azathioprine or 6-mercaptopurine must be discontinued ≥ 2 weeks prior to randomization
   - Probiotics (eg, Culturelle®, *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:

9. 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
10. 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. Subjects with an isolated total bilirubin and normal AST and ALT diagnosed with Gilbert's syndrome may participate
11. 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
12. 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. Nonpregnant 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) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal, or transdermal
   - Progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injected, or implanted
   - Intrauterine device (IUD)
   - Intrauterine hormone-releasing system
   - Bilateral tubal occlusion
   - Vasectomized partner, provided that partner is the sole sexual partner of the female-of-childbearing-potential trial subject 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 subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not acceptable

c. A male subject 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:

Subjects 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 subject 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 or indeterminate colitis or the presence or history of a fistula consistent with Crohn's disease

3. Diagnosis of 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 IV steroids given is acceptable)
5. Positive assay or stool culture for pathogens (ova and parasite examination, bacteria) or positive test for *Clostridioides difficile* (formerly known as *Clostridium difficile*) toxin at screening (If *C. difficile* is positive, the subject 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 subject 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 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 prerandomization 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 prerandomization 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 subjects 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:
    - Subjects 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
    - Subjects 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. Subjects 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 intravenous medication ≤ 14 days prior to randomization, or that may worsen (in the opinion of the Investigator) if the subject 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 (detectable HBV DNA, or positive for hepatitis B surface antigen [HBsAg], or negative for HBsAg and positive for antihepatitis B core antibody 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) or 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 sphingosine 1-phosphate 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. Treatment with ≥ 3 biologic agents or ≥ 2 biologics plus a JAK inhibitor approved for treatment of UC
26. Treatment with topical rectal 5-ASA, short-chain fatty acid enemas, or steroids ≤ 2 weeks prior to and 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 and 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. Chronic use of therapies that moderately/strongly inhibit/induce cytochrome P450 (CYP) 2C8 and 2C9 metabolism and inhibitors of UGT1A7 ≤ 4 weeks prior to randomization

Test product, formulation, mode of administration, and dose:

Etrasimod, 2 mg tablets, by mouth, once daily

Study duration:

The overall duration of this study is expected to be approximately 2.5 years.

Reference therapy, description, 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: 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)
- Mucosal healing: ES ≤ 1 (excluding friability) with histologic remission measured by a Geboes Index score < 2.0
- Symptomatic remission: SF subscore = 0 (or = 1 with a ≥ 1-point decrease from baseline) and RB subscore = 0

Primary efficacy endpoints:

- The proportion of subjects achieving clinical remission at Week 12
- The proportion of subjects achieving clinical remission at Week 52

Key secondary efficacy endpoints:

- The proportion of subjects achieving endoscopic improvement at Week 52
- The proportion of subjects achieving endoscopic improvement at Week 12
- The proportion of subjects achieving symptomatic remission at Week 52
- The proportion of subjects achieving symptomatic remission at Week 12
- The proportion of subjects in clinical remission at Week 52 and who had not been receiving corticosteroids for ≥ 12 weeks prior to Week 52
- The proportion of subjects with mucosal healing at Week 52
- The proportion of subjects with mucosal healing at Week 12
- The proportion of subjects achieving clinical remission at both Weeks 12 and 52

Pharmacokinetic assessments:

Plasma concentrations of etrasimod, and if warranted M3 (AR503641) and other metabolite(s) of interest, will be assessed from samples collected pre-dose and 4 hours post-dose (after 12-lead ECG) on Week 0/Day 1, and pre-dose (trough) at Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 52, and at the 2-Week and 4-Week Follow-Up visits. A PK sample should also be drawn, if possible, at the time of any 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.

Other assessments:

Biomarker endpoints:

- Change from baseline in level of fecal calprotectin at Weeks 2, 4, 8, 12, 24, and 52
- Change from baseline in level of high-sensitivity C-reactive protein at Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, and 52
- Change and percentage change from baseline in lymphocyte counts at Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, and 52

Health-related quality of life endpoints:

- Scores and change from baseline at Weeks 12 and 52 in the following:
  - Inflammatory Bowel Disease Questionnaire total score (IBDQ)
  - Ulcerative Colitis Patient-Reported Outcomes Signs and Symptoms (UC-PRO/SS)
  - Medical Outcomes Study 36-Item Short Form Health Survey, version 2 physical and mental component and domain scores (SF-36)
  - Work Productivity and Activity Impairment Questionnaire – Ulcerative Colitis (WPAI-UC)
  - Urgency numeric rating scale (NRS)
  - Abdominal pain NRS
- The proportion of subjects with UC-related hospitalizations
- The proportion of subjects requiring UC-related surgeries, including colectomy

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

Statistical methods:

Sample size

Based on a 2-group Fisher's exact test, a 1-sided significance level of 0.025, and a 2:1 randomization ratio, 420 total subjects (280 etrasimod, 140 placebo) are required to achieve 93.4% power to detect a difference of 13.5% in the primary endpoint of clinical remission at Week 52 between the etrasimod treatment group (23.5%) and the placebo treatment group (10.0%). With this sample size, there will be 96% power to detect a difference of 12.5% in the other primary endpoint of clinical remission at Week 12, assuming a placebo rate at 6.0%. The lower bound of overall power for both primary endpoints (as coprimary endpoints) is at least 90%; and since the two primary endpoints are expected to be at least moderately positively correlated, the actual overall power to reject both of their null hypotheses is likely to be greater than 90%.

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 subjects in remission, remission percentages, difference in remission percentages, odds ratio, and associated 95% confidence intervals (CIs) and p-values.

Testing strategy

There are multiple null hypotheses for the comparison of etrasimod and placebo in the primary and key secondary endpoints. The family-wise type-I error rate will be controlled at a fixed α level at 0.025 (1-sided) using the following testing procedure. First, the whole α will be spent on testing both primary endpoints. This study will be considered as an overall success only if both primary null hypotheses are rejected, each at the α level (as coprimary hypotheses). This study will be considered as a partial success if only one of the two primary null hypotheses are rejected at α/2 if the other has $p > \alpha$.

Only if both of the primary null hypotheses are rejected, each at the α level, can testing proceed for the 8 key secondary endpoints. The method for such testing will be specified in the Statistical Analysis Plan (SAP), and it will control for the multiplicity of the 8 key secondary endpoints. Any key secondary endpoint that fails to be significant at the α level by this method to control multiplicity will be considered exploratory and thereby would only have nominal p-values. All other endpoints will be evaluated at α level of significance and reported with nominal p-values, without multiplicity adjustment.

Pharmacokinetic analysis

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.

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, serious 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 subject 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.

Interim analysis

The Sponsor may conduct an interim analysis for sample size re-estimation based on blinded (aggregate) data to assess the appropriateness of the assumptions used in the original sample size calculation. The planned sample size will not be reduced as a result of the sample size re-estimation- to ensure sufficient exposure data for safety assessment. An interim SAP will provide detailed interim analysis specifications. The SAP charter will be finalized prior to any interim analysis and will be provided to regulatory agencies in a timely manner. This interim analysis will not be used to evaluate efficacy or safety.

TABLE OF CONTENTS

LIST OF APPENDICES

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADL	activities of daily living
ADR	adverse drug reaction
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
5-ASA	5-aminosalicylic acid
AST	aspartate aminotransferase
AV	atrioventricular
AZA	azathioprine
β-hCG	beta-human chorionic gonadotropin
BP	blood pressure
CBC	complete blood count
CD	Crohn's disease
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practices
CMH	Cochran-Mantel-Haenszel
CMP	clinical monitoring plan
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
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
EIMs	extraintestinal manifestations
ES	endoscopic score
ET	End-of-treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration

Abbreviation	Definition
FEV_1	forced expiratory volume at 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
HbA1c	hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRQoL	health-related quality of life
hs-CRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IGRA	interferon-gamma release assay
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	Intrauterine device
IV	intravenous
IWRS	Interactive Web Response System
JAK	Janus kinase
MAR	missing at random
MCS	Mayo clinic score
MDR	multi-drug resistant
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified Full Analysis Set
MMF	mycophenolate mofetil
MMS	modified Mayo score
6-MP	6-mercaptopurine

Abbreviation	Definition
NF	National Formulary
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drugs
OCT	optical coherence tomography
OLE	open-label extension
PFT	pulmonary function test
PGA	Physicians Global Assessment
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PPD	purified protein derivative
QTcF	Fridericia's corrected QT interval
RB	rectal bleeding
S1P	sphingosine 1-phosphate
SAE	serious adverse event
SAP	statistical analysis plan
SF	stool frequency
SF-36	Medical Outcomes Study 36-Item Short Form Health Survey
SOP	Standard Operating Procedures
TB	tuberculosis
TMF	trial master file
TNFα	tumor necrosis factor alpha
TST	tuberculin skin test
UC	ulcerative colitis
UC-PRO/SS	Ulcerative Colitis Patient-Reported Outcomes Signs and Symptoms
ULN	upper limit of normal
USP	United States Pharmacopeia
WBC	white blood cell
WPAI-UC	Work Productivity and Activity Impairment Questionnaire – Ulcerative Colitis

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 subjects 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 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 subjects 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 (Sandborn 2020). 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 subjects.

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 subjects at single doses up to 5 mg and repeated doses up to 4 mg once daily. Repeated doses of 2 mg have been evaluated in Phase 2 studies of subjects 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.

Detailed information regarding the known and expected benefits and risks and reasonably expected adverse events of etrasimod can be found in the IB.

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 subjects with macular edema or retinopathy, with assessment of optical coherence tomography (OCT) occurring throughout the study; and exclusion of subjects 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 subjects with a history of macular edema or retinopathy will be excluded from the study. All randomized subjects will be assessed by OCT at study entry, periodically throughout the treatment period, and as clinically indicated any time during the study.
- Subjects with certain cardiac risks will also be excluded from the study. Randomized subjects will be monitored in a period following dosing, and vital signs will be assessed for determination of the subject's health before discharge. Subjects 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 subjects with moderately to severely active UC and the current Phase 3 study.

The current study is a Phase 3 multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of etrasimod in subjects with moderately to severely active UC. Subjects who complete the total 52-week treatment or subjects with worsening disease after the Week 12 visit assessments (Section 5.1.1) will have the opportunity to enroll into an open-label extension (OLE) study 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.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective is to assess the efficacy of etrasimod on clinical remission in subjects with moderately to severely active UC after 12 and 52 weeks of treatment.

2.2. Secondary Objective

The secondary objective is to assess the efficacy of etrasimod on clinical response, symptomatic response and remission, endoscopic changes, corticosteroid-free remission, and mucosal healing in subjects with moderately to severely active UC at timepoints up to 52 weeks of treatment.

2.3. Safety Objective

The safety objective is to assess the long-term safety of etrasimod after daily doses of 2 mg for up to 52 weeks in subjects with moderately to severely active UC.

2.4. Other Objectives

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

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of etrasimod 2 mg in subjects with moderately to severely active UC. The study consists of a 28-Day Screening Period, a 12-Week Treatment Period, a 40-Week Treatment Period, and a 2-Week and 4-Week Follow-Up Period (Figure 1). Eligible subjects will be randomized (2:1 ratio) to receive either etrasimod (2 mg once daily) or matching placebo (once daily) in a double-blind fashion for up to 52 weeks of treatment (12-Week Treatment Period + 40-Week Treatment Period). 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 subject population will include (approximately 50% of subjects in each of the following categories):

1. Subjects who have had an inadequate response to, loss of response to, or intolerance to conventional therapy and are naïve to biologic or JAK inhibitor therapy.
2. Subjects who have had an inadequate response to, loss of response to, or intolerance to a biologic or JAK inhibitor (subjects in this category may have received prior conventional therapy).

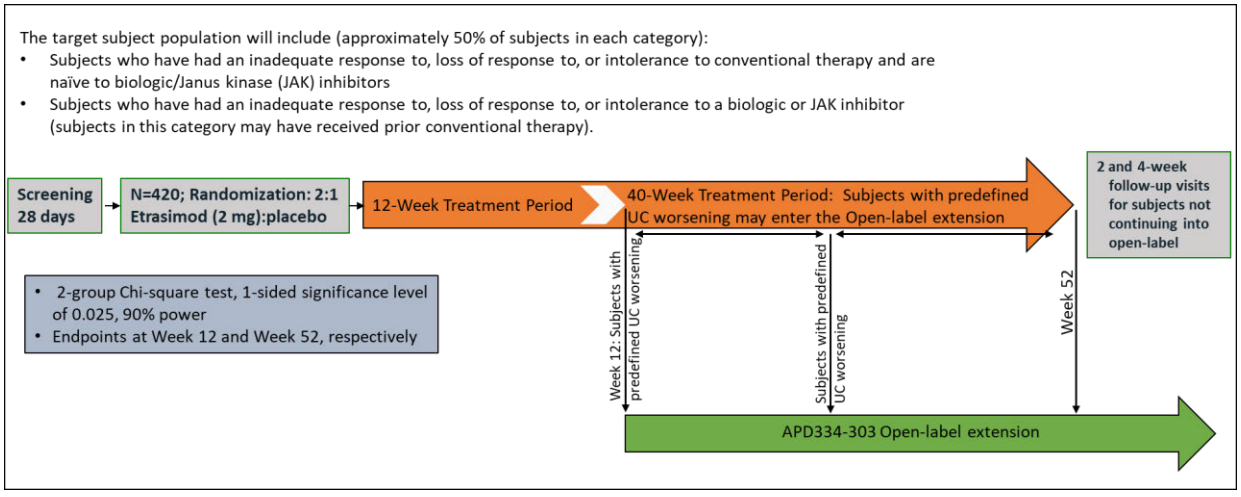
Subject eligibility will be determined during a 4-Week (28-Day) Screening Period. Entry criteria will be based on confirmation of moderately to severely active UC, defined by an MMS of 4 to 9, which includes an endoscopic score (ES) ≥ 2 and rectal bleeding (RB) score ≥ 1.

At the end of the 12-Week Treatment Period, subjects will undergo Week 12 efficacy and safety assessments and be evaluated for clinical response/remission as well as UC disease worsening. Subjects whose UC condition in the opinion of the Investigator has not improved or has worsened, compared with baseline (Week 0/Day 1), as defined in Section 5.1.1 and who meet other eligibility criteria will have the option to enter an OLE study (Study APD334-303).

Subjects must complete Week 12 to be eligible for the OLE. Subjects who do not meet disease worsening criteria, including those demonstrating clinical response/remission at Week 12 will continue into the 40-Week Treatment Period and continue their double-blind treatment. Disease worsening will continue to be monitored by Investigators through the 40-Week Treatment Period (ie, from Weeks 13 to 52). Subjects who either experience disease worsening in the 40-Week Treatment Period or complete all study procedures at Week 52 will have the option to enroll into the OLE study if they meet all eligibility criteria.

Subjects 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 visit (Table 7).

Figure 1: Study Design



JAK, Janus kinase; UC, ulcerative colitis

3.2. Rationale for Study Design

This study is designed to evaluate the efficacy and safety of etrasimod in subjects with moderately to severely active UC. Subjects may continue existing nonbiologic therapy for UC

(eg, 5-ASA, corticosteroids) per the concomitant medication and dose stabilization criteria. As preexisting background therapy is allowed, a placebo comparator is justified.

The duration of study treatment is up to 52 weeks, which includes 12- and 40-Week Treatment Periods. The 40-Week Treatment Period is expected to provide adequate time for separation of efficacy effects between etrasimod and placebo. The 2-Week and 4-Week Follow-Up visits will provide off-treatment safety information.

The etrasimod dose of 2 mg once daily is based on findings of previous Phase 1 and Phase 2 studies, and in particular data from the Phase 2 APD334-003 placebo-controlled study. In the APD334-003 study, subjects received etrasimod 1 mg, etrasimod 2 mg, or placebo. Subjects 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 (estimated least squares mean [standard error] difference from placebo: –1.27 [0.55]; p = 0.0100), and higher percentage of subjects 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 subjects, respectively; treatment-related TEAEs were reported for 7.7%, 10.0%, and 5.6% of subjects, respectively; serious adverse events (SAEs) were reported for 5.8%, 0%, and 11.1% of subjects, respectively; and TEAEs leading to discontinuation of study treatment were reported for 5.8%, 8.0%, and 0% of subjects, respectively. No subjects 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.

The coprimary endpoints of clinical remission at Weeks 12 and 52 as assessed using the MMS, are standard, widely used, and are in accordance with the nonbinding US Food and Drug Administration (FDA) Draft 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.

As detailed in Section 10.2, the study is powered to the primary endpoint for demonstrating a statistically significant difference in clinical remission between etrasimod therapy and placebo at Week 52. The 2:1 randomization scheme will maximize the number of subjects receiving a potentially beneficial therapy.

Subjects meeting predefined eligibility criteria from the end of the 12-Week Treatment Period and during the 40-Week Treatment Period will be eligible to enter the APD334-303 OLE study (Section 5.1.1) provided they meet all entry criteria.

3.3. Study Duration

The study consists of a 28-Day Screening Period, a 12-Week Treatment Period, a 40-Week Treatment Period, and a 2-Week and 4-Week Follow-Up Period. The study duration is expected to be approximately 2.5 years.

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

3.4. Independent Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be utilized to monitor the safety of subjects and to enhance the integrity and credibility of the study. The roles and responsibilities of the DMC are described in detail in the DMC Charter.

The DMC will abide by the principles set forth in the FDA Guidance for Industry, *Clinical Trial Sponsors, Establishment and Operation of Clinical Trial Data Monitoring Committees* (FDA 2006). As part of its role, the DMC will conduct reviews of accumulating safety and efficacy data at specified intervals during the conduct of the trial, according to the guidelines detailed in the DMC Charter. DMC recommendations to the study team will be communicated in a blinded fashion (ie, treatment assignment for individual subjects will not be shared). To ensure the scientific integrity of the study, members of the DMC will not be directly involved in the ongoing management of the study.

In addition to members of the DMC, an independent statistician responsible for interacting with the DMC will have access to unblinded study data. This statistician will not be directly involved in the conduct of the study.

4. SELECTION OF STUDY POPULATION

The study population consists of men, women and adolescents (hereafter referred to as men and women), 16 to 80 years of age, inclusive, with moderately to severely active UC.

4.1. Inclusion Criteria

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

1. Men or women 16 to 80 years of age, inclusive, at the time of assent/consent. Enrollment of subjects < 18 years should be conducted only if acceptable according to local laws and regulations
2. Ability to provide written informed consent or assent (parent or legal guardian must provide consent for a subject < 18 years of age who has assented to participate in the study or as required per local regulations) and to be compliant with the schedule of protocol assessments

Disease-specific inclusion criteria:

3. 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
4. Active UC confirmed by endoscopy with ≥ 10 cm rectal involvement. Subjects with proctitis only at baseline who meet the other eligibility criteria for inclusion, including the endoscopic and rectal bleeding criteria for moderate to severe disease, will be capped at 15% of the total subjects enrolled

5. Moderately to severely active UC defined as MMS of 4 to 9, including an ES of ≥ 2 and RB score ≥ 1
6. Received a surveillance colonoscopy (performed according to local standard) within 12 months before baseline to rule out dysplasia in subjects with pancolitis > 8 years duration or subjects with left-sided colitis > 12 years duration. Subjects 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:

7. 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. Corticosteroids
c. Thiopurines

Biologic therapy or JAK inhibitor therapy

a. Antitumor necrosis factor alpha (TNFα) antibodies (eg, infliximab, adalimumab, golimumab, or biosimilars)
b. Anti-integrin antibodies (eg, vedolizumab)
c. Anti-interleukin 12/23 antibodies (eg, ustekinumab)
d. JAK inhibitors (eg, tofacitinib)

Note: The medication used to qualify the subject for entry into this category must be approved for the treatment of UC in the country of use and the subject must have received an adequate course of therapy based on local guidelines for that therapy.

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 tofacitinib, the subject must have received a dosing regimen consistent with the local product labeling and/or institutional standard of care.

Concomitant treatments:

8. Subjects 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, budesonide at a stable dose ≤ 9 mg/day, or equivalent steroid) provided the dose has been stable for the 4 weeks immediately prior to the screening endoscopy assessment (Note: Subjects on existing oral corticosteroid therapy will be tapered during the 40-Week Treatment Period.)
   - Immunosuppressive agents such as oral azathioprine (AZA) or 6-mercaptopurine (6-MP) must be discontinued ≥ 2 weeks prior to randomization
   - Probiotics (eg, Culturelle®, *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:

9. 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
10. 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. Subjects with an isolated total bilirubin and normal AST and ALT diagnosed with Gilbert's syndrome may participate
11. 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
12. 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. Nonpregnant 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) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal, or transdermal
   - Progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injected, or implanted
   - Intrauterine device (IUD)
   - Intrauterine hormone-releasing system
   - Bilateral tubal occlusion
   - Vasectomized partner, provided that partner is the sole sexual partner of the female of childbearing potential trial subject 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 subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not acceptable

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

4.2. Exclusion Criteria

Subjects 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 subject 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 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 IV steroids given is acceptable)
5. Positive assay or stool culture for pathogens (ova and parasite examination, bacteria) or positive test for *Clostridioides difficile* (formerly known as *Clostridium difficile*) toxin at screening (If *C. difficile* is positive, the subject 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 subject 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 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 prerandomization 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 prerandomization 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 subjects 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 criteria:

- Subjects 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
- Subjects 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. Subjects 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 intravenous medication ≤ 14 days prior to randomization, or that may worsen (in the opinion of the Investigator) if the subject 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 (detectable HBV DNA, or positive for hepatitis B surface antigen [HBsAg], or negative for HBsAg and positive for antihepatitis B core antibody 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) or 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. Treatment with ≥ 3 biologic agents or ≥ 2 biologics plus a JAK inhibitor approved 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 and 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. Chronic use of therapies that moderately/strongly inhibit/induce cytochrome P450 (CYP) 2C8 and 2C9 metabolism and inhibitors of UGT1A7 ≤ 4 weeks prior to randomization

5. REMOVAL OF SUBJECTS FROM STUDY TREATMENT OR ASSESSMENT

5.1. Discontinuation from Study Treatment

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

- Worsening of disease (Note: If a subject discontinues double-blind treatment at any time starting with the Week 12 assessment, the subject may be eligible to enter the APD334-303 OLE [Section 5.1.1])
- Adverse event that in the judgement of the Investigator and/or Medical Monitor the subject should not continue study treatment
- Subject noncompliance with the protocol or study treatment that is considered significant by the Medical Monitor
- Investigator decision
- Withdrawal by subject or parent/guardian
- Lack of efficacy
- Lost to follow-up
- Study termination by Sponsor
- Other, non-adverse event

A subject'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
- Subjects 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 ECG changes at any time during the 4-hour monitoring period on Day 1 or Day 2 (as applicable) (Section 9.4.2.1)
- Subjects who have not met the discharge criteria on Day 1 after ≥ 4 hours of extended monitoring, or Day 2 by 4 hours post-dose (Table 4).
- Pregnancy (Section 9.10.9)
- 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.

Subjects who discontinue treatment prematurely, regardless of the reason, should be instructed to return for an Early Termination (ET) visit within 7 days of the last administration of study treatment (Table 7 and Table 8) and before initiation of any new treatments to complete all of the ET assessments. If a subject 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 of 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 administration of study treatment, the 4-Week Follow-Up visit is not required unless the absolute lymphocyte count (ALC) is not within normal limits.

5.1.1. Discontinuation from Double-Blind Treatment for Disease Worsening

Starting with the Week 12 assessment, subjects whose UC condition in the opinion of the Investigator has not improved or has worsened, compared with baseline (Week 0/Day 1), may be eligible to enroll in the OLE Study (APD334-303) provided their ES is ≥ 2 and they meet one of the following entry criteria:

- RB subscore ≥ 2 at 2 timepoints at least 7 days and no more than 14 days apart
- RB + SF subscores ≥ 4 at 2 timepoints at least 7 days and no more than 14 days apart
- RB subscore ≥ 2 or RB + SF subscores ≥ 4 (in any order) at 2 timepoints at least 7 days and no more than 14 days apart

For subjects discontinuing prior to Week 52, an endoscopic evaluation is required to confirm eligibility for the OLE. An endoscopy should be performed upon the appearance of UC symptoms but no more than 14 days after the second timepoint for symptom criteria above; however, a proctosigmoidoscopy does not need to be repeated if performed within the last 4 weeks.

5.2. Discontinuation from the Study

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

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

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

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

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to attend a required onsite, offsite, virtual, or hybrid visit:

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

Should the subject 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 subjects
- Subject 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 IECs/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 International Council for Harmonisation (ICH) guideline for Good Clinical Practice (GCP).

6. STUDY TREATMENTS

6.1. Treatments Administered

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

Table 1: Study Treatment

Study treatment name:	Etrasimod	Placebo
Dosage formulation:	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 [redacted]. APD334 [redacted] 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 2 mg.

The placebo tablet formulation is composed of excipients [redacted]. 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, subjects should wait and take their dose at the study site after blood draws for PK and after all pre-dose 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 eCRF.

6.3.1. Instructions for Missed Dose(s)

Subjects 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 subject 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 subject's electronic diary (eDiary), as indicated in the Schedule of Assessments, Table 7 and Table 8. Subjects should be instructed to contact the Investigator if they miss more than 2 consecutive doses.

Subjects who 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 must contact the Investigator to discuss treatment re-initiation. The subject 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 subject 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 Subjects to Treatment

Subjects 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.

Subjects 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 subject will be dispensed blinded study treatment at study visits (Table 7 and Table 8).

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 subject receives will not be disclosed to the Investigator, study site staff, subject, 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 subject emergency medical care. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted to provide appropriate medical care. Subject 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 subject'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 electronic case report form (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 subject's treatment assignment for the purpose of regulatory reporting.

If a subject's treatment assignment is unblinded prior to Week 12 for any reason, they will be discontinued from the study. Subjects who are unblinded on or after Week 12 may be eligible to enroll into the OLE study (Section 5.1.1).

6.6. Treatment Compliance

It is the Investigator's responsibility to ensure that subjects are correctly instructed on how to take their study treatment and that each subject 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. An up-to-date treatment inventory/dispensing record must be maintained as described in Section 8.4.

Subject compliance will be based on tablet count. Tablet counts < 80% or > 120% of the expected value between visits should be documented as a protocol deviation. If there is a discrepancy between the tablet count and the subject's compliance per the eDiary, it should be discussed with the subject and 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 subject 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 subjects who are not already receiving them. Immunosuppressive agents such as oral AZA or 6-MP must be discontinued ≥ 2 weeks prior to randomization.

Subjects 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, budesonide at a stable dose ≤ 9 mg/day, or equivalent steroid) is allowed to be continued during the 12-Week Treatment

Period provided the dose has been stable for the 4 weeks immediately prior to the screening endoscopy assessment; however, subjects will be tapered off corticosteroids during the 40-Week Treatment Period (Section 6.7.2.2).

6.7.2.2. Corticosteroid Taper

During the 12-Week Treatment Period, subjects are to maintain their stable baseline corticosteroid dose.

Following the Week 12 assessment, corticosteroids should be tapered for subjects entering the 40-Week Treatment Period. The recommended tapering schedule for oral corticosteroids (other than budesonide extended-release tablets [budesonide MMX]) is as follows:

a. Dose > 10 mg/day prednisone or equivalent: Taper daily dose by 5 mg/week until receiving 10 mg/day, and then continue tapering at 2.5 mg/week until 0 mg/day
b. Dose ≤ 10 mg/day prednisone or equivalent: Taper daily dose by 2.5 mg/week until 0 mg/day

The recommended tapering schedule for subjects receiving oral budesonide MMX 9 mg/day is to reduce tablets to 9 mg every other day for 2 weeks, followed by 9 mg every third day for 2 weeks, and then discontinue.

For subjects who cannot tolerate the corticosteroid taper without recurrence of clinical symptoms of either UC or steroid withdrawal, the corticosteroid dose may be increased (up to the dose at study entry if required), but tapering should begin again within 2 weeks.

6.7.3. Prohibited Concomitant Therapy

The following concomitant medications are prohibited during the study:

- 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 8 weeks after the last dose of study treatment
- Moderate/strong inhibitors or inducers of CYP2C8 and CYP2C9 (Table 2; for additional information, refer to (Flockhart 2019)

Table 2: Cytochrome P450 Inhibitors and Inducers

Cytochrome P450	Inhibitors (Strong/Moderate)	Inducers (Strong/Moderate)
CYP2C8	Clopidogrel, gemfibrozil, deferasirox, teriflunomide	Rifampin
CYP2C9	Fluconazole, amiodarone, felbamate, miconazole, piperine	Aprepitant, carbamazepine, enzalutamide, rifampin, ritonavir

CYP, cytochrome P450

- 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
- Inhibitors of UGT1A7
- 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), 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
- Intravenous 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. SUBJECT RESTRICTIONS

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

- Poppy seeds: Consumption of poppy seeds within 48 hours prior to drug screening may cause a positive drug screen. Subjects 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: Subjects 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 country requirement.

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 subject attends a virtual visit (see 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 subject 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

At each visit, previously dispensed study treatment tablets will be collected by the Investigator or qualified individual and compliance assessed.

The Investigator 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 and will be monitored by counting of unused medication from individual bottles returned by the subject at each visit.

8.5. Study Treatment Retention and Disposal

All study treatment will be reconciled by the clinical monitor and then returned or destroyed according to applicable country regulations. 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 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 Schedules of Assessments (Table 7 and Table 8). 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 subject should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the Schedules of Assessments (Table 7), 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 (see Section 9.6 and Table 7 and Table 8), subjects 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 subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

9.2. Subject Information

9.2.1. Informed Consent

The Investigator, or a person designated by the Investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative, parent(s), or legal guardian and the subject's assent (for a minor subject according to local regulations) when applicable, before any study-specific activity is performed (Section 11.3 for additional details).

9.3. Screening and Eligibility

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

Screening procedures must be completed within 28 days prior to receiving the first dose of study treatment (Table 7). The Screening Period may be extended for subjects who require additional diagnostic testing/consults to determine status of either latent TB or *C. difficile* infection. If the subject 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. pulmonary function tests [PFTs], optical coherence

tomography [OCT]) due to testing availability. The Medical Monitor must be consulted prior to extension in each case.

Subjects 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 subjects 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

Subjects 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 subject must be reconsented prior to each screening attempt.

Subjects with a Screening visit or Week 0/Day 1 prerandomization 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 subject requires prophylactic therapy for latent TB, they may be rescreened as outlined in Section 4.2.

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

9.3.3. Demography and Other Subject Characteristics

Demographics including year of birth, sex at birth, Hispanic ethnicity, and race as described by the subject 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. Subjects 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 (Section 4.1, Inclusion Criterion 7, for details).

All medications taken and procedures carried out within 30 days prior to the first study treatment administration 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 subject's eligibility to the study, a complete medical history of each subject 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 subject'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 heart rate, 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. Subjects 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), 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 subject 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 5-12 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 SF and RB are derived from the subject 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. Subjects 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 ≥ 2 and RB score ≥ 1, for the subject to be eligible for randomization.

– For the normal SF, it is essential for the subject to be asked to identify how many stools he or she has in a 24-hour period when in remission from UC. Subjects should be instructed that a stool is defined as a trip to the toilet when the subject has either a bowel movement, or passes blood alone, blood and mucus, or mucus only. If the subject does not report that he or she has achieved remission, then the subject 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: Prerandomization

At the Week 0/Day 1 visit (Table 7), prior to randomization, a 12-lead ECG in the supine position and resting vital signs in the sitting position (heart rate, 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.

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

- Sitting vital sign assessment: heart rate < 50 bpm OR systolic BP < 90 mm Hg OR diastolic BP < 55 mm Hg
- 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).

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

Subjects 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 7). 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). For the Week 12 through Week 48 Visits, and ET Visit, a study visit window of ± 7 days is permitted. For the Week 52 Visit, a study visit window of ± 14 days is permitted. Study visits should be scheduled for the morning.

The subscores for SF and RB are derived from the subject 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:

- Questionnaire administration
- Adverse event review
- Vital signs
- 12-lead ECG (as indicated in the Schedules of Assessments, Table 7 and Table 8)
- Physical examination
- EIMs (as indicated in the Schedules of Assessments, Table 7 and Table 8)
- PFT (as indicated in the Schedules of Assessments, Table 7 and Table 8)
- OCT (as indicated in the Schedules of Assessments, Table 7 and Table 8)
- Blood sample collection for laboratory tests and pre-dose PK sampling

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

Prerandomization (ie, pre-dose/baseline) vital signs (resting heart rate, systolic and diastolic BP, body temperature, and respiratory rate) will be used as the Baseline measurement. The pre-dose heart rate measurement will be used for comparison to the post-dose measurement. Subjects should receive the first dose of study treatment before 12:00 PM (noon).

First Dose Cardiac Monitoring

In-clinic cardiac monitoring, of at least 4 hours, will occur on Day 1 and will include the following (Table 3):

- Full baseline vital signs (heart rate, systolic and diastolic BP, body temperature, and respiratory rate) and a 12-lead ECG (taken with the subject in the supine position) will be assessed prerandomization.
- After the first dose of study treatment on Day 1, subjects must remain under observation in the clinic for at least 4 hours.
- At Hours 1, 2, and 3 (± 15 minutes) post-dose, the heart rate and systolic and diastolic BP will be assessed with the subject in the sitting position, with the time recorded. If the subject has a heart rate < 50 bpm or if cardiovascular symptoms develop, then the subject 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, heart rate and systolic and diastolic BP will be assessed with the subject in the sitting position and a 12-lead ECG (with the subject in the supine position) will be performed. Subjects may be discharged from the clinic after the 4-hour assessment if they meet the criteria

described in Table 4. Subjects not meeting the discharge criteria will require extended monitoring as described below.

- Subjects experiencing a clinically relevant treatment-related symptomatic event (eg, chest pain, dizziness, palpitations, or syncope) associated with reduction of the heart rate or clinically relevant 12-lead ECG changes at any time during the 4-hour monitoring period must be discontinued from treatment (Table 5).

Table 3: Procedures to be Performed During the Monitoring Period

Procedure	Pre-Dose	Hours 1, 2, 3 Post-Dose[a]	Hour 4 Post-Dose[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.

Table 4: Discharge Criteria After Cardiac Monitoring

Subjects will be released from the clinical site after dosing on Day 1 (but no sooner than 4 hours post-dose) when they fulfill the following discharge criteria:
• Heart rate ≥ 50 bpm or no more than 10 bpm lower than the pre-dose (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)

AV, atrioventricular
Note: Subjects 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.

Extended Cardiac Monitoring

Subjects who do not meet discharge criteria at 4-hours post-dose will require extended cardiac monitoring:

- Vital signs will be assessed hourly and 12-lead ECG may be performed, as clinically indicated, until the subject meets the discharge criteria (Table 4).
- The Medical Monitor should be contacted if the subject does not meet the discharge criteria after ≥ 4 hours of extended cardiac monitoring.
- Any subject 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 subjects 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 subject meets the discharge criteria (Table 4).
- Subjects 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 heart rate or clinically relevant change in 12-lead ECG, may be discharged provided they meet the

discharge criteria (Table 4), and as deemed appropriate by the Investigator; however, these subjects must return on Day 2 for the second dose and will be re-monitored as on Day 1. These subjects 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 subject meets the discharge criteria (Table 4).

Study Treatment Discontinuation Related to Post-dose Cardiac Monitoring

A complete list of reasons for study treatment discontinuation is provided in Section 5.1. Reasons for study treatment discontinuation specific to post-dose cardiac monitoring are provided in Table 5. The Medical Monitor should be contacted before discontinuing a subject.

Table 5: Discontinuation of Study Treatment-Related to Post-dose Cardiac Monitoring

Reasons for Study Treatment Discontinuation Related to Post-Dose Cardiac Monitoring[a]
• Subjects 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).
• Subjects who have not met the discharge criteria on Day 1 after ≥ 4 hours of extended monitoring, or Day 2 by 4 hours post-dose.

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

Cardiac Monitoring Upon Treatment Re-Initiation Following Dose Interruption

Subjects should undergo the same first dose cardiac monitoring procedures as the original treatment initiation when study treatment dosing is interrupted for:

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

9.4.3. Enrollment in Open-Label Extension Study APD334-303

At the Week 12 assessment a determination will be made regarding continuation into the 40-Week Treatment Period or eligibility for entry into the OLE (Section 5.1.1).

Subjects who discontinue treatment prematurely should have an ET visit as indicated in the Schedules of Assessments (Table 7 and Table 8). If the ET visit is within 4 weeks of the last proctosigmoidoscopy and biopsy, these procedures do not need to be repeated.

9.5. Follow-Up Period

For subjects not participating in the OLE study, a follow-up visit, will be performed at 2 and 4 weeks after the last administration of study treatment as indicated in the Schedules of Assessments (Table 7 and Table 8).

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, subjects 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 9.10.8.2.2).

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), virtual (eg, telephone, video conference), or 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 on different days within the study visit window.

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).

Pregnancy testing and central laboratory assessments (eg, blood, stool, and urine samples) can be performed by either onsite visit or offsite visit.

Assessments or procedures that may be conducted virtually, if allowed by local law and regulation, include for example: informed consent process including obtaining written informed consent, medical and medication history to assess eligibility criteria, review of demographic information, social history, AE query, review of concomitant medications, eDiary training, and compliance review/monitoring including study drug administration and questionnaires.

During a virtual assessment, a subject 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 subject 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. Subjects must return the dispensed bottle with the remaining tablets along with any empty bottles to the study site at the next onsite visit. See 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 Schedules of Assessments (Table 7 and Table 8).

9.7. Pharmacokinetics

Blood samples for analysis of etrasimod, and if warranted M3 (AR503641) and other metabolite(s) of interest, will be collected at the following timepoints from all subjects who received at least 1 dose of study drug (etrasimod or placebo):

- Pre-dose and at 4 hours (± 15 minutes) post-dose (after 12-lead ECG) on Week 0/Day 1
- Pre-dose (trough; within 60 minutes prior to dosing) at Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, and 52
- 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

Subjects 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, and if warranted M3 (AR503641) and other metabolite(s) of interest. 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, metabolite 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, [redacted] 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 subject-reported RB and SF scores; therefore, the importance of daily recording of RB and SF by subjects 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 subject-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 subject 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 subject-reported measure. This item reports the number of stools in a 24-hour period, relative to the normal number of stools for that subject in the same period, on a 4-point scale (Appendix 3). A stool is defined as a trip to the toilet when the subject 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 subject in a daily eDiary. The reference "normal" SF for that subject will be recorded electronically at the Screening Visit and is the number of stools in a 24-hour period when the subject is in remission. If the subject 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 total Mayo Score. The PGA summarizes the Investigator's assessment of the subject'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 7 and Table 8). 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), at Week 12, and at Week 52/Early Termination visit. Additional proctosigmoidoscopies may be performed to confirm disease worsening and are required for qualification into the OLE (Section 5.1.1).

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 endoscopic score. A detailed image review charter from the central reading laboratory will outline the endoscopic procedures, video recordings, and equipment. For each subject, 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 subjects with pancolitis > 8 years duration or subjects with left-sided colitis > 12 years without a surveillance colonoscopy within 12 months prior to baseline (Section 4.1, Inclusion Criterion 6), 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 [redacted]. Up to 4 biopsy pairs (ie, total 8) will be collected from the most affected area 15 to 25 cm from the anal verge. For subjects with proctitis only at baseline, biopsies should be taken 8 to 10 cm from the anal verge.

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 (Appendix 4) indices 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 7 and Table 8) specific systems (such as eyes, liver, skin, and joints) will be examined for EIMs for UC.

9.8.3. Additional Health-Related Subject-Reported Outcomes

Subject-reported quality of life instruments will be completed electronically and checked for completeness at the study site as indicated in the Schedules of Assessments (Table 7 and Table 8) and will be used in support of the efficacy outcomes.

Inflammatory Bowel Disease Questionnaire (IBDQ): The IBDQ is a validated 32-item questionnaire used to assess health-related quality of life (HRQoL) in subjects with IBD (UC and CD). Response to each of the questions is graded from 1 to 7 with overall score ranging from 32 (very poor HRQoL) to 224 (perfect HRQoL).

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 subject. 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 if and when available.

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

Work Productivity and Activity Impairment Questionnaire – Ulcerative Colitis (WPAI-UC): The WPAI-UC consists of 6 questions asking about the effect of UC on the subject's ability to work and perform regular activities.

Urgency Numeric Rating Scale (NRS): The urgency NRS is a single item that measures the severity for the urgency (sudden or immediate need) to have a bowel movement in the past 24 hours using an 11-point NRS ranging from 0 (no urgency) to 10 (worst possible urgency).

Abdominal Pain NRS: The abdominal pain NRS is a single item that measures the "worst abdominal pain in the past 24 hours" using an 11-point NRS ranging from 0 (no pain) to 10 (pain as bad as can imagine).

9.8.4. Efficacy-Related Biomarkers

Samples for biomarker assessments will be collected according to the Schedules of Assessments (Table 7 and Table 8). 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 subject 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 and follow-up periods. 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.

[redacted]

[redacted]

9.9. Genetics

Genetics will be evaluated in this study to assess genetic variation that may impact response to treatment, metabolism, and mechanism of action of etrasimod. DNA may be used for immunophenotyping by epigenetic profiling.

A blood sample for DNA isolation will be collected from subjects who have consented to participate in the genetic analysis component of the study. Participation is optional. Subjects who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the subject.

Details on the processes for collection and shipment and destruction of these samples can be found in the Laboratory Manual.

9.10. 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 9.10.8.1). Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

9.10.1. Physical Examination

Full and symptom-directed physical examinations will be performed according to the Schedules of Assessments (Table 7 and Table 8).

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.

9.10.2. Vital Signs

Resting vital signs measurements will be performed according to the Schedules of Assessments (Table 7 and Table 8) with the subject 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 subject'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. Subject's legs should not be crossed during the evaluation.

9.10.3. 12-Lead Electrocardiogram

All 12-lead ECGs will be performed according to Section 9.4.2.1 and the Schedules of Assessments (Table 7 and Table 8), 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 subject in the supine position. Every attempt should be made to ensure the subject 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 subject 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 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.

9.10.4. Pulmonary Function Test

Pulmonary function tests will be performed according to the Schedules of Assessments (Table 7 and Table 8) and includes FEV_1 and FVC measurements. All subjects will have PFTs performed at Screening, Week 12, and Week 52, 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 assessment is only required if clinically indicated.

Subjects with a history of mild pulmonary disease (eg, asthma, chronic obstructive pulmonary disease) will have additional PFTs performed at Week 32. Subjects 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.

Subjects 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 subjects and site staff is paramount, so it is at the Investigator's discretion whether PFT can be safely administered to trial subjects during the treatment period. The Investigator should evaluate on a case-by-case basis how best to proceed based on the subject'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, COVID-19 transmission), then this decision and rationale should be appropriately captured in the subject'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.

9.10.5. Ophthalmoscopy and Optical Coherence Tomography

A complete ophthalmoscopy and OCT assessment will be performed according to the Schedules of Assessments (Table 7 and Table 8). 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. 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 subject across timepoints.

Screening visit:

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

- Ophthalmologic history
- Best corrected visual acuity measurement (using Snellen chart internationally [if available])
- Ophthalmoscopy (may include contact lens biomicroscopy to examine the macula and optic disc). A dilated fundus exam should be performed in all subjects at the

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

- Measurement of central foveal thickness by OCT (recorded in micrometers; required for all subjects 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. Subjects 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). Subjects 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 subjects with uveitis findings on ophthalmic exam, additional testing should be considered (for example, fluorescein angiogram).

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

9.10.6. Tuberculosis Screening and Chest X-Ray

All subjects will complete TB screening to determine eligibility. A TB screening questionnaire will be completed during the Screening Period by the PI or delegated site staff for each subject and applicable information will be entered into the eCRF. For subjects residing in countries with a high burden of TB or multi-drug resistant (MDR) TB as identified by WHO, the TB screening questionnaire will be completed at every study visit (Appendix 2). For subjects who are receiving TB prophylaxis treatment, the TB questionnaire will be completed at every study visit (until TB prophylaxis treatment course is completed).

9.10.7. Clinical Laboratory Tests

Refer to Table 6 for the list of clinical laboratory tests to be performed and the Schedules of Assessments (Table 7 and Table 8) for timing and frequency for each test. 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 pre-dose. 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 subject'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 7 and Table 8), 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 subject 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 subjects with notable lymphopenia, please refer to Section 9.8.4.

Table 6: Clinical Laboratory Tests

SCREENING Only

Virology

HIV, HBsAg, 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, QuantiFERON

PREGNANCY TESTING

Serum pregnancy test human beta-chorionic gonadotropin (β-hCG) - Screening

Urine β-hCG (only for women of childbearing potential)

CLINICAL CHEMISTRY, HEMATOLOGY, AND COAGULATION

Hematology

Hematocrit
Hemoglobin
Mean corpuscular hemoglobin
Mean corpuscular hemoglobin concentration
Mean corpuscular volume
Platelet count
Red blood cell count
White blood cell count with differential[a]
TBNK[a]

Coagulation

Prothrombin time
Activated partial thromboplastin time
International normalized ratio

Serum Chemistry

Albumin
Alkaline phosphatase
Alanine aminotransferase
Aspartate aminotransferase
Bicarbonate
Blood urea nitrogen
C-reactive protein
Calcium
Chloride
Creatinine
Creatine kinase
Direct bilirubin
Glucose
Gamma-glutamyl transferase
Lactate dehydrogenase
Phosphorus
Potassium
Sodium
Thyroid-stimulating hormone
Thyroxine free
Total bilirubin
Triiodothyronine free
Total cholesterol
Total protein
Triglycerides
Uric acid

URINALYSIS

Appearance
Bilirubin
Color
Glucose
Ketones
Microscopic examination of sediment
Nitrite
Occult blood
pH
Protein
Specific gravity
Urobilinogen

Table 6: Clinical Laboratory Tests (Continued)

BIOMARKERS
Lymphocytes[a,b]
hs-CRP[b]
Fecal calprotectin[b]
Immunophenotyping
Proteomics
RNA Transcriptomics
Fecal microbiome
GENETICS
Genomic DNA (optional)
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 subject becomes symptomatic, including worsening or return of disease activity.
β-hCG, human beta-human chorionic gonadotropin; HBsAg, hepatitis B surface antigen; 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, and natural killer lymphocytes; WBC, white blood cells

9.10.7.1. Screening

9.10.7.1.1. Drugs of Abuse

A standard urine drug screen will be performed (Table 6). Subjects who test positive will be assessed for eligibility for study participation by the Investigator.

9.10.7.1.2. 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 Schedules of Assessments (Table 7 and Table 8). A monthly home pregnancy test in non-visit months should be performed in countries where allowed per local regulation and any positive result immediately reported to the study site. If not allowed per local regulations, this pregnancy test will be performed on site during an unscheduled visit. If at any point there is a case of a positive urine β-hCG test, the subject 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 subject will be withdrawn from the study treatment and all the necessary follow-up assessments will be conducted as per Section 9.10.9. If the serum test is negative, the subject 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.

9.10.7.1.3. Virology

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

9.10.7.2. Clinical Chemistry, Hematology, Coagulation, and Urinalysis

Clinical chemistry, hematology, coagulation, and urinalysis parameters that will be assessed during the study are identified in Table 6.

Subjects 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 9.6 for timing of blood draws for PK).

9.10.8. Adverse Events

9.10.8.1. Definitions

9.10.8.1.1. Adverse Event

An adverse event is any untoward medical occurrence in a subject or clinical investigational subject 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

9.10.8.1.2. 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 subject 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 subject's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a subject 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 subject 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.

9.10.8.1.3. 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).

9.10.8.1.4. 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 progressive multifocal leukoencephalopathy (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.

9.10.8.1.5. 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.

9.10.8.1.6. Relationship

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

Not Related:	The AE is definitely caused by the subject's clinical state or the study procedure/conditions.
Unlikely Related:	The temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
Probably Related:	The AE follows a reasonable temporal sequence from administration of the drug and cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental, or toxic factors, or other modes of therapy administered to the subject.
Related:	The AE 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.

9.10.8.2. Eliciting and Recording Adverse Events

9.10.8.2.1. Eliciting Adverse Events

Subjects 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.

9.10.8.2.2. Recording Adverse Events

The adverse event reporting period for safety surveillance begins when the subject 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.

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 subject, elicited during subject 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 be described on the eCRF in the narrative description field.

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.

9.10.8.2.3. 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.

9.10.8.3. Reporting Adverse Events

All SAEs are subject to reporting requirements.

9.10.8.3.1. Serious Adverse Events

Any adverse event considered serious by the Investigator or Sub-investigator or that meets serious criteria should be reported to the designated safety contact **within 24 hours of becoming aware of the event (or in India within 24 hours of event occurrence)**. Enter the SAE information into eCRF, and send other available pertinent information (eg, hospital records, laboratory results, etc) to the designated Sponsor Contact.

IQVIA Pharmacovigilance

[redacted]

If additional information is required or becomes available for a previously reported SAE, entry of the new information into eCRF should be completed **within 24 hours of awareness.**

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

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

9.10.8.3.2. Serious, Unexpected Adverse Drug Reactions

All ADRs that are both serious and unexpected are subject to expedited reporting to regulatory agencies. 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 AE is expected or unexpected.

9.10.9. Pregnancy

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

Details of all pregnancies in female subjects and female partners of male subjects 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 via the Pregnancy Report Form to the designated Sponsor Contact **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.

9.11. 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.

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

1. Closely monitor the subject for any AE/SAE and laboratory abnormalities and follow the AE reporting process, including contacting the Medical Monitor.
2. 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.
3. Document the total quantity of the excess dose, taking into consideration the duration of the overdose in the eCRF and the time frame.

Subjects 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 subject.

10. PLANNED STATISTICAL METHODS

10.1. General Considerations

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

10.2. Determination of Sample Size

Based on a 2-group Fisher's exact test, a 1-sided significance level of 0.025, and a 2:1 randomization ratio, 420 total subjects (280 etrasimod, 140 placebo) are required to achieve 93.4% power to detect a difference of 13.5% in the primary endpoint of clinical remission at Week 52 between the etrasimod treatment group (23.5%) and the placebo treatment group

(10.0%). With this sample size, there will be 96% power to detect a difference of 12.5% in the other primary endpoint of clinical remission at Week 12, assuming a placebo rate at 6.0%. The lower bound of overall power for both primary endpoints (as coprimary endpoints) is at least 90%; and since the two primary endpoints are expected to be at least moderately positively correlated, the actual overall power to reject both of their null hypotheses is likely to be greater than 90%.

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 subjects, who receive at least 1 dose of study treatment. Under this approach, subjects 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 subjects 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. Subjects 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 subjects, who receive at least 1 dose of study treatment and have a baseline and at least 1 post-randomization measurement. Under this approach, subjects 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 subjects 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 subjects who receive at least 1 dose of study treatment. For this set, subjects 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

Subjects with worsening of disease before Week 12 and subjects who meet the criteria for worsening disease after Week 12, as defined in Section 5.1.1, will be considered as having a treatment nonresponse outcome in the analysis of all endpoints, including the primary endpoint. In addition, subjects 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.

Subjects 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. Subjects who

discontinue the double-blind study for reasons other than worsening disease or 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, all subjects with missing data, regardless of reason for missingness, will be considered as non-responders.

In the main analysis of continuous or score endpoints, such as changes from baseline in MMS subscores, biomarker measures, urgency NRS, abdominal pain NRS, and health-related quality of life measures, subjects with missing data will be analyzed with their observed data only, 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 under several alternative assumptions regarding missing data, ie, data missing intermittently, after discontinuation from the double-blind study for reasons other than worsening diseases, or after initiation of excluded medications.

- An assumption of data missing at random (MAR) within each treatment group will be investigated. Missing data, eg, component scores of MMS at the planned assessment timepoints, will be imputed using multiple imputation methodology (Rubin 1987) under the MAR assumption. Binary responder-type endpoints will subsequently be computed from observed and imputed data and analyzed using the same method as in the primary analysis. Continuous endpoints will be analyzed using analysis of covariance based on observed and imputed values.
- 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 nonresponders among subjects 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 subjects with missing data. These subjects, regardless of the randomized treatment group, will be assumed to have a similar distribution of outcomes after discontinuation as subjects with available data in the placebo group. This is akin to modeling the missing outcomes as if the subjects continued on their background therapy only and accounting for the study effect observed in subjects 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:

- 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
- 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 of ≤ 1 (excluding friability)
- Endoscopic normalization: ES = 0
- Mucosal healing: ES of ≤ 1 (excluding friability) with histologic remission measured by a Geboes Index score < 2.0
- Symptomatic remission: SF subscore = 0 (or = 1 with a ≥ 1-point decrease from baseline) and RB subscore = 0
- Complete symptomatic remission: SF subscore = 0 and RB subscore = 0
- Symptomatic response: Decrease from baseline ≥ 30% in composite RB and SF subscores
- Noninvasive clinical response: A ≥ 30% decrease from baseline in composite RB and SF, and a ≥ 1-point decrease from baseline in RB subscore or an absolute RB subscore ≤ 1
- Histologic improvement: Geboes Index score < 3.1
- Histologic remission: Geboes Index score < 2.0
- Clinical remission using Total Mayo Clinic score: Total Mayo Clinic Score of ≤ 2 points with no individual subscore of > 1 point
- Clinical response using Total Mayo Clinic score: A ≥ 3-point and ≥ 30% decrease from baseline in Total Mayo Clinic score, and a ≥ 1-point decrease from baseline in RB subscore or an absolute RB subscore ≤ 1

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 (eg, Weeks 12 and 52). Complete details of the MMS symptom score computation method are provided Section 9.3.10 and Section 9.4.2.

10.6. Primary Endpoints

The primary efficacy endpoints will evaluate etrasimod versus placebo in:

- The proportion of subjects achieving clinical remission at Week 12
- The proportion of subjects achieving clinical remission at Week 52

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, histologic response and remission are based on the Geboes Index, and all other endpoints are based on MMS as defined in Section 10.5.

10.7.1. Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are:

- The proportion of subjects achieving endoscopic improvement at Week 52
- The proportion of subjects achieving endoscopic improvement at Week 12
- The proportion of subjects achieving symptomatic remission at Week 52
- The proportion of subjects achieving symptomatic remission at Week 12
- The proportion of subjects in clinical remission at Week 52 and who had not been receiving corticosteroids for ≥ 12 weeks prior to Week 52
- The proportion of subjects with mucosal healing at Week 52
- The proportion of subjects with mucosal healing at Week 12
- The proportion of subjects achieving clinical remission at both Weeks 12 and 52

10.7.2. Other Secondary Efficacy Endpoints

The other secondary endpoints are:

- The proportion of subjects who had not received corticosteroids for ≥4 weeks and achieved clinical remission at Week 52 among subjects receiving corticosteroids at baseline
- The proportion of subjects achieving clinical response at Week 52
- The proportion of subjects achieving clinical response at Week 12
- The proportion of subjects achieving clinical response at both Weeks 12 and 52
- The proportion of subjects with mucosal healing at both Weeks 12 and 52
- The proportion of subjects achieving endoscopic normalization at Week 52
- The proportion of subjects achieving endoscopic normalization at Week 12
- The proportion of subjects achieving endoscopic normalization at both Weeks 12 and 52
- The proportion of subjects achieving symptomatic remission at Weeks 2, 4, 8, 16, 20, 24, 32, 40, and 48
- The proportion of subjects achieving complete symptomatic remission at each study visit (Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, and 52)
- The proportion of subjects achieving noninvasive clinical response at each study visit (Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, and 52)

- The proportion of subjects achieving symptomatic response at each study visit (Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, and 52)
- The proportion of subjects achieving clinical remission at Week 52 among subjects achieving clinical response at Week 12

[redacted]

10.9. Other Efficacy-Related Endpoints

10.9.1. Health-Related Quality of Life

- Scores and change from baseline to Weeks 12 and 52 in the following:
  - IBDQ total score
  - UC-PRO/SS
  - SF-36, version 2, physical and mental component and domain scores
  - WPAI-UC
  - Urgency NRS

  - Abdominal pain NRS
- The proportion of subjects with UC -related hospitalizations
- The proportion of subjects requiring UC -related surgeries, including colectomy

10.9.2. Pharmacokinetics

- Plasma concentrations of etrasimod, and if warranted M3 (AR503641) and other metabolite(s) of interest, will be assessed from samples collected prior to dosing and 4 hours (± 15 minutes) post-dose (after 12-lead ECG) on Week 0/Day 1
- Plasma concentrations of etrasimod, and if warranted M3 (AR503641) and other metabolite(s) of interest, will be assessed from samples collected prior to dosing (trough) at Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 52 and at 2- 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.

10.9.3. Biomarkers

- Change from baseline in level of fecal calprotectin at Weeks 2, 4, 8, 12, 24, and 52
- Change from baseline in level of hs-CRP at Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, and 52
- Change and percentage change from baseline in lymphocyte counts at Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, and 52

10.10. 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
- Race
- 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 Total Mayo score ≤ 8 vs > 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 subjects in remission, remission percentages, difference in remission percentages, odds ratio, and associated 95% confidence intervals (CIs) and p-values.

There are multiple null hypotheses for the comparison of etrasimod and placebo in the primary and key secondary endpoints. The family-wise type-I error rate will be controlled at a fixed α level at 0.025 (1-sided) using the following testing procedure. First, the whole α will be spent on testing both of the primary endpoints. This study will be considered as an overall success only if both of the primary null hypotheses are rejected, each at the α level (as coprimary hypotheses). This study will be considered as a partial success if only one of the two primary null hypotheses are rejected at $\alpha/2$ if the other has $p > \alpha$.

Only if both of the primary null hypotheses are rejected, each at the α level, can testing proceed for the 8 key secondary endpoints. The method for such testing will be specified in the SAP, and it will control for the multiplicity of the 8 key secondary endpoints. Any key secondary endpoint that fails to be significant at the α level by this method to control multiplicity will be considered exploratory and thereby would only have nominal p-values. All other endpoints will be evaluated at α level of significance and reported with nominal p-values, without multiplicity adjustment.

Full details of the efficacy analysis 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 subject 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 12-lead ECG results will be tabulated.

10.13. Interim Analysis

The Sponsor may conduct an interim analysis for sample size re-estimation based on blinded (aggregate) data to assess the appropriateness of the assumptions used in the original sample size calculation. The planned sample size will not be reduced as a result of the re-estimation to ensure sufficient exposure data for safety assessment. An interim SAP will provide detailed interim analysis specifications. The SAP will be finalized prior to any interim analysis and will be provided to regulatory agencies in a timely manner. This interim analysis will not be used to evaluate efficacy or safety.

11. ETHICAL CONSIDERATIONS

11.1. Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP, ICH guidelines, and applicable regulatory requirements.

11.2. Institutional Review Board or Independent Ethics Committee Approval

Before initiating a study, the Investigator must have written and dated approval from the IRB/IEC for the study protocol, written ICF, subject recruitment materials and procedures (eg, advertisements or websites), and any other written information to be provided to subjects. Approval from the committee must be documented in a letter to the Investigator specifying the protocol number, protocol version, documents reviewed, and the date on which the committee met and granted the approval.

All documents subject to review during the study, including any modifications made to the protocol after receipt of IRB/IEC approval, must also be submitted to the committee for approval prior to implementation. The Investigator must also provide periodic reports as required and promptly report important safety information (ie, SAEs, new information that may adversely affect the safety of study subjects or the conduct of the study, deviations from or changes in the protocol to eliminate immediate harm to study subjects) and protocol violations, as appropriate, to the IRB/IEC.

As part of the Investigator's written application to the IRB/IEC, the Investigator should provide the committee with a current copy of the etrasimod IB. If the IB is updated during the study, the Investigator should supply an updated copy to the committee.

11.3. Informed Consent and Assent

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/assent (parent or legal guardian must provide consent for a subject < 18 years of age who has assented to participate in the study or as required per local regulations) may be obtained, the Investigator should provide the subject ample time and opportunity to inquire about details of the study and to decide whether to participate.

Prior to a subject's participation in the study, the IRB/IEC-approved ICF must be signed and personally dated by the subject and by the person who conducted the informed consent discussion. If a subject 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 subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written ICF or study materials to be available and/or supplied to subjects should receive the IRB/IEC's approval in advance of use. The subject will be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

During a subject's participation in the study, the subject 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 subjects.

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

In addition, prior to study participation, the subject must be informed that the records identifying the subject will not be made publicly available; if the results of the study are published, the subject'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 study subjects 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 subject, 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 subject's participation and/or the assessment of safety or efficacy in the study. Any significant protocol deviations affecting subject 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 subjects 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 subject 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 subject data in his/her own subject files. These subject 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 study subject. 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, subjects' 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:

- Subject 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 subjects 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 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.

15. REFERENCES

Brinkmann V, Billich A, Baumruker T, et al. Fingolimod (FTY720): Discovery and development of an oral drug to treat multiple sclerosis. *Nat Rev Drug Discov.* 2010;9(11):883-897.

FDA. Establishment and operation of clinical trial data monitoring committees. U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Clinical Trial Sponsors Web site. https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm127073.pdf. Published 2006. Accessed March 4, 2019.

FDA. Drug-induced liver injury: Premarketing clinical evaluation. U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry Web site. https://www.fda.gov/downloads/guidances/UCM174090.pdf. Published 2009. Accessed April 25, 2019.

FDA. Ulcerative colitis: Clinical trial endpoints. Guidance for Industry Web site. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM515143.pdf. Published 2016. Accessed March 1, 2019.

Flockhart DA. Drug Interactions Flockhart Table™. Indiana University, Department of Medicine, Clinical Pharmacology. https://drug-interactions.medicine.iu.edu/MainTable.aspx. Published 2019. Accessed November 15, 2019.

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

Kaser A, Zeissig S, Blumberg RS. Inflammatory bowel disease. *Annu Rev Immunol.* 2010;28:573-621.

Kornbluth A, Sachar DB, Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol.* 2010;105(3):501-523.

MacIntyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J.* 2005;26(4):720-735.

Marchal-Bressenot A, Salleron J, Boulagnon-Rombi C, et al. Development and validation of the Nancy histological index for UC. *Gut.* 2017;66(1):43-49.

Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. *Eur Respir J.* 2005a;26(1):153-161.

Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J.* 2005b;26(2):319-338.

Mosli MH, Feagan BG, Zou G, et al. Development and validation of a histological index for UC. *Gut.* 2017;66(1):50-58.

Nielsen OH, Li Y, Johansson-Lindbom B, Coskun M. Sphingosine-1-phosphate signaling in inflammatory bowel disease. *Trends Mol Med.* 2017;23(4):362-374.

Rowe WA, Lichtenstein GR. Inflammatory bowel disease. Medscape. https://emedicine.medscape.com/article/179037-overview. Published 2020. Accessed July 13, 2020.

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

Sandborn WJ, Peyrin-Biroulet L, Zhang J, et al. Efficacy and safety of etrasimod in a Phase 2 randomized trial of patients with ulcerative colitis. *Gastroenterology.* 2020;158:550-561.

Ungar B, Kopylov U. Advances in the development of new biologics in inflammatory bowel disease. *Ann Gastroenterol.* 2016;29(3):243-248. On file at Arena.

16. APPENDICES

APPENDIX 1: SCHEDULES OF ASSESSMENTS

Table 7: Schedule of Assessments – Screening and 12-Week 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 ± 3 Days	W4/D29 ± 3 Days	W8/D57 ± 3 Days	W12/D85 / Early Termination[a] ± 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		
IBDQ, UC-PRO/SS, SF-36, WPAI-UC, and abdominal pain and urgency NRS		X				X		
Adverse event assessment	X	X	X	X	X	X	X	X
Vital signs[j]	X[j]	X[j,k]	X	X	X	X	X	X

Evaluation	Screening Period	12-Week Treatment Period						
	–28 to –1	W0/D1	W2/D15 ± 3 Days	W4/D29 ± 3 Days	W8/D57 ± 3 Days	W12/D85 / Early Termination[a] ± 3 Days	2-Week Follow-Up Visit[b] ± 3 Days	4-Week Follow-Up Visit[b] ± 3 Days
12-lead ECG[l]	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	X[r]					X[r]	X[r]	
Urine drug screen[s]	X							
Pregnancy test[t]	X	X		X	X	X		X
Genomic DNA (optional)		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		
Stool sample for microbiome	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		
Concomitant medications and procedures[z]		X	X	X	X	X	X	X
Drug dispensation/ accountability		X	X	X	X	X[aa]		
Study treatment administration[bb]		X – Once daily						

[a] All visits beyond W0/D1 may be virtual/hybrid visits (Section 9.6). Subjects discontinuing prior to Week 12/Day 85 should have an Early Termination (ET) visit within 7 days of the last study treatment administration and before initiation of any new treatments. For subjects who complete Week 12, the Week 12 visit will be used to begin assessing eligibility for the APD334-303 OLE study.

[b] For subjects not participating in the APD334-303 OLE study, a follow-up visit will be performed at 2 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, subjects 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 D1 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 subjects will complete TB screening to determine eligibility (refer to Appendix 2). The QuantiFERON TB Gold and tuberculin skin test should not be performed in subjects previously diagnosed with TB infection. The TB questionnaire will be completed for all subjects during the Screening period and at every study visit for subjects residing in countries with a high TB burden or MDR TB as identified by the WHO. For subjects who are receiving TB prophylaxis treatment, the TB questionnaire will be completed at every study visit (until TB prophylaxis treatment course is completed).

[f] Subjects will be tested for HIV antibodies as well as HBV and HCV infection at screening (Section 9.10.7.1.3).

[g] Subjects 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 subject 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/Early termination visits. The subscores for SF and RB are derived from the subject 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 electronic subject 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 subjects in the sitting position will be performed at Screening and prior to randomization on Week 0/Day 1 (baseline). If the subject'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 subject 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 subject in the supine position will be obtained prior to blood sample collection at Screening and prior to randomization on Week 0/Day 1 (baseline). Subjects 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 a screen failure.

[m] After dosing on Day 1, a 12-lead ECG with the subject in the supine position will be performed 4 hours (± 15 minutes) post-dose as described in Section 9.4.2.1. Details regarding additional ECGs are provided in Section 9.10.3.

[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/Early Termination 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, specific systems (eyes, liver, skin and joints) will be examined for EIMs.

[p] A PFT will include FEV_1 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).

[q] The Screening pulmonary function test (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 9.10.4.

[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 9.10.5.

[s] Urine drug screen according to Table 6.

[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 subject will have study treatment interrupted and a serum sample submitted to the central laboratory for β-hCG testing (Section 9.10.7.1.2).

[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 the first dose of study treatment. 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 subject becomes symptomatic, including worsening or return of disease activity.

[w] To be read by a blinded central reader. Proctosigmoidoscopy/colonoscopy must be performed prior to randomization of treatment 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 pre-dose, 4 hours (± 15 minutes) post-dose on Week 0/Day 1 (PK sample to be collected after 12-lead ECG), and pre-dose (for trough level, within the 60-minute 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 subjects 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.

[y] Blood samples for biomarkers should be collected on the indicated days prior to the daily dosing as applicable. Biomarker sample collection is not required at ET visit.

[z] All concomitant medications and procedures should be collected from Day 1 (pre-dose) through the safety reporting period (Section 6.7).

[aa] Study treatment should be dispensed at Week 12 if the subject continues treatment in the 40-Week Treatment Period.

[bb] On days with scheduled study visits, subjects should not take their dose of study treatment at home in order to complete pre-dose study procedures. The dose will be taken at the study site 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; FEV_1, forced expiratory volume at 1 second; FVC, forced vital capacity; 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; IBDQ, Inflammatory Bowel Disease Questionnaire; MDR, multi-drug resistant; MMS, modified Mayo score; NRS, numeric rating scale; OCT, optical coherence tomography; OLE, open-label extension; PGA, Physicians Global Assessment; PK, pharmacokinetics; QTcF, Fridericia's corrected QT interval; RB, rectal bleeding; SF, stool frequency; SF-36, Medical Outcomes Study 36-Item Short Form Health Survey; TBNK, T lymphocytes, B lymphocytes, and Natural Killer lymphocytes; TB, tuberculosis; UC, ulcerative colitis; UC-PRO/SS, Ulcerative Colitis Patient-Reported Outcomes Signs and Symptoms; W, week; WHO, World Health Organization; WPAI UC, Work Productivity and Activity Impairment Questionnaire – Ulcerative Colitis

Table 8: Schedule of Assessments – 40-Week Treatment Period

Evaluation	40-Week Treatment Period							2-Week Follow-Up Visit[b] ± 3 Days	4-Week Follow-Up Visit[b] ± 3 Days
	W16/ D113 ± 7 Days	W20/ D141 ± 7 Days	W24/ D169 ± 7 Days	W32/ D225 ± 7 Days	W40/ D281 ± 7 Days	W48/ D337 ± 7 Days	W52/D365 ± 14 Days / Early Termination[a] ± 7 Days		
eDiary review	X	X	X	X	X	X	X		
MMS[c]							X		
Stool frequency and rectal bleeding subscore[d]	X	X	X	X	X	X	X		
PGA for total Mayo Clinic Score							X		
IBDQ, UC-PRO/SS, SF-36, WPAI-UC, and pain and urgency NRS							X		
Adverse event assessment	X	X	X	X	X	X	X	X	X
Vital signs[e]	X	X	X	X	X	X	X	X	X
12-lead ECG							X		
Physical examination[f]	X	X	X	X	X	X	X	X	X
Extraintestinal manifestations[g]							X	X	X
Pulmonary function test[h]				X[h]			X	X[h]	
Ophthalmoscopy with OCT[i]							X	X	
Pregnancy test[j]	X	X	X	X	X	X	X		X
CBC with differential and platelets	X	X	X	X	X	X	X	X	X
TBNK	X	X	X	X	X	X	X	X	X
Laboratory tests including hs-CRP[k]	X	X	X	X	X	X	X	X	
Stool sample/fecal calprotectin[l]			X				X		
Stool sample for microbiome							X		

Evaluation	40-Week Treatment Period							2-Week Follow-Up Visit[b] ± 3 Days	4-Week Follow-Up Visit[b] ± 3 Days
	W16/ D113 ± 7 Days	W20/ D141 ± 7 Days	W24/ D169 ± 7 Days	W32/ D225 ± 7 Days	W40/ D281 ± 7 Days	W48/ D337 ± 7 Days	W52/D365 ± 14 Days / Early Termination[a] ± 7 Days		
Flexible proctosigmoidoscopy/ colonoscopy and biopsy[m]							X		
PK assessments[n]	X	X	X	X	X	X	X	X[n]	X[n]
Biomarkers blood sample[o]							X		
Concomitant medications and procedures[p]	X	X	X	X	X	X	X	X	X
Tuberculosis questionnaire[q]	X	X	X	X	X	X	X	X	X
Tuberculosis test[q]							X		
Drug dispensation/accountability[r]	X	X	X	X	X	X	X[r]		
Study treatment administration[s]	Once daily								

[a] All visits beyond W0/D1 may be virtual/hybrid visits (Section 9.6). Subjects discontinuing treatment prior to Week 52/Day 365 should have an Early Termination (ET) visit within 7 days of the last study treatment administration and before initiation of any new treatments. If a subject discontinues at or before Week 16, a sigmoidoscopy and biopsy are not required. For subjects with worsening disease or who complete Week 52 and wish to enter the APD334-303 OLE study, the Week 52/Early Termination visit will be used to assess eligibility for the OLE study.

[b] For subjects discontinuing study treatment, 2-Week and 4-Week Follow-Up visits should be scheduled 2 weeks and 4 weeks after the Week 52/Early Termination visit and the indicated assessments performed; however, if the ET or Week 52 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 Week 52 visit is ≥ 4 weeks after the last dose 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, subjects should return for CBC with differential according to local standard of care (captured as subsequent Follow-Up visit or unscheduled visit).

[c] The Week 52 MMS will be calculated using the Week 52 proctosigmoidoscopy and SF and RB scores completed by the subject 7 days prior to the visit using the 3 most recent consecutive days prior to the actual day of the study visit excluding the day of bowel preparation.

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

[e] Safety vital signs will include resting heart rate and systolic and diastolic BP with subjects in the sitting position taken before dosing. The Day 1 safety monitoring (Section 9.4.2.1) should be repeated if a subject has had a dose interruption ≥ 2 consecutive days within the first week of treatment or ≥ 7 consecutive days after the first week of treatment.

[f] At Week 52, a complete physical examination (including assessments of the skin, head, eyes, ears, nose, throat, neck, thyroid, lungs, heart, abdomen, back, lymph nodes, extremities, and body weight) should be performed. All other visits should have a focused (complaints, signs, and symptoms) physical examination.

[g] During the specified full physical examination, specific systems (eyes, liver, skin, and joints) will be examined for EIMs.

[h] Pulmonary function tests will include FEV_1 and FVC measurements. Where locally available, DLCO measurements will also be performed (sites where DLCO is not available should consult the Sponsor or Sponsor's delegate). The Week 32 assessment is only required for subjects with a history of mild pulmonary disease (eg, asthma, chronic obstructive pulmonary disease). The 2-Week Follow-Up visit assessment is only required if clinically indicated. Details regarding additional PFTs are provided in Section 9.10.4.

[i] Details regarding ophthalmoscopy and OCT assessments are provided in Section 9.10.5. The 2-Week Follow-Up visit assessment is only required if clinically indicated.

[j] Urine pregnancy test for women of childbearing potential. A monthly home pregnancy test in non-visit months should be performed in countries where allowed per local regulation and any positive result immediately reported to the study site and a serum pregnancy test performed for confirmation. If not allowed per local regulations, this pregnancy test will be performed on site during an unscheduled visit.

[k] Clinical laboratory tests will include serum chemistry, hematology (including coagulation), urinalysis, and hs-CRP and should be obtained prior to the daily dosing.

[l] Stool sample is for fecal calprotectin (all indicated visits) and bacterial culture, ova, and parasite evaluation for *C. difficile* assay at any point in the study when a subject becomes symptomatic, including worsening or return of disease activity.

[m] To be read by a blinded central reader. If the ET visit is within 4 weeks of the last sigmoidoscopy and biopsy, these procedures do not need to be repeated.

[n] Pharmacokinetic blood samples are to be collected pre-dose (within the 60-minute period prior to dosing). 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 subjects 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.

[o] Blood samples for biomarkers should be collected on the indicated day prior to the daily dose as applicable. Biomarker sample collection is not required at ET visit.

[p] All concomitant medications and procedures should be collected through the safety reporting period (Section 6.7). For subjects receiving corticosteroid therapy during the 12-Week Treatment Period, corticosteroids should be tapered for subjects entering the 40-Week Treatment Period (Section 6.7.2.2).

[q] The QuantiFERON TB Gold and tuberculin skin test should not be performed in subjects previously diagnosed with TB infection. For subjects who are receiving TB prophylaxis treatment, the TB questionnaire will be completed at every study visit (until TB prophylaxis treatment course is completed).

[r] Study treatment should be dispensed as indicated. For subjects who consent and are eligible for the APD334-303 OLE study prior to Week 52, double-blinded study treatment may be dispensed in the event there is a gap between the last on treatment visit of the parent study and W0/D1 of the OLE. Study treatment may be dispensed at Week 52 if the subject qualifies for and has opted to participate in the APD334-303 OLE study but who do not enter the OLE study on the same day as their Week 52 visit.

[s] On days with scheduled study visits, subjects should not take their dose of study treatment at home in order to complete pre-dose study procedures. The dose will be taken at the study site 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; eDiary, electronic diary; EIM, extraintestinal manifestations; FEV_1, forced expiratory volume at 1 second; FVC, forced vital capacity; HR, heart rate; hs-CRP, high-sensitivity C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; MMS, modified Mayo score; NRS, numeric rating scale; OCT, optical coherence tomography; OLE, open-label extension; PGA, Physicians Global Assessment; PK, pharmacokinetics; RB, rectal bleeding; SF, stool frequency; SF-36, Medical Outcomes Study 36-Item Short Form Health Survey; TB, tuberculosis; UC, ulcerative colitis; UC-PRO/SS, Ulcerative Colitis Patient-Reported Outcomes Signs and Symptoms; W, week; WHO, World Health Organization; WPAI UC, Work Productivity and Activity Impairment Questionnaire – Ulcerative Colitis

APPENDIX 2: TUBERCULOSIS SCREENING

All subjects must undergo screening for a history of 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. Subjects 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. Subjects 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 subjects (refer to questionnaire below) during the Screening period.

c. For subjects residing in countries with a high burden of TB or MDR TB as identified by WHO, the TB screening questionnaire will be completed at every study visit (per protocol schedules of assessments). For subjects 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.

   – For a complete list of TB high burden and MDR TB high burden countries during the period 2016 to 2020, visit:

      – http://www.stoptb.org/countries/tbdata.asp

      – https://www.who.int/tb/publications/global_report/high_tb_burdencountrylists 2016-2020.pdf?ua=1

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

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

   – Subjects 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. Subjects with a newly identified positive IGRA (one retest is allowed with approval from the Medical Monitor per Section 9.3.1) 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. For subjects

diagnosed with latent TB infection and reside in countries with high burden of TB or MDR TB: A chest CT scan should be performed to rule out current/past pulmonary TB in the event the chest X-ray is equivocal.

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
   - Subjects will be considered to have a negative diagnostic test for TB if at least one of the following circumstances applies:
     - Negative QuantiFERON-TB Gold test.
     - Combination of a negative QuantiFERON-TB Gold test and negative purified protein derivative (PPD) TST (in countries where IGRA is not considered a validated test).
   - A combination of two indeterminant QuantiFERON-TB Gold tests and a negative PPD TST (in countries where IGRA is not considered a validated test). An indeterminant IGRA test result should be repeated. In the event that the second IGRA test result is also indeterminate, the subject 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 subject 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 subject'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 subjects receiving equivalent of prednisone > 15 mg/day for any medical conditions and subjects residing in countries identified by WHO as a high TB burden country or high MDR TB burden country.

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

Page 1 of 3

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."
_____
_____

_____ _____
Completed by (signature) **Date**

Page 2 of 3

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

_____ _____

Investigator (signature) **Date**

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 Mayo score ranges from 0 to 12, with higher scores indicating more severe disease.

a Each subject 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.

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 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

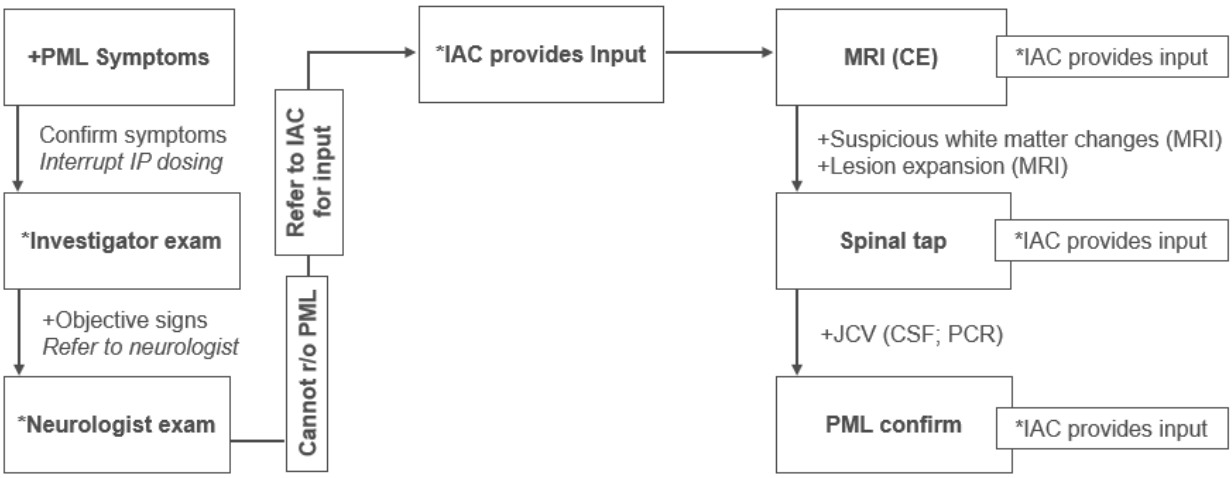
The Robarts Histopathology Index (RHI) is an evaluative index, derived from the Geboes score, that is designed to be reproducible and responsive to clinically meaningful change in disease activity over time. The total RHI score ranges from 0 (no disease activity) to 33 (severe disease activity) and is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

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

If a subject exhibits signs and symptoms suspicious for 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 (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



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.
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 subject does not have PML, or the IAC's review of the evidence concludes that PML is ruled out.

APPENDIX 6: INVESTIGATOR SIGNATURE

Study title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 52-Week Study to Assess the Efficacy and Safety of Etrasimod in Subjects with Moderately to Severely Active Ulcerative Colitis

Study number: APD334-301

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Investigator Signature	**Date**

Investigator Name and Credentials - Printed
Institution Name - Printed

APPENDIX 7: SPONSOR SIGNATURE

Study title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 52-Week Study to Assess the Efficacy and Safety of Etrasimod in Subjects with Moderately to Severely Active Ulcerative Colitis

This document is signed electronically; the electronic signature is the signature of record in countries and regions that recognize electronic signature. This signature page is provided to meet signature requirements in countries that do not recognize electronic signature; the hand-written signature on this page is the signature of record in countries and regions that do not recognize electronic signature.

[redacted]
Senior Vice President, Clinical Development, and Chief Medical Officer
Arena Pharmaceuticals, Inc.

[redacted]

Sponsor Signature

Dec 22-2020

Date

Name: Clinical Study Protocol: APD334-301 Amendment 4.0

Description: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 52-Week St

User Name: [redacted] Capacity: Cl	Meaning: Approval Task Date: 23-Dec-2020 02:10:14 GMT+0000

CLINICAL STUDY PROTOCOL
SUMMARY OF CHANGES

Protocol title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 52-Week Study to Assess the Efficacy and Safety of Etrasimod in Subjects with Moderately to Severely Active Ulcerative Colitis
Protocol number:	APD334-301
Version:	Amendment 1, 05 March 2019
Replaces version:	Original, 19 December 2018

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 1, 05 March 2019

Overall Rationale for the Amendment

The overall rationale for this amendment is to provide additional guidance for the cardiac monitoring procedures required on Day 1 after the first dose of study treatment. These additional monitoring procedures are based feedback from the Food and Drug Administration. In particular, post-dose safety vital signs, 12-lead ECGs, monitoring of subjects who do not meet the discharge criteria, and discontinuation rules have been revised.

Summary of Changes

Section No. and Name	Description of Change	Brief Rationale
Throughout	Minor editorial, formatting, and nomenclature revisions	Minor; therefore, have not been summarized
Synopsis: Study Design Synopsis: Statistical methods 3.1. Summary of Study Design 6.4. Method of Assigning Subjects to Treatment 10.12.1. Efficacy Analysis	Changed the first stratification factor from "failed biologic/JAK inhibitor therapy (yes/no)" to "naïve to biologic or JAK inhibitor therapy at study entry (yes/no)"	The terminology was changed from "failed" to "naïve" because the term "naïve" was originally intended when the protocol was written.
4.1. Inclusion Criteria: Prior treatment failure criteria: Inadequate response	Deleted the word "induction" from the description of prior therapy	The criterion applies to any regimen; not limited to induction
4.1. Inclusion Criteria: Prior treatment: Loss of response	Deleted "approved maintenance dosing" from prior treatment description	For clarification
Synopsis: "*Other general inclusion criteria"* 4.1. Inclusion Criteria: *Other general inclusion criteria:*	Updated criteria for hematological function	Given the mechanism of action of the drug in reducing peripheral lymphocytes, these changes in hematologic parameters may be important for safety reasons
5.1. Discontinuation of Study Treatment	Added: • Subjects will be discontinued from the study treatment if they experience a cardiovascular treatment-related symptomatic event (eg, chest pain, dizziness, palpitations, lightheadedness, shortness of breath, or syncope) associated with reduction of heart rate with clinically relevant ECG changes at any time during the post-dose 4-hour monitoring period. • Subjects who have not met the discharge criteria (Table 4) on Day 1 after ≥ 4 hours of extended monitoring, or Day 2 by 4 hours post-dose	Added as an extra safety precaution

Section No. and Name	Description of Change	Brief Rationale
5.1.1. Discontinuation from Double-Blind Treatment for Disease Worsening	Updated language specifying criteria for entry into the APD334-303 open-label extension study	To provide more clarity and guidance to Investigators
6.3.1. Instructions for Missed Dose(s)	Deleted instruction that vomiting of the tablet should be recorded in the subject's electronic diary (eDiary).	It is not intended that subjects record vomiting of study treatment
6.3.2. Dose Interruptions	Moved the description of symptoms and treatment for PML from Section 6.3.2 to Section 9.9.8.1.4 (Adverse Events of Special Interest).	Aligns the topic of the text with the Section header.
9.3.5. Prior and Ongoing Therapies	Modified text to state documentation of prior UC therapies should include the prior treatment response as one of the following: inadequate response to, loss of response to, or intolerance to	For proper documentation of response to prior UC therapies
9.3.10. Proctosigmoidoscopy/ Colonoscopy and Modified Mayo Score Derivation	For SF changed from "baseline" to "normal"	For consistency with Section 9.7.1 and for more appropriate description of the assessment
9.4.2.1. Guidance for Cardiac Monitoring Following Treatment Initiation or Re Initiation	Added new Section "Guidance for Cardiac Monitoring Following Treatment Initiation or Re-Initiation," with details relating to first dose cardiac monitoring, extended cardiac monitoring, and study treatment discontinuation related to post-dose cardiac monitoring	To provide additional guidance and details for vital sign and cardiac monitoring
9.7.1. Modified Mayo Score/Mayo Clinic Score	Deleted that stool frequency before initial onset of signs and symptoms of UC to be used as the reference SF would be recorded in the subject's eDiary	This will be recorded at screening in the eCRF, not in the subject's eDiary.
9.7.1.2. Endoscopic Biopsies	Modified the language on the biopsy location to specify collection from the most affected area 15 to 25 cm from the anal verge	To provide additional guidance
9.9.8.1.2. Serious Adverse Event	Deleted "Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study	Not relevant to this protocol

Section No. and Name	Description of Change	Brief Rationale
	target disease need not be captured as SAEs" from the definition of SAE	
9.9.8.2.2. Recording Adverse Events	Updated language that SAEs should be described in the narrative description field of the eCRF	To provide more clarity and guidance to Investigators and to align with updates in the Protocol template
9.9.8.3.1. Serious Adverse Events	Added contact information for reporting of SAEs	To provide more clarity and guidance to Investigators
9.10. Procedures for Overdose	Added new section	Provide information for investigators relating to subject overdose.
10.3. Analysis Sets	Renamed the analysis sets as follows: • Intent-to-treat population renamed Full Analysis Set (FAS) • Modified intent-to-treat population renamed Modified Full Analysis Set (mFAS) • Per-protocol population renamed Per Protocol Set • Safety population renamed Safety Set	For consistency with FDA Guidance "E9 *Statistical Principles for Clinical Trials"* (Section V. B. 1.), ICH E9 "*Statistical Principles"* (Section 5.2), and EMEA Guidance "ICH Topic 39 *Statistical Principles for Clinical Trials*" (Section V.2).
10.10. Subgroup Analyses	Added new section describing subgroup analyses	Sponsor decision
Table 7, Schedule of Assessments, *12-lead ECG row*	Added a 12-lead ECG at the Week 12/Early Termination visit.	Sponsor decision
Table 7, Schedule of Assessments, Footnote "a"	Modified text to clarify that for subjects who complete Week 12 and are eligible to enter the APD334 303 OLE study, the Week 12 visit will be used to assess eligibility for the OLE and may also serve as the Day 1 visit of the OLE	For clarification and guidance for Investigators
Table 7, Schedule of Assessments, Footnote "k"	Rewrote to be consistent with new cardiac monitoring text	For document consistency

Section No. and Name	Description of Change	Brief Rationale
Table 8, Schedule of Assessments, Footnote “a”	Modified text to clarify that the Week 52/Early Termination visit will be used to assess eligibility for the OLE and may also serve as the Day 1 visit of the OLE	For clarification and guidance for Investigators
Table 8, Schedule of Assessments	Added an additional row entitled “12-lead ECG”, indicating that a 12-lead ECG will be conducted at the Week 52/Early Termination visit.	Sponsor decision
Appendix 5: Investigator Signature Page	Updated to new signature page format	Formatting revision
Added Appendix 6: Country Specific Requirements	Insertion of Sponsor signature page for a hand-written signature	To meet signature requirements in countries that do not recognize electronic signature

CLINICAL STUDY PROTOCOL
SUMMARY OF CHANGES

Protocol title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 52-Week Study to Assess the Efficacy and Safety of Etrasimod in Subjects with Moderately to Severely Active Ulcerative Colitis
Protocol number:	APD334-301
Version:	Amendment 2.0, 20 December 2019
Replaces version:	Amendment 1, 05 March 2019

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 2.0, 20 December 2019

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the safety or physical/mental integrity of subjects.

Overall Rationale for the Amendment

The overall rationale for this amendment is to address update criteria for early (ie, prior to Week 52) enrollment in the open-label study and eligibility criteria (eg, list of prior therapy failures or non-response, contraception use, cardiovascular disease history, and prior therapy washout period). Additional instructions for safety monitoring related to 12-lead electrocardiogram, pulmonary function tests, and ophthalmoscopy and optical coherence tomography testing. Further instructions for Quantiferon TB Gold and tuberculin skin test were added. In addition, a 4-Week Follow-Up visit was added.

Summary of Changes

Section No. and Name	Description of Change	Brief Rationale
Throughout	Minor editorial, formatting, and nomenclature revisions	Minor and do not affect the conduct of the protocol; therefore, have not been summarized
Title Page	Added NCT number	Administrative change
	Updated title of Sponsor's Responsible Medical Officer to: [redacted]	Administrative change due to organizational update
	Updated Amendment 2.0 Version date: 20 December 2019	Administrative change
	Added Protocol History table	To summarize protocol amendment history
Synopsis: Study design 3.1. Summary of Study Design	Removed "Randomized subjects who experience UC exacerbation during the 12 Week Treatment Period will be considered as having a treatment nonresponse and should be managed according to the local standard of care."	For additional clarity and guidance to Investigators
Synopsis: Study design 3.1. Summary of Study Design	Revised entry criteria into open-label extension starting at the Week 12 visit and continuing through the 40-Week Treatment Period for subjects who experience UC worsening	To provide greater clarity
3.3. Study Duration	Added "The End of Study is the date when the last subject completes his/her last study visit."	For additional clarity and guidance to Investigators
Synopsis: Eligibility criteria: Inclusion Criterion 1 4.1. Inclusion Criteria: Inclusion Criterion 1	Added "Enrollment of subjects < 18 years should be conducted only if acceptable according to local laws and regulations"	To satisfy local regulations that allow inclusion of minors (under 18 years) in clinical trials only after the results from adults are available
Synopsis: Eligibility criteria: Inclusion Criterion 4 4.1. Inclusion Criteria: Inclusion Criterion 4	Changed to state "Subjects with proctitis only at baseline who meet the other eligibility criteria for inclusion, including the endoscopic and rectal bleeding criteria for moderate to severe disease, will be capped at 15% of the total subjects enrolled"	For additional clarity and guidance to Investigators

Section No. and Name	Description of Change	Brief Rationale
Synopsis: Eligibility criteria: Inclusion Criterion 6 4.1. Inclusion Criteria: Inclusion Criterion 6	Added "according to routine practice" to removal of any adenomatous polyps	For clarification on eligibility criteria
Synopsis: Eligibility criteria: Inclusion Criterion 7 4.1. Inclusion Criteria: Inclusion Criterion 7	Added interleukin 12/23 antibodies (eg, ustekinumab) to list of biologic therapies for JAK inhibitor therapies	Added due to recent FDA approval for treatment of moderately to severely active ulcerative colitis
	Added to note regarding qualifying therapy that "the subject must have received an adequate course of therapy based on local guidelines for that therapy"	To ensure that subjects had received adequate prior qualifying therapy
Synopsis: Eligibility criteria: Inclusion Criteria 9 and 10 4.1. Inclusion Criteria: Inclusion Criteria 9 and 10	Vital signs and screening ECG have been deleted	Now covered in new Exclusion Criterion 8
Synopsis: Eligibility criteria: Inclusion Criterion 10 (formerly Inclusion Criterion 12) 4.1. Inclusion Criteria: Inclusion Criterion 10 (formerly Inclusion Criterion 12	Updated adequate hepatic function for ALT and AST to levels $\leq 2.0 \times$ ULN (from levels $\leq 3.0 \times$ ULN)	Extra safety precaution
Synopsis: Eligibility criteria: Inclusion Criterion 12 (formerly Inclusion Criterion 15) 4.1. Inclusion Criteria: Inclusion Criterion 12 (formerly Inclusion Criterion 15)	Updated contraception language	To be in accordance with the contraception guidance from Clinical Trials Facilitation and Coordination Group (CTFG)
Synopsis: Eligibility criteria: Exclusion Criterion 7 4.2. Exclusion Criteria: Exclusion Criterion 7	Deleted hematologic, hepatic, pulmonary, and ophthalmological conditions from criterion. Alcohol/drug abuse/dependence (formerly Exclusion Criterion 21) and cognitive impairment were added.	Covered in other specific exclusion criteria

Section No. and Name	Description of Change	Brief Rationale
Synopsis: Eligibility criteria: Exclusion Criteria 8 and 9 4.2. Exclusion Criteria: Exclusion Criteria 8 and 9	Combined Exclusion criteria 8 and 9 and updated the criterion for cardiovascular function exclusion	To be in compliance with the precautions mentioned in previous study protocols submitted in France and in line with the fingolimod information
Synopsis: Eligibility criteria: Exclusion Criterion 8 4.2. Exclusion Criteria: Exclusion Criterion 8 and throughout	Updated PR interval criterion from ≤ 200 ms for inclusion to > 200 ms for exclusion	More appropriately fits within new cardiovascular function exclusion criterion
Synopsis: Eligibility criteria: Exclusion Criterion 12 4.2. Exclusion Criteria: Exclusion Criterion 12 (formerly Inclusion Criterion 13)	Updated TB exclusion criterion language	For greater clarity and additional guidance to Investigators and to harmonize with programmatic language
Synopsis: Eligibility criteria: Exclusion Criterion 13 (formerly Exclusion Criterion 14) 4.2. Exclusion Criteria: Exclusion Criterion 13 (formerly Exclusion Criterion 14)	Updated and modified active infection exclusion criterion to "≤ 28 days prior to randomization, required intravenous medication ≤ 14 days prior to randomization, or that may worsen (in the opinion of the Investigator) if the subject is treated with a drug having immunosuppressant effects (ie, etrasimod)."	To better define infection source as any active infection
Synopsis: Eligibility criteria: Exclusion Criterion 17 4.2. Exclusion Criteria: Exclusion Criterion 17	Updated and modified history of opportunistic infection exclusion criterion to "History of an opportunistic infection (eg, *Pneumocystis jirovecii*, cryptococcal meningitis, progressive multifocal leukoencephalopathy) or history of disseminated herpes simplex or disseminated herpes zoster."	To better define infection history
Synopsis: Eligibility criteria: Exclusion Criterion 21 4.2. Exclusion Criteria: Exclusion Criterion 21	Added "21. Hypersensitivity to etrasimod or any of the excipients or placebo compounds" as a new exclusion criterion	Added at the request of regulatory authorities. All subsequent exclusion criteria were renumbered accordingly.
Synopsis: Eligibility criteria: Exclusion Criterion 21 4.2. Exclusion Criteria: Exclusion Criterion 21	Deleted criterion and moved to Exclusion Criterion 7	To avoid redundancies

Section No. and Name	Description of Change	Brief Rationale
Synopsis: Eligibility criteria: Exclusion Criterion 23 (formerly Exclusion Criterion 24) 4.2. Exclusion Criteria: Exclusion Criterion 23 (formerly Exclusion Criterion 24)	Updated washout period for therapy to "Treatment with a biologic agent within 8 weeks or within 5 elimination half-lives for a small-molecule agent prior to randomization"	To improve clarity and provide additional guidance to Investigators regarding wash-out period
Synopsis: Eligibility criteria: Exclusion Criterion 27 (formerly Exclusion Criterion 28) 4.2. Exclusion Criteria: Exclusion Criterion 27 (formerly Exclusion Criterion 28)	Changed methotrexate washout from within 16 weeks to 8 weeks of screening	To provide greater access to the study
Synopsis: Eligibility criteria: Exclusion Criterion 31 (formerly Exclusion Criterion 32) 4.2. Exclusion Criteria: Exclusion Criterion 31 (formerly Exclusion Criterion 32)	Modified exclusionary drugs by deleting leflunomide and adding dimethyl fumarate, or pyrimidine synthesis inhibitors	To add classes rather than specific drugs
Synopsis: Efficacy assessments: Definitions	Updated symptomatic remission: SF subscore = 0 (or = 1 with a $\geq$ 1-point decrease from baseline) and RB subscore = 0	Minor update to symptomatic remission definitions to align with regulatory authority requests
Synopsis: Efficacy assessments: Key secondary efficacy endpoints 10.7.1. Key Secondary Efficacy Endpoints	Updated key secondary endpoints to include: • The proportion of subjects achieving symptomatic remission at Week 52 • Proportion of subjects achieving symptomatic remission at Week 12	Update to key secondary efficacy endpoints to align with regulatory authority requests
Synopsis: Pharmacokinetic Assessments 10.9.2. Pharmacokinetics Table 7: Schedule of Assessments – Screening and 12-Week Treatment Period	Added PK samples at the 2-Week and 4-Week Follow-Up visits	To ensure appropriate PK data are available after end of treatment

Section No. and Name	Description of Change	Brief Rationale
Table 8: Schedule of Assessments – 40-Week Treatment Period		
Synopsis: Statistical Methods – Interim analysis – Testing strategy 10.13. Testing strategy, Interim analysis	Updated number of key secondary endpoints from 6 to 8	For internal consistency due to addition of new key secondary endpoints
Synopsis: Statistical Methods – Interim analysis 10.13. Interim Analysis	Deleted DMC review and clarified analysis would be on blinded data to assess the appropriateness of the assumptions used in the original sample size calculation to ensure sufficient exposure data for safety assessment. Also clarified that the interim analysis will not be used to evaluate efficacy or safety.	To clarify DMC oversight and that the interim analysis will not be used to evaluate efficacy or safety
1.3. Benefit/Risk Assessment	Updated to state that repeated doses of up to 4 mg (changed from 3 mg) once daily have been assessed in healthy adult subjects and repeated doses of 2 mg have been evaluated in Phase 2 studies of subjects with moderately to severely active UC.	To be up to date with the IB
	Added “and as clinically indicated any time during the study.” to times when OCT will be performed	As an extra safety precaution
3.1. Summary of Study Design	Updated text regarding entry/rollover into the OLE	For greater clarity
3.3. Study Duration	Added “The End of Study is the date when the last subject completes his/her last study visit.”	To define the “End of the Study”
4.1. Inclusion Criteria, Inclusion Criterion 7	Modified definition of inadequate response to be “Signs and symptoms of persistently active disease despite a history of completing a dosing regimen.” A new note was added that says: “Note: To be considered inadequate response, loss of response, and intolerance after treatment with a biologic or tofacitinib, the subject must have received a dosing regimen consistent with the local product labeling and/or institutional standard of care.”	For additional guidance to Investigators
5.1. Discontinuation from Study Treatment	Added confirmed diagnosis of active TB to list of reasons for discontinuation of study treatment	Added safety precaution
	Modified criteria	To provide greater clarity and guidance for Investigators

Section No. and Name	Description of Change	Brief Rationale
5.1. Discontinuation from Study Treatment 9.5. Follow-Up Period Table 7: Schedule of Assessments – Screening and 12-Week Treatment Period (footnote "b") Table 8: Schedule of Assessments – 40-Week Treatment Period (footnote "b")	Changed ALC criterion for continued follow-up from "80% of baseline value" to "within normal limits"	To provide guidance to Investigators
5.1.1. Discontinuation from Double-Blind Treatment for Disease Worsening	Modified criteria for entry into the OLE prior to Week 52 to include 2 symptom assessments (previously 1) at least 7 days and no more than 14 days apart	For confirmation of non-improvement or disease worsening
	Modified statement regarding required endoscopic evaluation to confirm eligibility for OLE prior to Week 52 to state the endoscopy should be performed "upon the appearance of UC symptoms but no more than 14 days after the second timepoint for symptom criteria"	To provide additional guidance for Investigators
5.2. Discontinuation from the Study	Added "Deviation/noncompliance with the study protocol that in the judgement of the Investigator and/or Medical Monitor the subject should not continue study treatment" to list of reasons for discontinuation from the study	To provide additional guidance for Investigators
6.3. Dosage and Administration	Clarified that the time of PK sample collection and last dosing prior to the PK sample should be documented in the eCRF	For additional clarification and guidance to Investigators
6.3.1. Instructions for Missed Dose(s)	Statement added that "Subjects who 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 must contact the Investigator to discuss treatment re-initiation. The subject 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."	Added for compliance and additional safety precaution
6.5. Blinding	Modified text regarding unblinding and added statement that "If a subject's treatment assignment is unblinded prior to Week 12 for any reason, they will be discontinued from the	To provide additional clarity

Section No. and Name	Description of Change	Brief Rationale
	study. Subjects who are unblinded on or after week 12 may be eligible to enroll into the OLE study (Section 5.1.1)."	
6.7.3. Prohibited Concomitant Therapy	Deleted "Treatment with medications with a known impact on the cardiac conduction system and QT prolonging drugs with a known risk of torsades de pointes (https://www.uspharmacist.com/article/drug-induced-qt-prolongation for additional information)"	Based on results of the QT study
	Changed the duration of time after stopping study treatment that subjects should not receive live vaccines from 2 weeks to 8 weeks	Safety precaution
	Added tofacitinib to list of prohibited immunosuppressive agents	Added for completeness
	Deleted leflunamide and added dimethyl fumarate, or pyrimidine synthesis inhibitors	For consistency with Exclusion Criterion 31
	Moved immunoadsorption columns and intravenous immunoglobulin or plasmapheresis from prohibited concomitant medications to prohibited concomitant procedures	More accurately reflect the prohibited procedure
9.3.4. Social History	Added language regarding standard drug test at screening "A standard urine drug screen will be performed. Subjects who test positive will be assessed for eligibility in study participation by the Investigator."	Additional safety precaution
9.3.8. Pulmonary Function Test	Deleted "Subjects experiencing a decline in PFT values (FEV_1 and/or FVC) below 50% of the predicted values should be discontinued from study treatment and scheduled for a follow-up visit."	Covered in Section 5.1 – Discontinuation from Study Treatment
9.3.10. Proctosigmoidoscopy/ Colonoscopy and Modified Mayo Score Derivation	Modified language regarding screening proctosigmoidoscopy/ colonoscopy by "Preferably, proctosigmoidoscopy/colonoscopy should be performed after other criteria for inclusion (eg, laboratory criteria) have been met."	For clarity to Investigator. New statement added to minimize unnecessary proctosigmoidoscopies/colonoscopies
	Modified language regarding screening proctosigmoidoscopy/ colonoscopy review by "Proctosigmoidoscopy/colonoscopy should be performed prior to randomization to treatment to	For clarity regarding timing of review with respect to procedure.

Section No. and Name	Description of Change	Brief Rationale
	allow central reader review (may take approximately 5-12 days) and confirmation of eligibility.	
9.3.10. Proctosigmoidoscopy/ Colonoscopy and Modified Mayo Score Derivation – Determination of MMS score to qualify for randomization	Added language that subjects "who do not have a minimum of 7 days of eDiary data prior to bowel preparation" will not be eligible for randomization	To ensure adequate and reliable baseline MMS score
	Deleted "Note that the day prior to, day of, and day after proctosigmoidoscopy cannot be used for calculating MMS because of the required bowel preparation for the procedure."	Not necessary as the scoring algorithm described in the paragraph above clearly "ignores" the diary entries on and after the bowel preparation day.
9.4.1. Week 0/Day 1: Prerandomization	Added "OR diastolic BP < 55 mm Hg" as part of vital sign criterion for exclusion from randomization	Added to match Section 4.2 Exclusion Criteria
9.4.2. Treatment Period	Added additional language describing the MMS calculation "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."	For additional guidance to Investigators
9.4.2. Treatment Period – First Dose Cardiac Monitoring	Updated language for 5th bullet point to "…reduction of the heart rate or clinically relevant 12-lead ECG changes at any time during the 4-hour monitoring period must be discontinued from treatment."	For clarity and additional guidance to Investigators
9.4.3. Enrollment in Open-Label Extension Study APD334-303 Table 7: Schedule of Assessments – Screening and 12-Week Treatment Period – Footnote "a" Table 8: Schedule of Assessments – 40-Week Treatment Period – Footnote "a"	Deleted language stating that for eligible subjects, the Week 12 visit (or Week 52 visit) could be used as the Day 1 visit for the OLE	No longer applicable

Section No. and Name	Description of Change	Brief Rationale
9.5. Follow-Up Period	Updated text to add additional description of the eye examination	Updated for internal consistency and to provide additional guidance to Investigators
9.5. Follow-Up Period Table 7: Schedule of Assessments – Screening and 12-Week Treatment Period Table 8: Schedule of Assessments – 40-Week Treatment Period	Added 4-Week follow-up visit and modified language to include "If the Early Termination 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 Early Termination or Study Completion visit is ≥ 4 weeks after the last dose of study treatment, the 4-Week Follow-Up visit is not required."	Added for additional safety follow-up
9.7.3. Additional Health-Related Subject-Reported Outcomes	Corrected WPAI UC description to state it consists of 6 questions	Corrected the number of questions in the WPAI
9.7.4. Efficacy-Related Biomarkers	Updated language when ALC is confirmed to be < 200 cells/μL to state "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 the risk of 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."	For clarity and additional guidance to Investigators
9.9.3. 12-Lead Electrocardiogram	Updated text to describe when unscheduled ECGs should be performed and provide additional information regarding QTc prolongation and criteria under which restart of study treatment may be permissible	For clarity and additional guidance to Investigators
9.9.4. Pulmonary Function Test	Added new text describing PFTs to state "All subjects will have PFTs performed at Screening, Week 12, and Week 52, or at the Early Termination visit.	For clarity and additional guidance to Investigators

Section No. and Name	Description of Change	Brief Rationale
	Subjects with a history of mild pulmonary disease (eg, asthma, chronic obstructive pulmonary disease) will have additional PFTs performed at Week 32. Subjects 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."	
9.9.5. Ophthalmoscopy and Optical Coherence Tomography	Detailed the rationale and procedure for the ophthalmoscopy and OCT assessment.	For clarity and additional guidance to Investigators
9.9.6. Tuberculosis Screening and Chest X-Ray	Added that for subjects residing in countries with a high burden of TB as identified by WHO or if receiving TB prophylaxis therapy, a TB screening questionnaire will be administered prior to randomization and at every study visit (Appendix 2).	As an added safety precaution
9.9.7. Clinical Laboratory Tests Table 6	Moved QuantiFERON from "Virology" to "Others"	Not a virology test
9.9.7.1.1. Drugs of Abuse	Updated text	To provide greater clarity to Investigators
9.9.7.1.2. Pregnancy Testing	Added language stipulating home pregnancies tests will be performed "in countries where allowed per local regulation" and "If not allowed per local regulations, this pregnancy test will be performed on site during an unscheduled visit."	To be in compliance with local regulations
9.9.8.1.4. Adverse Events of Special Interest	Added "Guidance for the Assessment of Potential Progressive Multifocal Leukoencephalopathy is provided in Appendix 5."	To provide extra guidance to Investigators
9.9.8.3.2. Serious, Unexpected Adverse Drug Reactions	Updated wording to specify that "the IB in effect during the study will serve as the Reference Safety Information for determining whether an AE is expected or unexpected"	The previous language was incomplete and the new is consistent with CTFG guidance regarding RSI/IB
9.10. Procedures for Overdose	Added text and guidance for monitoring subjects	For additional guidance to Investigators
10.4. Missing Data	Clarified that subjects with worsening of disease prior to Week 12 and subjects who meet the criteria for worsening disease after Week 12, as defined in Section 5.1.1, will be considered as having a treatment nonresponse outcome in the analysis of all endpoints, including the primary endpoint.	For clarification and internal document consistency

Section No. and Name	Description of Change	Brief Rationale
10.5. Efficacy Endpoint Definitions	Added definitions for symptomatic remission, clinical remission using the Total Mayo Clinic score, and clinical response using the Total Mayo Clinic score	To provide definitions for selected endpoints in the protocol
10.7.1. Key Secondary Efficacy Endpoints	Added 2 additional key secondary endpoints: • The proportion of subjects achieving symptomatic remission at Week 52 • The proportion of subjects achieving symptomatic remission at Week 12	Added to align with regulatory authority requests
10.12.1. Efficacy Analysis	Deleted "using Hochberg's method" from "This study will be considered as a partial success if only one of the two primary null hypotheses are rejected at $\alpha/2$ if the other has $p > \alpha$."	The method will be specified in the SAP
13.2. Study Documentation and Records Retention	Updated language regarding record availability to record retention for "2 years after the appropriate regulatory authorities have been notified of the discontinuation of clinical development of the investigational product."	To provide greater clarity regarding the regulatory requirements
Table 7, Schedule of Assessments	Added TB Questionnaire	To facilitate TB assessments of study subjects
Table 7, Schedule of Assessments, Footnote "a"	Modified text to clarify that for subjects who complete Week 12 the Week 12 visit will be used to assess eligibility for the OLE	For clarification and guidance for Investigators
Table 7, Schedule of Assessments, Footnote "e"	Added additional language to the TB Footnote stipulating that the Quantiferon TB Gold and tuberculin skin test should not be performed in subjects previously diagnosed with TB infection and that the TB questionnaire will be administered at every study visit for subjects residing in countries with a high TB burden as identified by the WHO.	To facilitate TB assessments of study subjects
	Added "…or if receiving TB prophylaxis therapy"	To ensure screening inclusion for individuals diagnosed with TB even if they do not reside in countries with a high TB burden as identified by the WHO
Table 7, Schedule of Assessments, Footnote "k"	Deleted "Additionally, subjects 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."	No longer applicable

Section No. and Name	Description of Change	Brief Rationale
Table 8, Schedule of Assessments	Added new rows for TB Screening and Questionnaire and Week 52/Early Termination visit TB testing and associated footnote "q"	Additional safety precaution
	Added "…or if receiving TB prophylaxis therapy"	To ensure screening inclusion for individuals diagnosed with TB even if they do not reside in countries with a high TB burden as identified by the WHO
Table 8, Schedule of Assessments, Footnote "a"	Deleted text "and may also serve as the Day 1 visit of the OLE" to clarify that the Week 52/Early Termination visit will be used to assess eligibility for the OLE	For clarification and guidance for Investigators
Table 8, Schedule of Assessments Footnote "r"	Added language that subjects who consent and are eligible for the APD334-303 OLE study prior to Week 52 may also be dispensed study treatment.	To ensure subjects can continue study treatment without interruption prior to entry into the OLE
Appendix 2 Tuberculosis Screening	Updated Appendix	For additional guidance to Investigators and to harmonize across studies
Appendix 5: Guidance for The Assessment Of Potential Progressive Multifocal Leukoencephalopathy	Added new Appendix 5 Guidance for The Assessment Of Potential Progressive Multifocal Leukoencephalopathy	Added to align with regulatory authority requests
Appendix 6: Investigator Signature Page	Updated to new signature page format	Formatting revision
Appendix 7: Country-Specific Requirements	Deleted Appendix 7	Appendix was not relevant

CLINICAL STUDY PROTOCOL
SUMMARY OF CHANGES

Protocol title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 52-Week Study to Assess the Efficacy and Safety of Etrasimod in Subjects with Moderately to Severely Active Ulcerative Colitis
Protocol number:	APD334-301
Version:	Amendment 3.0, 07 February 2020
Replaces version:	Amendment 2.0, 20 December 2019

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 3.0, 07 February 2020

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the safety or physical/mental integrity of subjects.

Overall Rationale for the Amendment

The overall rationale for this amendment is provide clarification and further instructions for tuberculosis testing and to update the tuberculosis screening questionnaire. A correction was made to the entry criteria for enrollment in the OLE study. Additionally, lack of efficacy was added as a reason a subject may discontinue from double-blind treatment. Clarifications were made to Ophthalmoscopy and Optical Coherence Tomography testing. In addition, minor corrections were made for consistency within the protocol.

Summary of Changes

Section No. and Name	Description of Change	Brief Rationale
Throughout	Minor editorial, formatting, and nomenclature revisions	Minor and do not affect the conduct of the protocol; therefore, have not been summarized
Title Page	Updated Amendment 3.0; Version date: 07 February 2020	Administrative change
Protocol History	Updated protocol history table	Administrative change
Synopsis: Study design 5.1.1 Discontinuation from Double-Blind Treatment for Disease Worsening	Entry criteria for enrollment in the OLE study was updated by changing "RB subscore ≥ 2 **and** RB + SF subscores ≥ 4 (in any order) at 2 timepoints at least 7 days and no more than 14 days apart" to "RB subscore ≥ 2 **or** RB + SF subscores ≥ 4 (in any order) at 2 timepoints at least 7 days and no more than 14 days apart".	Correction
Synopsis: Eligibility criteria 4.2 Exclusion Criteria (Exclusion Criterion 5)	Updated pathogen nomenclature to *Clostridioides difficile* (formerly known as *Clostridium difficile*)	Update was made due to the reclassification of *Clostridium difficile* to *Clostridioides difficile* based on the adoption by the US Centers for Disease Control and Prevention.
Synopsis: Eligibility criteria 4.2 Exclusion Criteria (Exclusion Criterion 8) 9.9.3 12-Lead Electrocardiogram Table 7, Schedule of Assessments Footnote "l"	The use of the terms "males" and "females" was updated to "men" and "women" in reference to QTcF ranges.	Standardization of terms for consistency with Study APD334-302 and Study APD334-303 protocol terminology.
Synopsis: Eligibility criteria 4.2 Exclusion Criteria (Exclusion Criterion 12)	A change was made to clarify that subjects with history of untreated or inadequately treated latent TB infection, active **or latent** TB infection at screening will be excluded. No changes were made to the list of exceptions to this exclusion criteria.	Clarification
Synopsis: Efficacy assessments	"The proportion of subjects in clinical remission at Week 12" was changed to "The proportion of subjects achieving clinical remission at Week 12". "The proportion of subjects in clinical remission at Week 52" was changed to "The proportion of subjects achieving clinical remission at Week 52".	Update in terminology was made for consistency with other efficacy endpoints.

Section No. and Name	Description of Change	Brief Rationale
Synopsis: Pharmacokinetic assessments	The following sentence was restructured from "Plasma concentrations of etrasimod, M3 (AR503641), and other metabolite(s) of interest (if warranted) will be assessed from samples collected pre-dose…" to "Plasma concentrations of etrasimod, and if warranted M3 (AR503641) and other metabolite(s) of interest, will be assessed from samples collected pre-dose…".	For clarity to Investigator
Synopsis: Other assessments 10.9.3. Biomarkers Table 7, Schedule of Assessments, Footnote "u"	Added the Week 2 timepoint to the endpoint of change from baseline in level of fecal calprotectin.	Correction was made for consistency with the Schedule of Assessments, Table 7.
Synopsis 10.12.1 Efficacy Analysis	The term "analysis" was updated to "primary analysis".	For consistency with terminology in Section 10.4 (Missing Data)
5.1 Discontinuation from Study Treatment	Lack of efficacy was added as a reason why a subject may discontinue from double-blind treatment.	Correction
9.3.1 Tuberculosis Screening and Chest X-Ray	Added additional instructions on TB testing with regards to retesting.	For clarity to Investigator
9.3.10 Proctosigmoidoscopy/ Colonoscopy and Modified Mayo Score Derivation	Changed "should" to "must".	For clarity to Investigator
9.6 Pharmacokinetics	The following sentence was restructured from "Blood samples for analysis of etrasimod, M3 (AR503641), and other metabolite(s) of interest (if warranted) levels will be collected…" to "Blood samples for analysis of etrasimod, and if warranted M3 (AR503641) and other metabolite(s) of interest, will be collected…".	For clarity to Investigator
	Week 16 was added to the list of pre-dose pharmacokinetic samples.	Correction. Added for consistency with Table 8, Schedule of Assessments for PK assessments.

Section No. and Name	Description of Change	Brief Rationale
9.6 Pharmacokinetics (continued)	The following sentence was restructured from "Blood samples will be processed for collection of plasma fractions for determination of the concentrations of etrasimod, M3 (AR503641), and other metabolite(s) of interest (if warranted) will be collected at the following timepoints…" to "Blood samples will be processed for collection of plasma fractions for determination of the concentrations of etrasimod, and if warranted M3 (AR503641) and other metabolite(s) of interest, will be collected at the following timepoints…".	For clarity to Investigator
9.7.1 Modified Mayo Score/Mayo Clinic Score	Changed "daily subject-reported RB and SF subscores" to "daily subject-reported RB and SF scores".	Correction in terminology
	Changed "for a given day" to "in a 24-hour period".	For clarity to Investigator
9.9.1 Physical Examination	Added "skin" to the list of assessments for the full physical examination.	For consistency with Table 7, Footnote "n" and Table 8, Footnote "f".
9.9.5 Ophthalmoscopy and Optical Coherence Tomography	Updated language to allow use of Snellen chart for best corrected visual acuity measurement if available.	To provide allowance on methods to measure best corrected visual acuity in the scenario where Snellen chart may not be available.
	Clarification was made to include fluorescein angiogram as an example of testing of subjects with a suspicion of macular edema or subjects with uveitis findings on ophthalmic exam.	For clarity to Investigator
9.9.6 Tuberculosis Screening and Chest X-Ray	Added a statement to clarify that a TB screening questionnaire will be completed during the Screening Period for all subjects. Clarified that for subjects residing in countries with a high burden of TB or multi-drug resistant (MDR) TB as identified by WHO, the TB screening questionnaire will be completed at every study visit. Added additional instructions that subjects receiving TB prophylaxis treatment will complete a TB questionnaire at every study visit (until TB prophylaxis treatment course is completed).	For clarity to Investigator
	Removed "prior to randomization" with regards to administration of the TB screening questionnaire.	Correction

Section No. and Name	Description of Change	Brief Rationale
9.9.7 Clinical Laboratory Tests, Table 6 9.9.7.1.2 Pregnancy Testing Table 7 (Footnote "s") Table 8 (Footnote "j")	Changed "females of childbearing potential" to "women of childbearing potential".	For consistency with terminology in Clinical Trials Facilitation Group, Recommendations related to contraception and pregnancy testing in clinical trials.
10.4 Missing Data	"Subjects who experience worsening of disease prior to Week 12…" was changed to "Subjects with worsening of disease before Week 12".	For consistency with Study APD334-302 and Study APD334-303 protocol.
	"Subjects who discontinue the double-blind study for reasons other than worsening disease or missing study assessments while continuing with the study treatment will be considered as having missing data..." was changed to "Subjects who discontinue the double-blind study for reasons other than worsening disease or adverse event related to UC will be considered as having missing data..."	Correction
10.7 Secondary Endpoints	Moved text from Section 10.7.2 to Section 10.7 and updated the text to provide a reference and detail on all endpoints.	For clarity to Investigator
10.9.2 Pharmacokinetics	Changed "Plasma concentrations of etrasimod, M3 (AR503641), and other metabolite(s) of interest (if warranted) will be assessed…" to "Plasma concentrations of etrasimod, and if warranted M3 (AR503641) and other metabolite(s) of interest, will be assessed…".	For clarity to Investigator
Table 7, Schedule of Assessments	Tuberculosis "screening" was changed to "test". "Flexible proctosigmoidoscopy and biopsy" was changed to "Flexible proctosigmoidoscopy/colonoscopy and biopsy".	Updated terminology for consistency with other etrasimod protocols.
Table 7, Schedule of Assessments, Footnote "e"	Added a statement to clarify that a TB screening questionnaire will be completed for all subjects during the Screening Period. Clarified that for subjects residing in countries with a high burden of TB or multi-drug resistant (MDR) TB as identified by WHO, the TB screening questionnaire will be completed at every study visit. Added additional instructions that for subjects receiving TB prophylaxis treatment, the TB questionnaire will be completed at every study visit (until TB prophylaxis treatment course is completed).	For clarity to Investigator

Section No. and Name	Description of Change	Brief Rationale
Table 7, Schedule of Assessments, Footnote "v"	Modified language regarding screening proctosigmoidoscopy/ colonoscopy to state "Proctosigmoidoscopy/colonoscopy must be performed prior to randomization of treatment to allow central reader review (may take approximately 5 to 12 days)".	For clarity to Investigator and consistency with Section 9.3.10.
Table 8, Schedule of Assessments	Tuberculosis screening was removed from Week 16.	Correction
	"Flexible proctosigmoidoscopy and biopsy" was changed to "Flexible proctosigmoidoscopy/colonoscopy and biopsy".	Updated terminology for consistency with other etrasimod protocols.
Table 8, Schedule of Assessments, Footnote "q"	Removed "All subjects will complete TB screening to determine eligibility".	A correction was made as result of removing the Week 16 tuberculosis screening from the Schedule of Assessments.
	Added additional instructions that for subjects receiving TB prophylaxis treatment, the TB questionnaire will be completed at every study visit (until TB prophylaxis treatment course is completed).	For clarity to Investigator
Appendix 2, Tuberculosis Screening	Added a statement to clarify that a TB questionnaire will be completed for all subjects (see below) during the Screening period. Removed "prior to randomization" with regards to administration of the TB screening questionnaire. Added additional instructions that subjects receiving TB prophylaxis treatment the TB questionnaire will be completed at every study visit (until TB prophylaxis treatment course is completed).	For clarity to Investigator
	Added additional details regarding the TB questionnaire.	For clarity to Investigator
	Added clarification that "one retest is allowed with approval from Medical Monitor per Section 9.3.1" for a newly identified positive IGRA at Screening.	For additional guidance to Investigators and for consistency with changes made to Section 9.3. in APD334-301 Amendment 2.0.
	Removed list of countries identified as having a high TB burden.	A link with reference to the complete list of countries with TB high burden and multi-drug resistant TB high burden was also added so this text was no longer necessary.
	The Tuberculosis Screening Questionnaire was updated.	Updates were made to the source document worksheet.

CLINICAL STUDY PROTOCOL
SUMMARY OF CHANGES

Protocol title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 52-Week Study to Assess the Efficacy and Safety of Etrasimod in Subjects with Moderately to Severely Active Ulcerative Colitis
Protocol number:	APD334-301
Version:	Amendment 4.0, 22 December 2020
Replaces version:	Amendment 3.0, 07 February 2020

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 4.0, 22 December 2020

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the safety or physical/mental integrity of subjects.

Overall Rationale for the Amendment

The overall rationale for this amendment is to update the subject enrollment number and include guidance for conducting virtual and offsite visits. Also, information on anti-arrhythmic drugs was added to prohibited concomitant therapies and the corticosteroid-free remission secondary endpoint was updated. Language was updated regarding timing of screening optical coherence tomography (OCTs) and pulmonary function tests (PFTs). Additionally, an exclusion criterion was added regarding treatment with topical rectal Chinese medicine, enemas or suppositories prior to randomization. Minor corrections were made for consistency within the protocol.

Summary of Changes

Section No. and Name	Description of Change	Brief Rationale
Throughout	Minor editorial, formatting, and nomenclature revisions	Minor and do not affect the conduct of the protocol; therefore, have not been summarized
Title Page	Updated Amendment 4.0; Version date: 22 December 2020	Administrative change
Title Page Appendix 7, Sponsor Signature	Revised Sponsor's Responsible Medical Officer name and title to [redacted]	Administrative change
Protocol History	Updated protocol history table	Administrative change
Protocol Synopsis: Number of subjects (planned) Protocol Synopsis: Statistical Methods 3.1. Summary of Study Design, Figure 1 10.2. Determination of Sample Size	Updated to enrollment to 420 subjects	To increase the joint statistical power of the co-primary endpoints to at least 90% and enable a more robust assessment in the per protocol analysis due to anticipated impact by COVID-19 pandemic
Protocol Synopsis: Eligibility criteria 4.1. Inclusion Criteria (Inclusion Criterion 7c [Biologic therapy or JAK inhibitor therapy])	Revised "interleukin 12/23 antibodies" to "anti-interleukin 12/23 antibodies"	For nomenclature accuracy and consistency with Inclusion Criterion 7c (Biologic therapy or JAK inhibitor therapy)
Protocol Synopsis: Eligibility criteria 4.1. Inclusion Criteria (Inclusion Criterion 8)	Removed "antidiarrheals (eg, loperamide, diphenoxylate with atropine) for control of chronic diarrhea"	To avoid potentially confounding medication use
Protocol Synopsis: Eligibility criteria 4.1. Inclusion Criteria (Inclusion Criterion 12b)	Added "nonpregnant" to "female of childbearing potential"	To provide additional clarity that only nonpregnant females are eligible
Protocol Synopsis: Eligibility criteria 4.1. Inclusion Criteria (Inclusion Criterion 12c)	Added the words "subject with a pregnant or nonpregnant female of childbearing potential partner" and revised 4 weeks to "30 days"	To provide further clarity for male contraception criteria
Protocol Synopsis: Eligibility criteria 4.2. Exclusion Criteria (Exclusion Criterion 1)	Revised to: "Physician judgment that the subject is likely to require hospitalization for medical care or surgical intervention of any kind for UC (eg, colectomy) within 12 Weeks following randomization"	Revised to make the reference point within the 12 weeks following randomization, not before randomization

Section No. and Name	Description of Change	Brief Rationale
Protocol Synopsis: Eligibility criteria 4.2. Exclusion Criteria (Exclusion Criterion 8)	Revised second bullet to: "History or presence of second-degree or third-degree atrioventricular block, sick sinus syndrome, or periods of asystole for > 3 seconds without a functional pacemaker"	Corrected "defibrillator" to "pacemaker" as this is the appropriate device for these conditions
	Revised the first bullet to: "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"	Revised to clarify exclusion applies to the 6 months preceding screening and the screening period (inclusive)
	Revised bullets 4 and 5 to: "Screening or Week 0/Day 1 prerandomization…"	Corrected use of "and" and replaced with "or," an error that was not updated when the text was moved from an inclusion to exclusion criterion in the ELEVATE protocols
	Revised sixth bullet to: "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"	To clarify that the exclusion criterion about any change or expected (planned) change to anti-arrhythmic drugs should be 1 week <u>before or after</u> randomization
Protocol Synopsis: Eligibility criteria 4.2. Exclusion Criteria (Exclusion Criterion 23)	Revised language to: "Treatment with a biologic agent ≤ 8 weeks or a small molecule agent ≤ 5 elimination half-lives and detectable drug level prior to randomization"	Refined for clarity and to add exclusion based on detectable drug levels. For example, a subject with ≤ 8 weeks on a biologic but no detectable drug levels will not be excluded
Protocol Synopsis: Eligibility criteria 4.2. Exclusion Criteria (Exclusion Criterion 24)	Revised criterion to: "Treatment with an investigational therapy ≤ 3 months prior to randomization"	"Within" implies before and after randomization but investigational therapies cannot be received after randomization
Protocol Synopsis: Eligibility criteria 4.2. Exclusion Criteria (Exclusion Criterion 26)	Revised text about timing of topical treatments to: "Treatment with topical rectal 5-ASA, short-chain fatty acid enemas, or steroids ≤ 2 weeks prior to and during screening"	Revised to ensure clarity and consistent descriptions as to the timing and potential impact of other treatments and procedures relative to the screening period and start of treatment. This will ensure that screening results can be best interpreted and reduce potential safety or confounding impacts on etrasimod treatment

Section No. and Name	Description of Change	Brief Rationale
Protocol Synopsis: Eligibility criteria 4.2. Exclusion Criteria (Exclusion Criterion 27)	Added exclusion criterion "Treatment with topical rectal traditional medicine (eg, Chinese medicine), herb enemas, or suppositories ≤ 2 weeks prior to randomization"	Added to avoid potentially confounding treatments that could impact the ability to evaluate etrasimod
Protocol Synopsis: Eligibility criteria 4.2. Exclusion Criteria (Exclusion Criterion 28)	Revised language about timing of methotrexate to: "Treatment with methotrexate ≤ 8 weeks prior to and during screening or cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil (MMF) ≤ 16 weeks prior to and during screening"	Revised to ensure clarity and consistent descriptions as to the timing and potential impact of other treatments and procedures relative to the screening period and start of treatment. This will ensure that screening results can be best interpreted and reduce potential safety or confounding impacts on etrasimod treatment
Protocol Synopsis: Eligibility criteria 4.2. Exclusion Criteria (Exclusion Criterion 29)	Revised criterion to: "Receipt of a live vaccine ≤ 4 weeks prior to randomization"	"Within" implies before and after randomization but live vaccines cannot be received after randomization
Protocol Synopsis: Eligibility criteria 4.2. Exclusion Criteria (Exclusion Criterion 33)	Revised criterion to: "Treatment with IV immune globulin or plasmapheresis ≤ 3 months prior to randomization"	"Within" implies before and after randomization but IV immune globulin or plasmapheresis treatments cannot be administered after randomization
Protocol Synopsis: Eligibility criteria 4.2. Exclusion Criteria (Exclusion Criterion 34)	Revised criterion to: "Chronic use of therapies that moderately/strongly inhibit/induce cytochrome P450 (CYP) 2C8 and 2C9 metabolism and inhibitors of UGT1A7 ≤ 4 weeks prior to randomization"	"Within" implies before and after randomization but therapies that moderately/strongly inhibit/induce cytochrome P450 (CYP) 2C8 and 2C9 metabolism and inhibitors of UGT1A7 cannot be administered after randomization
Protocol Synopsis, Efficacy assessments 10.7.1. Key Secondary Efficacy Endpoints	Revised the following endpoint: "The proportion of subjects in clinical remission at Week 52 and who had not been receiving corticosteroids for ≥ 12 weeks prior to Week 52"	To evaluate the overall impact of etrasimod treatment on long-term treatment and achievement of clinical remission while either eliminating or preventing the use of corticosteroids.
1.3. Benefit/Risk Assessment	Added the following sentence: "Considering the significant unmet need for safe and effective, orally administered treatments for UC, etrasimod may potentially provide therapeutic benefit via S1P receptor modulation."	Added a statement regarding potential benefit of S1P-receptor modulation in UC to add balance to the Benefit/Risk section

Section No. and Name	Description of Change	Brief Rationale
5.3. Subjects "Lost to Follow-Up" Prior to Last Scheduled Visit	Added "onsite, offsite, virtual, or hybrid" to read "the following actions must be taken if a subject fails to attend a required onsite, offsite, virtual or hybrid visit"	Modification to include offsite, virtual, and hybrid study visit types
6.6. Treatment Compliance	Added the following sentence: "If there is a discrepancy between the tablet count and the subject's compliance per the eDiary, it should be discussed with the subject and noted in the source documents."	To provide further guidance on drug accountability procedures.
6.7. Concomitant Therapy	Revised first paragraph as follows: "All over-the-counter and prescribed concomitant medications, blood products, ~~all~~ procedures, vitamins, and holistic products, ~~and radiotherapy~~ administered during the Screening Period and during the study ~~will be collected from Day 1 (pre dose)~~ through the safety reporting period must be recorded in the eCRF, as appropriate. ~~Any medication given for a study protocol related adverse event should be recorded from the time of informed consent/assent.~~	To expand the collection of concomitant medications starting with the screening period and through the duration of the study and to provide additional clarity for information to be captured.
6.7.2. Allowed Concomitant Therapy	Removed "All medications (over-the-counter and prescribed) that are taken by subjects and all procedures that are performed during the Screening Period and during the study must be recorded in the eCRF"	Relocated to Section 6.7.
6.7.3. Prohibited Concomitant Therapy	Added the following bullet to the list of prohibited concomitant medications: "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"	To clarify that the exclusion criterion about any change or expected (planned) change to anti-arrhythmic drugs should be 1 week before and after randomization
	Added siponimod and ozanimod to list of prohibited concomitant medications	Due to recent approvals for these agents

Section No. and Name	Description of Change	Brief Rationale
6.7.3. Prohibited Concomitant Therapy (Continued)	Removed "while enrolled in this study" in reference to major elective surgery	Redundant text
8.2. Study Treatment Storage and Handling	Added "In the case where a subject attends a virtual visit (see 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 subject 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 instructions will be provided separately."	To address potential need for an alternate method to provide study treatment in accordance with information in the Instructions for IP shipment from Site to Subject(s) for ELEVATE UC 52 (Study APD334-301)/ELEVATE UC OLE (Study APD334-303) memo and to align with other protocols.
8.4. Study Treatment Accountability	Relocated and revised the following sentences to Section 9.6, Virtual/Hybrid Visits: "Subjects will record tablet self-administration daily in an eDiary that will be reviewed at each treatment visit by study site staff." Removed "in the IWRS"	To provide guidance on drug accountability procedures in the event of a virtual visit in the context of other virtual visit activities
9.1. General Instructions	Revised the second bullet point as follows: "Results of all protocol required procedures ~~must~~ will be recorded in the eCRF whenever applicable." Revised the seventh bullet point as follows: "~~On~~For onsite and offsite study ~~day~~ visits (see Section 9.6 and Table 7 and Table 8), subjects should take their study treatment ~~at the study site~~ after blood draws for PK and after all pre-dose assessments and procedures have been completed."	To indicate that only those procedures which require eCRF documentation should be documented. To account for multiple visit types.

Section No. and Name	Description of Change	Brief Rationale
9.3. Screening and Eligibility	Added the following sentences: "The 28-day Screening Period may also be extended on a case-by-case basis to accommodate reasonable delays in specific screening assessments (eg, pulmonary function tests [PFTs], optical coherence tomography [OCT]) due to testing availability. The Medical Monitor must be consulted prior to extension in each case"	To protect the health of the subjects and provide flexibility in light of the COVID-19 pandemic. This will replace the provisions provided in the Pulmonary Function Testing communication of 07 April 2020 and theCOVID-19 Memo 2. This will serve to replace the memo and communication.
9.3.6. Ulcerative Colitis History/Medical History	Revised the following sentence as follows: "The history should include recent blood donations (~~within~~ ≤ 30 days prior to the screening period), illnesses, and participation in other investigational drug studies"	For clarity about timing relative to screening period
9.3.10. Clinical Laboratory Assessments	New section. Added and modified section as follows and moved the following text from Section 9.3.11 (formerly Section 9.3.10) to this new section: Screening samples for complete blood count (CBC) with differential, platelet count, lymphocyte counts, T lymphocytes, B lymphocytes, natural killer lymphocytes (TBNK), ~~CD4 T-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~~the first dose of study treatment~~. In the case of new clinical laboratory abnormalities detected prior to randomization~~the first dose~~, the eligibility of the subject should be reconsidered with the guidance of the Medical Monitor. Subsequent sections were renumbered accordingly.	Correction. The text in this section was erroneously contained in Section 9.3.11 "Proctosigmoidoscopy/Colonoscopy and Modified Mayo Score Derivation" Revised timing of screening samples for clarity.
9.4.2. Treatment Period	Revised the following sentences: "For the Week 12 through Week 48Visits, and ET Visit, a study visit window of ± 7 days is permitted. For the Week 52 Visit, a study visit window of ± 14 days is permitted."	To enable critical visit assessments to be made in the event that facilities are inaccessible due to various logistic or operational constraints

Section No. and Name	Description of Change	Brief Rationale
9.5. Follow-Up Period Appendix 1: Schedules of Assessments, Table 7: Schedule of Assessments, Footnote b	Revised the following sentence: "If the Early Termination or Study Completion visit is ≥ 2 weeks after the last administration of study treatment, the 2-Week Follow-Up visit is not required"	For clarity and internal consistency given that the objective of the follow-up is to understand any withdrawal effect, so it must be timed from last dose
9.6. Virtual/Hybrid Visits	New section. Subsequent sections were renumbered accordingly.	To reduce patient burden and allow flexibility, certain procedures may now be conducted offsite and/or virtually while ensuring subject safety and study integrity. To address items previously accounted for in the "Instruction for IP Shipment from Site to Subjects and Performing Associated Drug Accountability, Pulmonary Function Testing", and "Coronavirus Disease 2019 (COVID-19) Memo #2" memos related to the COVID-19 pandemic, which should become inactive upon completion of this amendment
9.8.1.1. Endoscopy	Revised the following sentence as follows: "For subjects with pancolitis > 8 years duration or subjects with left-sided colitis > 12 years without a surveillance colonoscopy within 12 months ~~of~~ prior to baseline …"	For clarity in regards to timing of surveillance colonoscopy which cannot occur after baseline
9.8.1.2. Endoscopic Biopsies	Added the following sentence: "Post-randomization detected polyps or suspicious findings during endoscopy will be managed as per local standard of care."	To provide instructions for handling of polyps or suspicious findings after randomization

Section No. and Name	Description of Change	Brief Rationale
9.10.4. Pulmonary Function Test Appendix 1: Schedules of Assessments, Table 7: Schedule of Assessments, Footnote q	Added the following sentences: "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 results from the Week 12/Early Termination visit are abnormal. The 2-Week Follow-Up visit assessment is only required if results from the Week 12/Early Termination visit are abnormal."	To clarify timing and reduce patient burden, the necessity of conducting PFTs has been updated if they have been performed in the last 4 weeks
	Revised text to: "When available, DLCO measurements will also be performed. When DLCO is not available, sites should consult the Sponsor or Sponsor's delegate."	To provide flexibility in location and capacity for DLCO measurements
9.10.4. Pulmonary Function Test	Added paragraph: "The safety of trial subjects and site staff is paramount, so it is at the Investigator's discretion whether PFT can be safely administered to trial subjects during the treatment period. The Investigator should evaluate on a case-by-case basis how best to proceed based on the subject'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, COVID-19 transmission), then this decision and rationale should be appropriately captured in the subject'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."	To ensure subject safety, PFT may be conducted as deemed appropriate by the Investigator while maintaining study integrity and in accordance with the Pulmonary Function Test communication of 07 April 2020 as related to the COVID-19 pandemic and will replace that communication instruction.

Section No. and Name	Description of Change	Brief Rationale
9.10.5. Ophthalmoscopy and Optical Coherence Tomography Appendix 1: Schedules of Assessments, Table 7: Schedule of Assessments, Footnote r	Added the following sentence: "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."	To clarify timing and reduce patient burden, the necessity of conducting OCTs has been updated if they have been performed in the last 4 weeks
9.10.5. Ophthalmoscopy and Optical Coherence Tomography	Added the following sentence: "The 2-Week Follow-Up visit assessment is only required if clinically indicated."	To reduce patient burden, the necessity of conducting OCTs during follow up is only required if clinically indicated
	Removed "for example, autorefraction" revising the following sentence as follows: "Best corrected visual acuity measurement (using Snellen chart internationally [if available])"	Removed example to avoid confusion at some sites
	Removed the following sentence from the Screening Visit" and Scheduled Post-Screening Visits lists: "Retinal photographs will be taken"	To provide flexibility, clarity, and guidance as to necessary vs optional procedures as pertains to eye exams as this is not considered an essential safety evaluation given that OCT is being conducted

	Changed the following procedures to optional and provided additional detail as follows:
	• Optional procedures in case of clinically significant abnormalities on ophthalmic exam may include, but are not limited to:
	  ○ Retinal photographs
	  ○ Intraocular pressure	

Section No. and Name	Description of Change	Brief Rationale
9.10.7. Clinical Laboratory Tests, Table 6	Revised Footnote a as follows: "Total WBC, neutrophil, lymphocyte, and ~~CD4 T cell counts~~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."	Correction for accuracy given that Investigators can access the whole blood cell and differential values at Screening
	Revised Footnote b as follows: "Investigators will remain blinded to the results after randomization"	
9.10.8.3.1. Serious Adverse Events	Removed the following sentence: "All other hospitalizations, including elective hospitalizations for any condition that was not preexisting, will be reported as an SAE."	To correct the SAE definition of "elective hospitalization" to eliminate the inclusion of non-urgent/non-emergent events not requiring hospital admission, which would result in an inaccurate assessment of the safety profile of the study drug
10.4. Missing Data	Added "for binary responder type endpoints" for handling missing data	Additional detail provided for clarity
	Revised for continuous or score endpoints as follows: "subjects with missing data will be ~~handled using last observation carry~~ forward analyzed with their observed data only" instead of "using last observation carry forward".	To reflect Arena's current thinking on the missing data handling method

Section No. and Name	Description of Change	Brief Rationale
10.7.2. Other Secondary Efficacy Endpoints	Replaced the endpoint: "The proportion of subjects achieving clinical remission at Week 52 and corticosteroid-free since Weeks 16, 24, 32, 40 and 48" with the following endpoint: "The proportion of subjects who had not received corticosteroids for ≥ 4 weeks and achieved clinical remission at Week 52 among subjects receiving corticosteroids at baseline"	Expanded the endpoint to analyze subjects in clinical remission at the end of the study (Week 52) who were corticosteroid-free for ≥ 4 weeks at any time during the study. This analysis will enable an evaluation of the impact of etrasimod on achieving clinical remission while eliminating the use of corticosteroids.
[redacted]	[redacted]	[redacted]
14.1. Investigator Responsibilities	Revised sentences below as follows: "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." "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."	Updated language to reflect Arena standard protocol language for this section and account for current standards

Section No. and Name	Description of Change	Brief Rationale
14.2. Sponsor Responsibilities	Revised the paragraph as follows: "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."	Updated language to reflect Arena standard protocol language for this section and account for current standards
Appendix 1: Schedules of Assessments, Table 7: Schedule of Assessments, Screening and 12-Week Treatment Period, Footnote a	Added the following sentence: "All visits beyond W0/D1 may be virtual or hybrid visits (Section 9.6)."	Updated to account for modifications in Section 9.6 (see above)

Section No. and Name	Description of Change	Brief Rationale
Appendix 1: Schedules of Assessments, Table 7: Schedule of Assessments, Footnotes p and q	Split footnote "p" into "p" and "q" as follows: [p] A PFT will include FEV_1 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). [q] The Screening pulmonary function test (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 9.10.4.	To delineate and clarify the PFT timing information for the specific PFT assessments
Appendix 1: Schedules of Assessments, Table 8: Schedule of Assessments	Revised column header as follows: "W52/D365 ± 14 Days/Early Termination[a] ± 7 Days"	To enable critical visit assessments to be made in the event that facilities are inaccessible due to various logistic or operational constraints
Appendix 1: Schedules of Assessments Table 7: Schedule of Assessments, Footnote y Table 8: Schedule of Assessments, Footnote o	Added "Biomarker sample collection is not required at Early Termination visit."	Footnote added to clarify sample collection needed at Early Termination
Appendix 1: Schedules of Assessments, Table 7: Schedule of Assessments, Footnote r Table 8: Schedule of Assessments, Footnote h and Footnote i	Revised second sentence in the footnote to: "The 2-Week Follow-Up visit assessment is only required if clinically indicated."	To reduce patient burden, the necessity of conducting OCTs during follow up is only required if clinically indicated