CLINICAL STUDY PROTOCOL

Protocol number:	APD334-308
Protocol title:	A Phase 3, Double-Blind, Placebo-Controlled, 40-Week Extension Study to Assess the Efficacy and Safety of Etrasimod in Japanese Subjects with Moderately to Severely Active Ulcerative Colitis
Brief title:	ELEVATE UC 40 JAPAN: Etrasimod Versus Placebo for the Treatment of Moderately to Severely Active Ulcerative Colitis in Japanese Subjects
Study drug:	Etrasimod (APD334)
Indication:	Ulcerative colitis
Phase:	3
Sponsor name:	Arena Pharmaceuticals, Inc. 6154 Nancy Ridge Drive San Diego, CA 92121 USA
Sponsor's responsible medical officer	PPD MD, MHS, FACC PPD
Clinical lead:	PPD PhD PPD Tel: PPD E-mail: PPD
SAE reporting:	IQVIA Pharmacovigilance Phone: 1-800-761-6501 (access code 00-663-5111) Fax: 0034-800-401163 Email (preferred method): ArenaSafety@iqvia.com
Version:	Original 0.0, dated 15 April 2020
Sponsor approval:	This protocol was approved by the Sponsor's Responsible Medical Officer or delegate. The electronic signature manifest is appended.

Confidentiality Statement

PROTOCOL SYNOPSIS

Sponsor: Arena Pharmaceuticals, Inc.

Name of investigational study drug: Etrasimod (APD334)

Protocol number: APD334-308

Protocol title: A Phase 3, Double-Blind, Placebo-Controlled, 40-Week Extension Study to Assess the Efficacy and Safety of Etrasimod in Japanese Subjects with Moderately to Severely Active Ulcerative Colitis

Phase: 3

Region: Japan

Objectives:

Primary:

The primary objective is to assess the efficacy of etrasimod on clinical remission in Japanese subjects with moderately to severely active ulcerative colitis (UC) at timepoints up to 52 weeks of treatment (12 weeks in Study APD334-302 plus 40 weeks in Study APD334-308; Figure 1).

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 Japanese subjects with moderately to severely active UC at timepoints up to 52 weeks of treatment (12 weeks in Study APD334-302 plus 40 weeks in Study APD334-308).

Safety:

The safety objective is to assess the long-term safety of etrasimod in Japanese subjects with moderately to severely active UC after daily doses of 2 mg for up to 52 weeks (12 weeks in Study APD334-302 plus 40 weeks in Study APD334-308).

CCI [redacted]

Study design:

This is a multicenter, double-blind, placebo-controlled extension study of APD334-302 (12-week, randomized, double-blind, placebo-controlled induction study) to evaluate the efficacy and safety of etrasimod 2 mg in Japanese subjects with moderately to severely active UC. Study APD334-308 consists of a 40-Week Treatment Period and a 4-Week Follow-Up Period.

Japanese subjects who completed the Week 12 visit of Study APD334-302 are eligible for the APD334-308 study. The Week 12 visit of Study APD334-302 serves as the Day 1 visit of Study APD334-308. Subjects will continue with the same blinded treatment assigned in Study APD334-302 for a total treatment duration of 52 weeks (12 weeks in Study APD334-302 plus 40 weeks in Study APD334-308).

End of 40-Week Double-Blind Treatment Period

Disease worsening will be monitored by Investigators through the Treatment Period. Subjects who either experience disease worsening or complete all study procedures at Week 52 will have the option to enroll into the APD334-303 open-label extension (OLE) study if they meet all eligibility criteria. Subjects may be eligible to enroll in the OLE study provided their endoscopic score (ES) is ≥ 2 and they meet one of the following entry criteria:

- Rectal bleeding (RB) subscore ≥ 2 at 2 timepoints at least 7 days and no more than 14 days apart
- RB + stool frequency (SF) subscore ≥ 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 study. An endoscopy should be performed upon the appearance of UC symptoms but no more than 14 days after the second timepoint for entry 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 on treatment visit/Early Termination visit.

Number of subjects (planned):

Approximately 35 Japanese subjects are planned to be enrolled into this study.

Eligibility criteria:

Inclusion criteria:

Subjects are eligible to enroll into this study if they fulfill ALL of the following:

1. Must have completed the Week 12 visit of Study APD334-302
2. Ability to provide written informed consent or assent (parent or legal guardian must provide consent for a subject < 20 years of age or as required per local regulations who has assented to participate in the study) and to be compliant with the schedule of protocol assessments. Enrollment of subjects < 20 years should be conducted only if acceptable according to local laws and regulations.
3. Eligible women of childbearing potential must fulfill the following:
   a. Have a negative urine beta-human chorionic gonadotropin (β-hCG) pregnancy test at the Week 12 visit of Study APD334-302
   b. Not breastfeeding
4. 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) oral hormonal contraception associated with inhibition of ovulation
- Progestogen-only oral hormonal contraception associated with inhibition of ovulation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner, provided that partner is the sole sexual partner of the female of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success
- Sexual abstinence (complete sexual abstinence defined as refraining from heterosexual intercourse for the entire period of risk associated with study treatments). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the 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 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:

1. If the Investigator considers the subject to be unsuitable for any reason to participate in the study

Exclusions related to general health

2. Subjects requiring partial or total colectomy during the APD334-302 study
3. Subjects requiring treatment with prohibited concomitant medications as defined in Section 6.7.3

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 years.

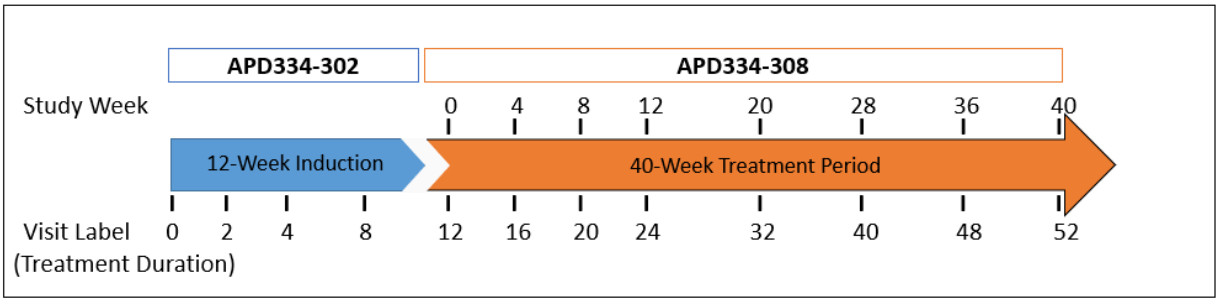
Reference therapy, description, mode of administration:

Placebo tablets, by mouth, once daily

Efficacy assessments:

Study visit labels in this protocol refer to the cumulative weeks of treatment from Week 0/Day 1 of Study APD334-302 (Figure 1).

Figure 1: Study Visits



Note: Weeks at the top refer to study weeks in Study APD334-308. Weeks at the bottom refer to the cumulative weeks of treatment starting with Study APD334-302 and continuing onto Study APD334-308.

The modified Mayo score (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: SF, RB, and ES. The ES will be determined by central reading.

Definitions:

- Baseline: Baseline refers to the last non-missing measurement on or before the first dose in Study APD334-302.
- 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 52

Key secondary efficacy endpoints:

- The proportion of subjects achieving endoscopic improvement at Week 52
- The proportion of subjects achieving symptomatic remission at Week 52
- The proportion of subjects, who had not been receiving corticosteroids for ≥ 12 weeks, achieving clinical remission at Week 52 among subjects receiving corticosteroids at APD334-302 study entry
- The proportion of subjects with mucosal healing at Week 52
- The proportion of subjects achieving clinical remission at both Week 12 of Study APD334-302 and Week 52 of Study APD334-308

Pharmacokinetic assessments:

Plasma concentrations of etrasimod and, if warranted, M3 (AR503641) and other metabolite(s) of interest, will be assessed from samples collected predose (trough) at Weeks 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 serious adverse event (SAE) or adverse event leading to study treatment discontinuation.

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

Other assessments:

CCI

CCI

Safety assessments:

Safety will be assessed using monitoring of adverse events, clinical laboratory findings, 12-lead electrocardiograms (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

Approximately 35 Japanese subjects in the parent Study APD334-302, and those subjects may be eligible to enroll in Study APD334-308.

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) naive to biologic or Janus kinase (JAK) inhibitor therapy at APD334-302 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.

Data from this study will be integrated with the global studies (Study APD334-301 and Study APD334-302) for the summaries of efficacy and safety, including the bridging analyses for the Japanese subjects to the global population.

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.

Safety analysis

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

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

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
bpm	beats per minute
CBC	complete blood count
CD	Crohn's disease
CFR	Code of Federal Regulations
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
EDC	electronic data capture
EIMs	extraintestinal manifestations
ES	endoscopic score
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEV_1	forced expiratory volume at 1 second
FVC	forced vital capacity

Abbreviation	Definition
GCP	Good Clinical Practice
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
ICCC	In-Country Caretaker for Clinical Trial
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
IWRS	Interactive Web Response System
JAK	Janus kinase
MAR	missing at random
J-GCP	Japan Good Clinical Practice
MCS	Mayo clinic score
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified Full Analysis Set
MMF	mycophenolate mofetil
MMS	modified Mayo score
6-MP	6-mercaptopurine
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

Abbreviation	Definition
PP	Per Protocol
QTcF	Fridericia's corrected QT interval
RB	rectal bleeding
RHI	Robarts Histopathology Index
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 procedure
TB	tuberculosis
TEAE	treatment-emergent adverse event
TMF	trial master file
TNF	tumor necrosis factor
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
WHO	World Health Organization
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 2017).

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. 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

Common 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 returned to approximately baseline levels within 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 multicenter, double-blind, placebo-controlled extension study of Study APD334-302 (12-week, randomized, double-blind, placebo-controlled induction study) to evaluate the efficacy and safety of etrasimod in Japanese subjects with moderately to severely active UC. The study consists of a 40-Week Treatment Period and a 4-Week Follow-Up Period.

Subjects who complete the total 52-week treatment or subjects with worsening disease (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 Japanese patients with UC.

1.4. Visit Labeling

Study APD334-308 is a 40-week extension study for Japanese subjects who completed Study APD334-302 (12-week, randomized, double-blind, placebo-controlled induction study). Subjects will maintain the same blinded treatment assignment as in Study APD334-302. The total duration of treatment for subjects who complete this study is 52 weeks.

To maintain consistency with global Study APD334-301 (52-week, randomized, double-blind, placebo-controlled study), visit labels in this protocol will represent the cumulative treatment duration since first dose in Study APD334-302. The Week 12 visit in Study APD334-302 is the first visit in this protocol and is labeled as Week 12 (Figure 1).

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective is to assess the efficacy of etrasimod on clinical remission in Japanese subjects with moderately to severely active UC at timepoints up to 52 weeks of treatment (12 weeks in Study APD334-302 plus 40 weeks in Study APD334-308).

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 Japanese subjects with moderately to severely active UC at timepoints up to 52 weeks of treatment (12 weeks in Study APD334-302 plus 40 weeks in Study APD334-308).

2.3. Safety Objective

The safety objective is to assess the long-term safety of etrasimod in Japanese subjects with moderately to severely active UC after daily doses of 2 mg for up to 52 weeks (12 weeks in Study APD334-302 plus 40 weeks in Study APD334-308).

CCI [redacted]

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

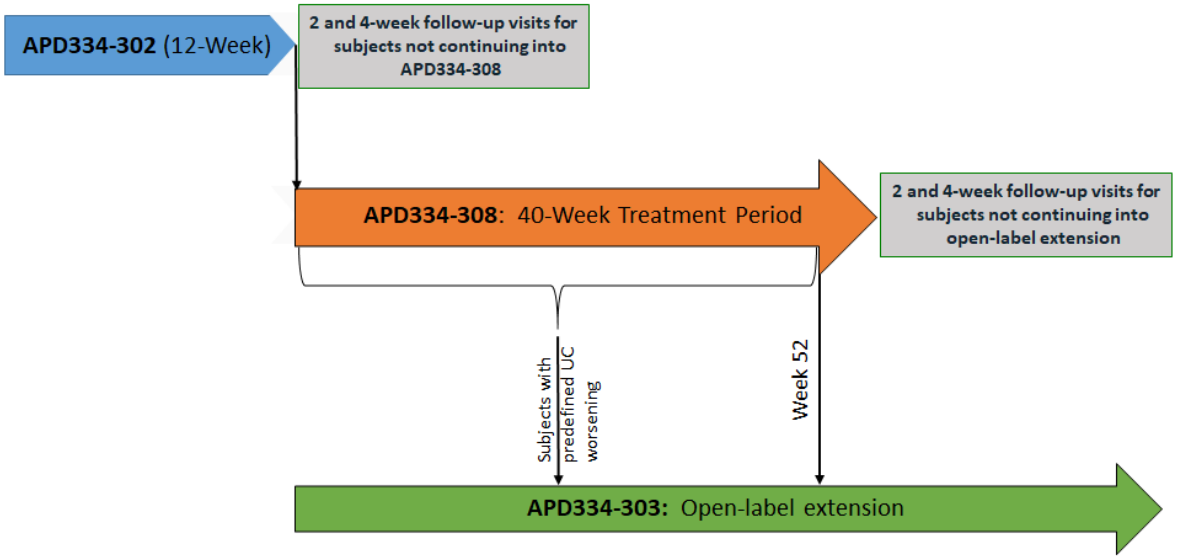
This is a multicenter, double-blind, placebo-controlled extension study of APD334-302 (12-week, randomized, double-blind, placebo-controlled induction study) to evaluate the efficacy and safety of etrasimod 2 mg in Japanese subjects with moderately to severely active UC. The study consists of a 40-Week Treatment Period and a 4-Week Follow-Up Period (Figure 2).

Japanese subjects who completed the Week 12 visit of Study APD334-302 are eligible for this study. The Week 12 visit of Study APD334-302 serves as the Day 1 visit of this study. Subjects will continue with the same blinded treatment assigned in Study APD334-302 for a total treatment duration of 52 weeks (12 weeks in Study APD334-302 plus 40 weeks in Study APD334-308).

Disease worsening will be monitored by Investigators through the treatment period. Subjects who either experience disease worsening or complete all study procedures at Week 52 will have the option to enroll into the APD334-303 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 2: Study Design



3.2. Rationale for Study Design

This study is designed to evaluate the efficacy and safety of etrasimod in Japanese 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 weeks in Study APD334-302 and 40 weeks in Study APD334-308. This 40-week study will provide subjects with 52 weeks of treatment exposure and enable bridging of efficacy and safety of Japanese subjects to the global population treated in Study APD334-301. 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 primary endpoint of clinical remission at Week 52 as assessed using the modified Mayo Score (MMS) is standard, widely used, and is 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.

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.

Subjects meeting predefined eligibility criteria during the 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 APD334-308 study consists of a 40-Week Treatment Period and a 4-Week Follow-Up Period. The study duration is expected to be approximately 2 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 APD334-308 study:

1. Must have completed the Week 12 visit of Study APD334-302
2. Ability to provide written informed consent or assent (parent or legal guardian must provide consent for a subject < 20 years of age or as required per local regulations who has assented to participate in the study) and to be compliant with the schedule of protocol assessments. Enrollment of subjects < 20 years should be conducted only if acceptable according to local laws and regulations.
3. Eligible women of childbearing potential must fulfill the following:
   a. Have a negative urine beta-human chorionic gonadotropin (β-hCG) pregnancy test at the Week 12 visit of Study APD334-302
   b. Not breastfeeding
4. 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) oral hormonal contraception associated with inhibition of ovulation
      – Progestogen-only oral hormonal contraception associated with inhibition of ovulation
      – Intrauterine device (IUD)
      – Intrauterine hormone-releasing system
      – Bilateral tubal occlusion
      – Vasectomized partner, provided that partner is the sole sexual partner of the female of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success

- Sexual abstinence (complete sexual abstinence defined as refraining from heterosexual intercourse for the entire period of risk associated with study treatments). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the 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:

1. If the Investigator considers the subject to be unsuitable for any reason to participate in the study

Exclusions related to general health

2. Subjects requiring partial or total colectomy during the APD334-302 study
3. Subjects requiring treatment with prohibited concomitant medications as defined in Section 6.7.3

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, the subject may be eligible to enter the APD334-303 OLE study [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 (forced expiratory volume at 1 second [FEV_1] and/or forced vital capacity [FVC]) below 50% of the predicted values
- Confirmed diagnosis of clinically significant macular edema
- Confirmed diagnosis of active tuberculosis (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 the first or second day after re-initiation of treatment after a dose interruption of ≥ 7 days (Section 9.4.1)
- Subjects who have not met the discharge criteria on the first day of re-initiation of treatment after ≥ 4 hours of extended monitoring, or on the second day of re-initiation by 4 hours postdose.
- Pregnancy (Section 9.8.9)
- Suspected drug-induced liver injury as defined by the 2009 FDA Guidance for Industry (FDA 2009):
  - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 8 × upper limit of normal (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 visit within 7 days of the last study treatment administration (Table 7) and before initiation of any new treatments to complete all of the early termination assessments. If a subject discontinues due to pregnancy, they are not required to complete the endoscopy. If the Early Termination visit is within 4 weeks of the last sigmoidoscopy and biopsy, these procedures do not need to be repeated.

If the Early Termination visit is ≥ 2 weeks of 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 visit is ≥ 4 weeks of the last dose 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

Subjects whose UC condition in the opinion of the Investigator has not improved or has worsened compared with baseline assessment (Week 0/Day 1 in Study APD334-302), may be eligible to enroll in the OLE study (Study APD334-303) provided their ES is ≥ 2 and they meet one of the following entry criteria during Study APD334-308:

- Rectal bleeding (RB) subscore ≥ 2 at 2 timepoints at least 7 days and no more than 14 days apart
- RB + stool frequency (SF) subscore ≥ 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 return to the clinic for a required study 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 Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the termination of the study in accordance with applicable regulations.

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice (GCP)

6. STUDY TREATMENTS

6.1. Treatments Administered

During Study APD334-302, subjects were randomly assigned to 1 of 2 treatment groups (etrasimod or placebo) in a 2:1 ratio. Subjects will continue their treatment assignments during this study. 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 L-arginine (the arginine salt of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)acetic acid), which is an off-white to light-brown solid with an aqueous solubility of approximately 1.38 mg/mL at pH = 8.9 and 30°C. APD334 L-arginine is manufactured, packaged, tested, and released in compliance with current Good Manufacturing Practice.

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

6.3. Dosage and Administration

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

6.3.1. Instructions for Missed Dose(s)

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). 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 ≥ 7 consecutive days 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 9.4.1 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 9.4.1 should be performed any time a subject misses study treatment for ≥ 7 consecutive days.

6.4. Method of Assigning Subjects to Treatment

During Study APD334-302, subjects were randomly assigned to 1 of 2 treatment groups (etrasimod or placebo) in a 2:1 ratio and will continue their treatment assignments in this study.

Each subject will be dispensed blinded study treatment at study visits (Table 7) using an Interactive Web Response System (IWRS).

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 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.

Subjects who are unblinded may be eligible to enroll into the OLE study (Section 5.1.1).

During the clinical conduct of Study APD334-308, the Sponsor may lock and unblind Study APD334-302 for regulatory filings outside of Japan. Prior to unblinding Study APD334-302, a data disclosure plan will be finalized which will provide such details as access to and disclosure of treatment information, as well as description of the structure and process of blinded and unblinded study teams.

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 fully 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.

6.7. Concomitant Therapy

All concomitant medications, blood products, vitamins, holistic products, and radiotherapy administered will be collected from the first day of this study through the safety reporting period. Any medication given for a study protocol-related adverse event should be recorded from the time of informed consent/assent. All concomitant therapy ongoing during Study APD334-302 at the time of transition into Study APD334-308 will be recorded in the APD334-308 eCRF.

6.7.1. Required Concomitant Therapy

Not applicable

6.7.2. Allowed Concomitant Therapy

All medications (over-the-counter and prescribed) that are taken by subjects and all procedures that are performed during the study must be recorded in the eCRF. Concomitant medications for medical conditions other than UC are permitted as clinically indicated with the exception of prohibited medications and procedures (Section 6.7.3).

6.7.2.1. Permitted Medications for the Treatment of Ulcerative Colitis

Oral 5-ASA, oral corticosteroids, medicinal probiotics, and antidiarrheals are allowed according to the following guidelines. These products should not be started during the treatment period in subjects who are not already receiving them.

- Oral 5-ASA compounds provided the dose is stable
- Oral corticosteroid therapy (prednisone at a stable dose ≤ 20 mg/day or equivalent steroid) provided the dose is stable

- Probiotics (eg, *Saccharomyces boulardii*) provided the dose is stable
- Antidiarrheals (eg, loperamide) for control of chronic diarrhea

Subjects on existing oral corticosteroid therapy will be tapered during the treatment period (Section 6.7.2.2).

6.7.2.2. Corticosteroid Taper

Corticosteroids should be tapered for subjects entering this study. The recommended tapering schedule for oral corticosteroids 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

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

- Inhibitors of UGT1A7 (there are currently no known UGT1A7 inhibitors)
- 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, azathioprine [AZA], 6-mercaptopurine [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 mycophenolate mofetil (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)
- 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 while enrolled in this study
- 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:

- 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).

8.3. Study Treatment Preparation

Not applicable

8.4. Study Treatment Accountability

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

Subjects will record tablet self-administration daily in an eDiary that will be reviewed at each treatment visit by study site staff. At each visit, previously dispensed study treatment tablets will be collected by the Investigator or qualified individual and compliance assessed.

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

8.5. Study Treatment Retention and Disposal

Proteomics 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 or the investigational product manager will contact the Sponsor (or contract research organization [CRO]) for approval of such action. Final reconciliation will be performed at study completion.

9. STUDY ASSESSMENTS AND PROCEDURES

9.1. General Instructions

- Study procedures and their timing are summarized in the Schedule of Assessments (Table 7). Protocol waivers or exemptions are not allowed
- Results of all protocol-required procedures must be recorded in the eCRF
- 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 Schedule of Assessments, 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
- On study day visits, subjects should take their study treatment at the study site after blood draws for PK and after all predose 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. Eligibility

Subject eligibility for this study will be assessed based on protocol inclusion and exclusion criteria (Section 4.1 and Section 4.2).

9.4. Treatment Period

At the Week 12 visit of Study APD334-302, subjects will have procedures performed according to the schedule for Study APD334-302. Eligibility for Study APD334-308 will be determined at the Week 12 visit of Study APD334-302 and subjects will be consented/assented. For female subjects, a negative pregnancy test as part of Week 12 APD334-302 procedures is required for entry into Study APD334-308.

After confirmation of eligibility, the 40-Week Treatment Period will begin (Table 7). A study visit window of ± 7 days is permitted at each visit. Study visits are labeled relative to Day 1 visit date in Study APD334-302 (Figure 1).

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 Schedule of Assessments; Table 7)
- Physical examination
- Extraintestinal manifestations (EIMs; as indicated in the Schedule of Assessments; Table 7)
- PFT (as indicated in the Schedule of Assessments; Table 7)
- OCT (as indicated in the Schedule of Assessments; Table 7)
- Blood sample collection for laboratory tests and predose PK sampling

9.4.1. Guidance for Cardiac Monitoring Following Treatment Re-Initiation

If the dose is interrupted for ≥ 7 days, upon re-initiation of treatment subjects are to have cardiac monitoring performed. Predose vital signs (resting heart rate, systolic and diastolic blood pressure (BP), body temperature, and respiratory rate) will be used for comparison to postdose measurements. Re-initiation of study treatment should occur before 12:00 PM (noon).

First Dose Cardiac Monitoring

In-clinic cardiac monitoring, of at least 4 hours, will occur on the day of treatment re-initiation, and will include the following (Table 3):

- Full 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 predose
- After the first dose of study treatment following re-initiation, subjects must remain under observation in the clinic for at least 4 hours

- At Hours 1, 2, and 3 (± 15 minutes) postdose, 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	Predose	Hours 1, 2, 3 Postdose[a]	Hour 4 Postdose[a]
Blood pressure and heart rate[b]	X	X	X
12-lead ECG	X		X
Assess discharge criteria			X

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

Table 4: Discharge Criteria After Cardiac Monitoring

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

Note: 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.
AV, atrioventricular

Extended Cardiac Monitoring

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

- Vital signs will be assessed hourly and 12-lead ECG may be performed, as clinically indicated, until the 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 the first re-initiation day must return on the second re-initiation day for the second dose and will be re-monitored as on the first day. These subjects will be discontinued from study treatment if they do not meet the discharge criteria at 4 hours after the second re-initiation 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 the second re-initiation day for the second dose and will be re-monitored as on the first day. These subjects must be discontinued from treatment if they do not meet the discharge criteria at 4 hours after the second re-initiation dose and extended cardiac monitoring should be continued until the subject meets the discharge criteria (Table 4).

Study Treatment Discontinuation Related to Postdose Cardiac Monitoring

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

Table 5: Discontinuation of Study Treatment Related to Postdose Cardiac Monitoring

Reasons for Study Treatment Discontinuation Related to Postdose 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 the first and second re-initiation days (as applicable).
• Subjects who have not met the discharge criteria on the first re-initiation day after ≥ 4 hours of extended monitoring, or on the second day by 4 hours postdose.

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

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

Subjects whose UC condition in the opinion of the Investigator has not improved or has worsened compared with baseline assessment (obtained on or before the first dose in Study APD334-302) may be eligible for entry into OLE Study APD334-303 (Section 5.1.1).

Subjects who discontinue treatment prematurely should have an Early Termination visit as indicated in the Schedule of Assessments (Table 7). If the Early Termination 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 dose of study treatment as indicated in the Schedule of Assessments (Table 7).

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.

If the absolute peripheral lymphocyte count is not within normal limits at the 4-Week Follow-Up visit, subjects should return for complete blood count (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 dose of study treatment (Section 9.8.8.2.2).

CCI [redacted]

CCI [redacted]

9.7. Efficacy Assessments

The components of the MMS are used to calculate several of the primary, secondary, and CCI [redacted] The definitions for MMS components are outlined in Section 10.5.

9.7.1. 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.

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 carried over from the parent Study APD334-302 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.

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). Consistent with regulatory guidance, the PGA will not be used for primary or secondary efficacy assessment in this study.

9.7.1.1. Endoscopy

A flexible proctosigmoidoscopy, performed with a video endoscope following cleansing preparation (oral or rectal cathartic), will be performed at the 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.

9.7.1.2. Endoscopic Biopsy

Biopsies will be obtained at each endoscopy to support assessment of the histopathology endpoints and, where permitted, for the assessment of CCI [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 of Study APD334-302, biopsies should be taken 8 to 10 cm from the anal verge.

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.

9.7.2. Extraintestinal Manifestations

During the specified full physical examinations (Table 7), specific systems (such as eyes, liver, skin, and joints) will be examined for EIMs for UC.

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

9.8. 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 9.8.8.1). Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

9.8.1. Physical Examination

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

Full physical examination includes the following assessments:

- General inspection
- Weight
- 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.

9.8.2. Vital Signs

Resting vital signs measurements will be performed according to the Schedule of Assessments (Table 7) 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.

9.8.3. 12-Lead Electrocardiogram

All 12-lead ECGs will be performed according to Section 9.4.1 and the Schedule of Assessments (Table 7), 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 Fridericia's corrected QT interval (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.

9.8.4. Pulmonary Function Test

Pulmonary function tests will be performed according to the Schedule of Assessments (Table 7) and includes FEV_1 and FVC measurements. All subjects will have PFTs performed at Week 52 or at the Early Termination visit.

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.

At sites where available, diffusing capacity of the lungs for carbon monoxide (DLCO) measurements will also be performed (sites where DLCO is not available 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).

CCI [redacted]

CCI [redacted]

9.8.6. Tuberculosis Questionnaire

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).

9.8.7. Clinical Laboratory Tests

Refer to Table 6 for the list of clinical laboratory tests to be performed and the Schedule of Assessments (Table 7) 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 predose. The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF (results of the total WBC and ALC will be reviewed and monitored as described in Section 9.7.4). 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 Schedule of Assessments (Table 7) 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 9.7.4.

Table 6: Clinical Laboratory Tests

PREGNANCY TESTING		
Urine β-hCG (only for women of childbearing potential)		
CLINICAL CHEMISTRY, HEMATOLOGY, AND COAGULATION		
Hematology	**Serum Chemistry**	
CD4 T-cell count[a]	Alanine aminotransferase	Potassium
Hematocrit	Albumin	Sodium
Hemoglobin	Alkaline phosphatase	Thyroid-stimulating hormone
Mean corpuscular hemoglobin	Aspartate aminotransferase	Thyroxine free
Mean corpuscular hemoglobin concentration	Bicarbonate	Total bilirubin
Mean corpuscular volume	Blood urea nitrogen	Total cholesterol
Platelet count	C-reactive protein	Total protein
Red blood cell count	Calcium	Triglycerides
White blood cell count with differential[a]	Chloride	Triiodothyronine free
Coagulation	Creatinine	Uric acid
Activated partial thromboplastin time	Creatine kinase	
International normalized ratio	Direct bilirubin	
Prothrombin time	Gamma-glutamyl transferase	
	Glucose	
	Lactate dehydrogenase	
	Phosphorus	
TUBERCULOSIS TESTING		
QuantiFERON		
URINALYSIS		
Appearance	Microscopic examination of sediment	Specific gravity
Bilirubin	Nitrite	Urobilinogen
Color	Occult blood	
Glucose	pH	
Ketones	Protein	

Table 6: Clinical Laboratory Tests (Continued)

CCI
CCI

[a] 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. Refer to Section 9.7.4 for additional details.

[b] CCI

9.8.7.1. Pregnancy Testing

Urine pregnancy tests (β-hCG) should be performed as indicated in the Schedule of Assessments (Table 7). A monthly home pregnancy test in non-visit months should be performed and any positive result immediately reported to the study site. If a home pregnancy test is unavailable, the 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 9.8.9. 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.

9.8.7.2. 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).

9.8.8. Adverse Events

9.8.8.1. Definitions

9.8.8.1.1. 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

9.8.8.1.2. 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.

9.8.8.1.3. 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).

9.8.8.1.4. 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.

9.8.8.1.5. 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.

9.8.8.1.6. Relationship

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

Not Related:	The adverse event is definitely caused by the subject's clinical state or the study procedure/conditions.
Unlikely Related:	The temporal association between the adverse event and the drug is such that the drug is not likely to have any reasonable association with the adverse event.
Probably Related:	The adverse event 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 adverse event follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to the study treatment administration should be considered and investigated. The Investigator should consult the IB and the Product Information of marketed products within the drug class, when applicable. For each adverse event/SAE, the Investigator must document in the medical notes that he/she has reviewed the adverse event/SAE and has provided an assessment of causality. There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor; however, it is very important that the Investigator always make an initial assessment of causality for every event before the initial transmission of the SAE to the Sponsor. The Investigator may change his/her opinion of causality based on subsequent receipt of information and send an SAE follow-up report with the updated causality assessment. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

9.8.8.2. Eliciting and Recording Adverse Events

9.8.8.2.1. 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.

9.8.8.2.2. 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 study treatment administration. 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.

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.

9.8.8.2.3. 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.

9.8.8.3. Reporting Adverse Events

All SAEs are subject to reporting requirements.

9.8.8.3.1. Serious Adverse Events

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

In case of electronic data capture (EDC) connectivity issues (eg, the eCRF cannot be accessed by the Investigator), the Investigator must complete a Back-Up Paper SAE Report Form and send the form to the designated Sponsor Contact (IQVIA) within **24 hours of investigator awareness of the event.** Once the EDC connectivity is restored, the investigator must enter all pertinent information from the Back-Up Paper SAE Report Form into the eCRF as soon as possible.

For the reporting of Pregnancy/Pregnancy Outcome SAEs, and SAEs occurring after the protocol-defined collection period, the investigator must complete a Back-Up Paper SAE Report Form and send the form to the Sponsor Contact (IQVIA) **within 24 hours of investigator awareness** of the event.

IQVIA Pharmacovigilance

Phone: 1-800-761-6501 (access code 00-663-5111)

Fax: 0034-800-401163

Email (*preferred method*): ArenaSafety@iqvia.com

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. All other hospitalizations, including elective hospitalizations for any condition that was not preexisting, will 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.

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

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

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

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

9.8.8.3.2. 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.

9.8.9. 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.

9.9. 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 adverse event/SAE and laboratory abnormalities and follow the adverse event 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 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). Unless stated otherwise, baseline refers to the last non-missing measurement on or before the first dose in Study APD334-302.

10.2. Determination of Sample Size

Approximately 35 Japanese subjects in the parent Study APD334-302, and those subjects may be eligible to enroll in Study APD334-308.

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 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 in Study APD334-302, regardless of the treatment received during Study APD334-308.

Per Protocol (PP) Set: The PP 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 PP definition.

Modified Full Analysis Set (mFAS): The mFAS will consist of all subjects who receive at least 1 dose of study treatment and have a baseline and at least 1 post-Week 12 measurement. Under this approach, subjects will be counted in the treatment group to which they were randomized in Study APD334-302, regardless of the treatment received during Study APD334-308. 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 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, 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 non-responders 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 handled using last observation carry forward, or a mixed-effect model with repeated measures. Detailed methods will be provided in the SAP.

Sensitivity Analyses for Missing Data

Sensitivity analyses may 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 non-responders 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:

- Baseline: Refer to Section 10.1
- 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, Week 52). Complete details of the MMS symptom score computation method is provided Section 9.4.

10.6. Primary Endpoint

The primary efficacy endpoint will evaluate etrasimod versus placebo in:

- 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 symptomatic remission at Week 52
- The proportion of subjects, who had not been receiving corticosteroids for ≥ 12 weeks, achieving clinical remission at Week 52 among subjects receiving corticosteroids at APD334-302 study entry
- The proportion of subjects with mucosal healing at Week 52
- The proportion of subjects achieving clinical remission at both Week 12 of Study APD334-302 and Week 52 of Study APD334-308

10.7.2. Other Secondary Efficacy Endpoints

The other secondary endpoints are:

- The proportion of subjects achieving clinical response at Week 52
- The proportion of subjects achieving clinical response at both Week 12 of Study APD334-302 and Week 52 of Study APD334-308
- The proportion of subjects with mucosal healing at both Week 12 of Study APD334-302 and Week 52 of Study APD334-308
- The proportion of subjects achieving endoscopic normalization at Week 52
- The proportion of subjects achieving endoscopic normalization at both Week 12 of Study APD334-302 and Week 52 of Study APD334-308
- The proportion of subjects achieving symptomatic remission at Weeks 16, 20, 24, 32, 40, and 48

- The proportion of subjects achieving complete symptomatic remission at each study visit (Weeks 16, 20, 24, 32, 40, 48, and 52)
- The proportion of subjects achieving noninvasive clinical response at each study visit (Weeks 16, 20, 24, 32, 40, 48, and 52)
- The proportion of subjects achieving symptomatic response at each study visit (Weeks 16, 20, 24, 32, 40, 48, and 52)
- The proportion of subjects achieving clinical remission at Week 52 and corticosteroid-free since Weeks 16, 24, 32, 40, and 48
- The proportion of subjects achieving clinical remission at Week 52 among subjects in clinical response at Week 12 of Study APD334-302

CCI [redacted]

[redacted]

[redacted]

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, provided there are at least 3 etrasimod subjects and 3 placebo subjects within each level of a subgroup. 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. This refers to age collected at Screening in Study APD334-302.
- Baseline oral corticosteroid usage (yes or no)
- Naive 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) naive to biologic or JAK inhibitor therapy at APD334-302 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).

Due to the limited number of subjects anticipated to enroll in this study, there will be no hypothesis testing on any efficacy endpoint. Inferential statistics will be limited to 95% CIs.

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

Not applicable

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 informed consent form (ICF), subject recruitment materials and procedures (eg, advertisements or websites), and any other written information to be provided to subjects, via the head of the study site. Approval from the committee must be documented in a letter to the head of the study site 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 < 20 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 law. 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

13.2.1. Clinical Study Site

Materials to be retained:

The head of clinical study site shall retain records, including documents and data, which relate to clinical study in accordance with ICH guideline for Good Clinical Practice (GCP) and Japan-GCP (J-GCP).

Retention period:

The head of clinical study sites shall retain records for a required period in accordance with ICH-GCP and J-GCP. However, the Investigator/the study center must arrange for retention of study records at the study center for at least 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. A record keeping manager shall be designated in retaining each record.

13.2.2. Principal Investigator

The Principal Investigator shall retain records, including documents and data, which relate to the clinical study in accordance with instruction from the head of the clinical study site.

13.2.3. Institutional Review Board (IRB)

Materials to be retained:

The person who establishes the IRB shall retain records, including documents and data, which relate to the clinical study in accordance with ICH-GCP and J-GCP.

Retention period:

The person who establishes the IRB shall retain records for required period in accordance with ICH-GCP and J-GCP. However, if the Sponsor requests to retain records longer than described, the person who establishes the IRB will discuss retention period and method with the Sponsor.

13.2.4. Sponsor and ICCC

Materials to be retained:

Sponsor and ICCC shall retain records, including documents and data, which relate to the clinical study in accordance with ICH-GCP and Japan GCP (J-GCP).

Retention period:

The Sponsor and the ICCC shall retain records for required period in accordance with ICH-GCP and J-GCP.

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). The Investigator is responsible for compliance with applicable sections of 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 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 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, ensuring proper monitoring of the investigation(s), ensuring the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the Investigational New Drug (IND) application, maintaining an effective IND with respect to the investigations, and ensuring the FDA, 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 G. 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 2017. Updated October, 2017. Accessed May, 2019.

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

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: SCHEDULE OF ASSESSMENTS

Table 7: Schedule of Assessments

Visit Label (Based on Continuation from Study APD334-302)	**W12/ D85[a] ± 7 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 / Early Termination[b] ± 7 Days**	**2-Week Follow-Up Visit[c] ± 3 Days**	**4-Week Follow-Up Visit[c] ± 3 Days**
Evaluation										
Informed consent	X									
Inclusion/exclusion criteria	X									
eDiary review[d]		X	X	X	X	X	X	X		
MMS[e]								X		
Stool frequency and rectal bleeding subscore[f]		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[g]		X	X	X	X	X	X	X	X	X
12-lead ECG								X		
Physical examination[h]		X	X	X	X	X	X	X	X	X
Extraintestinal manifestations[i]								X	X	X
Pulmonary function test[j]					X			X	X	
Ophthalmoscopy with OCT[k]								X	X	
Pregnancy test[l]		X	X	X	X	X	X	X		X
CBC with differential and platelets		X	X	X	X	X	X	X	X	X
CD4 T-cell count		X	X	X	X	X	X	X	X	X

Visit Label (Based on Continuation from Study APD334-302)	**W12/ D85[a] ± 7 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 / Early Termination[b] ± 7 Days**	**2-Week Follow-Up Visit[c] ± 3 Days**	**4-Week Follow-Up Visit[c] ± 3 Days**
Evaluation										
Laboratory tests including hs-CRP[m]		X	X	X	X	X	X	X	X	
Stool sample/fecal calprotectin[n]				X				X		
Stool sample for microbiome								X		
Flexible proctosigmoidoscopy/ colonoscopy and biopsy [o]								X		
PK assessments[p]		X	X	X	X	X	X	X	X	X
Biomarkers blood sample[q]								X		
Concomitant medications and procedures[r]		X	X	X	X	X	X	X	X	X
Tuberculosis questionnaire[s]		X	X	X	X	X	X	X	X	X
Tuberculosis test[s]								X		
Drug dispensation/accountability[t]	X	X	X	X	X	X	X	X		
Study treatment administration[u]	Once daily									

[a] Subjects are continuing treatment from 12-week Study APD334-302. The Week 12 visit of Study APD334-302 serves as the Day 1 visit of this study. Subjects will be reconsented for this study. Screening for eligibility will be performed for Study APD334-302 and only modified eligibility criteria will be assessed for this study (Section 4.1 and Section 4.2). Visit labels and windows are relative to Week 0/Day 1 of Study APD334-302.

[b] Subjects discontinuing treatment prior to Week 52/Day 365 should have an Early Termination 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.

[c] 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 Early Termination 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 Early Termination 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).

[d] Subjects will continue eDiary entries through the Eligibility Visit and during the treatment period. The subject eDiary will be reviewed by study site staff at each treatment visit.

[e] 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.

[f] Stool frequency and RB subject-reported outcomes recorded daily using eDiary. The RB and SF subscores will be calculated as indicated in Section 9.7.1.
[g] Safety vital signs will include resting heart rate and systolic and diastolic BP with subjects in the sitting position taken before dosing. Safety monitoring (Section 9.4.1) should be performed if a subject has had a dose interruption ≥ 7 consecutive days.
[h] 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.
[i] During the specified full physical examination, specific systems (eyes, liver, skin, and joints) will be examined for EIMs.
[j] 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 results from the Week 52/Early Termination visit are abnormal. Details regarding additional PFTs are provided in Section 9.8.4.
[k] Details regarding ophthalmoscopy and OCT assessments are provided in Section 9.8.5. The 2-Week Follow-Up visit assessment is only required if results from the Week 52/Early Termination visit are abnormal.
[l] Urine pregnancy test for women of childbearing potential. A monthly home pregnancy test in non-visit months should be performed and any positive result immediately reported to the study site and a serum pregnancy test performed for confirmation. If home pregnancy test is not available, the pregnancy test will be performed on site during an unscheduled visit.
[m] Clinical laboratory tests will include serum chemistry, hematology (including coagulation), urinalysis, and hs-CRP and should be obtained prior to the daily dosing.
[n] 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.
[o] To be read by a blinded central reader. If the Early Termination visit is within 4 weeks of the last sigmoidoscopy and biopsy, these procedures do not need to be repeated.
[p] Pharmacokinetic blood samples are to be collected predose (within the 60-minute period prior to dosing). A PK sample should be taken, if possible, at the time of any SAE or AE 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.
[q] Blood samples for biomarkers should be collected on the indicated day prior to the daily dose as applicable.
[r] All concomitant medications and procedures should be collected through the safety reporting period (Section 6.7). For subjects who received corticosteroid therapy during the APD334-302 study, corticosteroids should be tapered entering this study (Section 6.7.2.2).
[s] QuantiFERON TB Gold and tuberculin skin test should not be performed in subjects previously diagnosed with TB infection. The TB questionnaire will be completed at every study visit for subjects receiving TB prophylaxis therapy.
[t] 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 Study APD334-308 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.
[u] On days with scheduled study visits, subjects should not take their dose of study treatment at home in order to complete predose study procedures. The dose will be taken at the study site after all predose assessments and procedures have been completed. At the Week 12 visit, subjects should take study treatment after confirmation of eligibility and enrollment into Study APD334-308.

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; 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; SAE, serious adverse event; 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; WPAI-UC, Work Productivity and Activity Impairment Questionnaire – Ulcerative Colitis

APPENDIX 2: TUBERCULOSIS SCREENING

All subjects will have undergone screening for a history of TB infection and testing for latent/active TB infection in the APD334-302 study. 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. The IGRA or TST is NOT required at Week 52 for subjects with a history of active/latent TB infection.
   - Subjects receiving TB prophylaxis treatment during the APD334-302 must have documentation of treatment with an acceptable TB prophylaxis treatment regimen (with a plan to complete the TB treatment course during study participation) 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).

b. 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.

c. 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

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

Site #: _____
Subject #: _____

Tuberculosis Screening Questionnaire
Source Document Worksheet

Instructions:

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

Was the Tuberculosis Screening questionnaire completed? Yes/No

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

If no, specify reason:

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

Study Visit Number: _____

Section 1: Questions to ask the subject

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

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

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

Site #: _____
Subject #: _____

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

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

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

Site #: _____
Subject #: _____

Section 2: To be completed by the investigator

I. The participant is on concomitant medication(s) with immunosuppressive effects: Yes / No

If yes, specify medication(s) (name, dosage):

Medication #1:

Medication #2:

Medication #3:

Medication #4:

II. TB QuantiFERON or Tuberculin Skin Test result: _____ Date: _____

Chest x-ray/computer tomography (CT) scan done to rule out pulmonary TB? Yes / No

If yes, date of chest x-ray or CT scan: _____

Any evidence of active pulmonary TB disease on chest x-ray or CT scan? Yes / No

Other assessment completed? Yes/ No

If yes, specify assessment: _____

If yes, date of other assessment: _____

Any evidence of active TB disease on assessment? Yes / No

III. Upon review of the responses and discussion with the participant, I recommend the following:

___Perform screening test for latent TB infection

____ Perform additional assessments to rule out active TB disease

____ Refer to physician TB expert for evaluation and treatment

____ Follow up at the next TB-designated study visit and repeat TB screening questionnaire

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

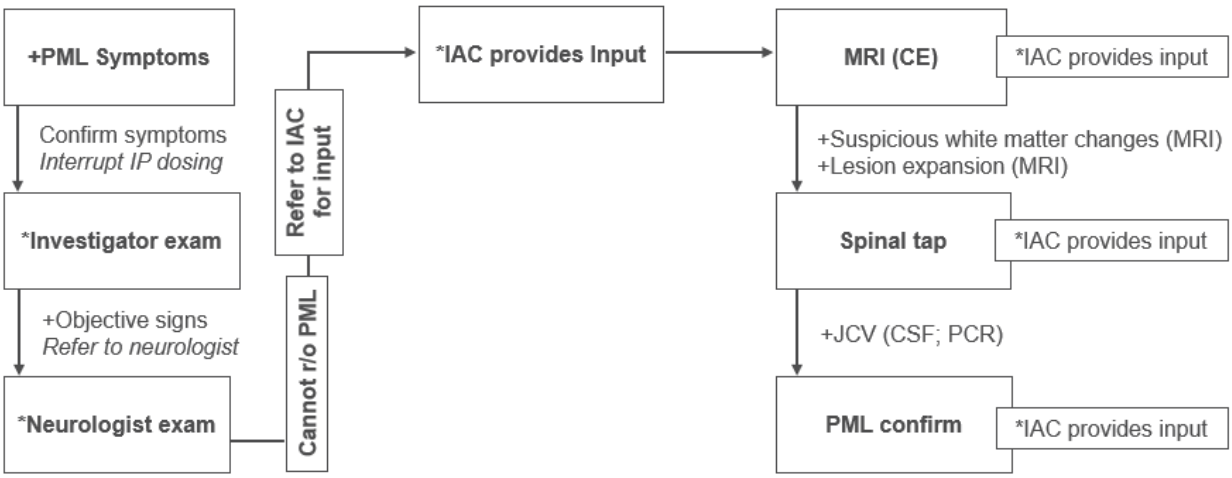
The RHI is an evaluative index, derived from the Geboes score, that is designed to be reproducible and responsive to clinically meaningful change in disease activity over time. The total RHI score ranges from 0 (no disease activity) to 33 (severe disease activity) and is calculated as follows: RHI = 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 3.

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 3: 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, Double-Blind, Placebo-Controlled, 40-Week Extension Study to Assess the Efficacy and Safety of Etrasimod in Japanese Subjects with Moderately to Severely Active Ulcerative Colitis

Study number: APD334-308

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, Double-Blind, Placebo-Controlled, 40-Week Extension Study to Assess the Efficacy and Safety of Etrasimod in Japanese 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.

PPD MD, MHS, FACC
PPD
.

Sponsor Signature **Date**