

CLINICAL STUDY PROTOCOL

Protocol title:	A Multicenter, Randomized, Double-Blind, Parallel-Group Study to Assess the Efficacy and Safety of Oral Etrasimod as Induction and Maintenance Therapy for Moderately to Severely Active Crohn's Disease
Protocol number:	C5041006 (APD334-202 or APD334-202EU)
Version:	Amendment 4.0, dated 31 January 2024
Compound name or number:	Etrasimod (APD334)
Study phase:	2/3
Indication:	Crohn's disease
EudraCT number	2020-004775-40
Sponsor name:	Arena Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer Inc.
Sponsor approval:	This protocol was approved by the Sponsor's Responsible Medical Officer or delegate. The electronic signature manifest is appended.

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PROTOCOL HISTORY

Document	Amendment Type	Date
Amendment 4.0	Global	31 January 2024
Amendment 3.0	Global	22 December 2022
Amendment 2.7	Country-Specific	08 July 2022
Amendment 2.6	Region-specific	26 April 2021
Amendment 2.5	Region-specific	01 March 2021
Amendment 2.4	Country-Specific	11 December 2020
Amendment 2.3	Country-Specific	13 November 2020
Amendment 2.2	Region-specific	02 November 2020
Amendment 2.1	Country-Specific	08 July 2020
Amendment 2.0	Global	11 June 2020
Amendment 1.2	Country-specific	15 April 2020
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Amendment 1.0	Global	19 September 2019
Original Protocol	Not applicable	21 June 2019

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PROTOCOL SYNOPSIS

Sponsor: Arena Pharmaceuticals, Inc.
Name of investigational study drug: Etrasimod (APD334)
Protocol title: A Multicenter, Randomized, Double-Blind, Parallel-Group Study to Assess the Efficacy and Safety of Oral Etrasimod as Induction and Maintenance Therapy for Moderately to Severely Active Crohn's Disease
Protocol number: C5041006 (APD334-202 or APD334-202EU)
Phase: 2/3
Countries/regions (planned): The global study will be conducted in North, South, and Central America; Asia Pacific; Europe; Middle East; and Africa.
Objectives: <u>Primary Objectives</u> <i>Substudy A – Phase 2 (optional substudy under Study Protocol APD334-202EU)</i> - To evaluate the safety, tolerability, and efficacy of 2 doses of etrasimod as induction therapy in subjects with moderately to severely active Crohn's disease (CD) <i>Substudy 1 – Phase 2b Cohort 1</i> - To evaluate the dose-response relationship of 2 doses of etrasimod versus placebo as induction therapy in subjects with moderately to severely active CD - To select an oral etrasimod dose, based on efficacy and safety, for continued development <i>Substudy 1 – Phase 2b Cohort 2</i> - To evaluate the dose-response relationship of 2 doses of etrasimod versus placebo as induction therapy in subjects with moderately to severely active CD - To select an oral etrasimod dose, based on efficacy and safety, for continued development along with data generated from SS1 Phase 2b Cohort 1 <i>Substudy 2 – Induction (Phase 3)</i> - To evaluate the efficacy of the selected etrasimod dose versus placebo as induction therapy in subjects with moderately to severely active CD <i>Substudy 3 – Maintenance (Phase 3)</i> - To evaluate the efficacy of etrasimod versus placebo as maintenance therapy in subjects with moderately to severely active CD <i>Substudy 4 – Long-Term Extension</i> - To evaluate the long-term safety and tolerability of etrasimod in subjects with moderately to severely active CD <u>Secondary Objectives</u> <i>Substudy A – Phase 2 (optional substudy under Study Protocol APD334-202EU)</i> - To evaluate the long-term safety, tolerability, and efficacy of etrasimod in subjects with moderately to severely active CD

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- To evaluate the pharmacokinetic (PK) and pharmacodynamic effects of etrasimod as induction and maintenance therapy, including changes in lymphocytes, C-reactive protein (CRP), and fecal calprotectin (FCP) in subjects with moderately to severely active CD

Substudy 1 – Phase 2b Cohort 1 and Cohort 2

- To evaluate the safety, tolerability, and efficacy of etrasimod in subjects with moderately to severely active CD
- To provide a subset of the target study population, etrasimod responders, to be evaluated in Substudy 3 – Maintenance

Substudy 2 – Induction (Phase 3)

- To evaluate the safety and tolerability of the selected etrasimod Phase 3 dose (3 mg or 2 mg) versus placebo as induction therapy in subjects with moderately to severely active CD
- To provide a subset of the target study population, etrasimod responders, to be evaluated in Substudy 3 – Maintenance

Substudy 3 – Maintenance (Phase 3)

- To evaluate the efficacy of etrasimod on sustained clinical remission and endoscopic response, endoscopic remission, and corticosteroid-free clinical remission in subjects with moderately to severely active CD
- To characterize the safety and tolerability of etrasimod as maintenance therapy in subjects with moderately to severely active CD

Substudy 4 – Long-Term Extension

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

Study Design:

This is a Phase 2/3, multicenter, randomized, double-blind, study that comprises 5 substudies designed to evaluate the efficacy, safety, and tolerability of etrasimod as therapy in subjects with moderately to severely active CD who are refractory or intolerant to at least 1 of the current therapies for CD (ie, corticosteroids, immunosuppressants, or biologics). Subjects who are refractory or intolerant to corticosteroids and/or immunosuppressants may be either previously exposed or naïve to biologics. Randomized subjects will remain on stable doses of 5-aminosalicylic acid compounds, low dose oral corticosteroids, and/or antidiarrheal medications as background therapy for CD; however, corticosteroid tapering is required in SS3-M and may be required in SS4-E in subjects who continue treatment beyond the Induction Period. The 5 substudies are presented in the study schematic and described below.

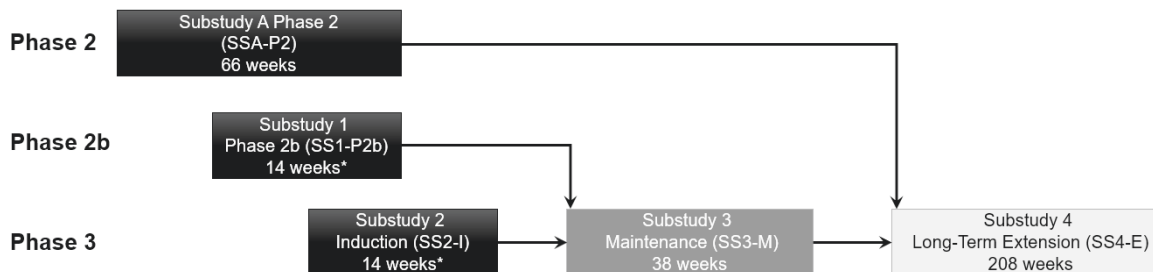
Substudy A – Phase 2 (SSA-P2): A Phase 2, randomized, double-blind, substudy to assess the safety, tolerability, and efficacy of oral etrasimod therapy in subjects with moderately to severely active CD that supports the selection of an induction and maintenance dose(s) for Phase 3.

Substudy 1 – Phase 2 (SS1-P2b Cohort 1 and Cohort 2): A Phase 2b randomized, double-blind, placebo-controlled, dose-ranging induction substudy to evaluate etrasimod as induction therapy and select an induction and maintenance dose(s) for continued evaluation in Phase 3.

Substudy 2 – Induction (SS2-I): A Phase 3 randomized, double-blind, placebo-controlled substudy to evaluate etrasimod as induction therapy.

Substudy 3 – Maintenance (SS3-M): A Phase 3 randomized, double-blind, placebo-controlled substudy to evaluate etrasimod as maintenance therapy.

Substudy 4 – Long-Term Extension (SS4-E): A long-term extension (LTE) substudy for subjects from SSA-P2 and SS3-M who complete at least 52 weeks of treatment.



*Subjects in SS1-P2b and SS2-I who do not meet prespecified clinical or endoscopic response criteria (defined in Section 3.1.2) at Week 14 will complete a 6-week Extended Induction Period and may then be eligible for SS3-M. SSA-P2, Substudy A – Phase 2; SS1-P2b, Substudy 1 – Phase 2b; SS2-I, Substudy 2 – Induction; SS3-M, Substudy 3 – Maintenance; SS4-E, Substudy 4 – Long-Term Extension

Number of subjects (planned):

SSA-P2: Approximately 50 subjects are planned to be enrolled in the substudy with 25 subjects expected in each treatment group.

SS1-P2b: Approximately 150 subjects (Cohort 1) are planned to be enrolled in the substudy with 50 subjects expected in each of the 3 treatment groups. Approximately 135 subjects are planned to be enrolled in Cohort 2 with 45 subjects expected in each of the 3 treatment groups.

SS2-I: Approximately 400 subjects are planned to be enrolled in the substudy with approximately 300 subjects expected in etrasimod treatment group and approximately 100 subjects in the placebo treatment group.

SS3-M: Up to 1125 subjects from SS1-P2b, SS2-I, and Study APD334-305 (a separate Phase 3 study of etrasimod in subjects with CD) may be enrolled in SS3-M.

SS4-E: Up to 1175 subjects from both SS3-M and SSA-P2 are planned to be enrolled in this substudy.

Eligibility criteria:

Key inclusion criteria:

3. Subjects 18 to 80 years of age, inclusive, at the time of consent
4. Ability to provide written informed consent and to be compliant with the schedules of protocol assessments
5. Have CD for ≥ 3 months prior to randomization, involving the ileum and/or colon, at a minimum; diagnosis may be confirmed at any time in the past by endoscopy and histopathology. The screening endoscopy and histopathology reports may serve as source documents for subjects who do not have diagnostic endoscopy reports in their medical chart
6. Have moderately to severely active CD at **Screening**, defined as:
 - Crohn's Disease Activity Index (CDAI) score ≥ 220 and ≤ 450 , AND
 - Unweighted average worst daily abdominal pain (AP) score ≥ 2 (using a 4-point scale; ie, 0 [none] to 3 [severe]) OR unweighted average daily loose/watery stool frequency (SF) (Bristol Stool Form Scale [BSFS] type 6 or 7) score ≥ 4 , AND

- Simple Endoscopic Score in Crohn's disease (SES-CD) of ≥ 6 or SES-CD ≥ 4 for subjects with isolated ileal disease

7. Demonstrated inadequate response, loss of response to, or intolerance to ≥ 1 of the following therapies for the treatment of CD (refer to [Appendix 9](#), refer to [Appendix 11](#) for Israel specific criteria):

- Oral corticosteroids (eg, prednisone [or its equivalent] or budesonide)
- Immunosuppressants (eg, azathioprine, 6-mercaptopurine, or methotrexate)
- Tumor necrosis factor alpha (TNF α) antagonists (eg, infliximab, adalimumab, certolizumab pegol, or biosimilars)
- Integrin receptor antagonist (eg, vedolizumab)
- Interleukin-12/-23 antagonist (eg, ustekinumab)

8. Females of childbearing potential must be nonpregnant

9. Females of childbearing potential and males must agree to use contraception (refer to Section 4, Inclusion Criterion 7 for SSA-P2, SS1-P2b, or SS2-I; Inclusion Criterion 6 for SS3-M; and Inclusion Criterion 4 for SS4-E)

Key exclusion criteria:

1. History of inadequate response (ie, primary non-response) to agents from ≥ 2 classes of biologics marketed for the treatment of CD (ie, TNF α antagonists, interleukin-12/-23 antagonist, and integrin receptor antagonist, refer to [Appendix 9](#))
2. Have ulcerative colitis, indeterminate colitis, microscopic colitis, ischemic colitis, radiation colitis, diverticular disease-associated colitis, toxic megacolon, or active infectious colitis or test positive for *Clostridioides difficile* toxin at Screening
3. Have functional or post-operative short-bowel syndrome or any associated complications that may require surgery or interfere with efficacy assessments
4. Had surgical treatment for intra-abdominal abscesses ≤ 8 weeks prior to randomization or surgical treatment for perianal abscesses ≤ 4 weeks prior to randomization
5. Had intestinal resection ≤ 24 weeks prior to randomization or other intra-abdominal surgeries ≤ 12 weeks prior to randomization. Subjects who have undergone previous colonic resection or ileocelectomy must have > 25 cm of colon remaining
6. Have an ileostomy or a colostomy
7. Have a serious infection requiring intravenous antibiotic(s)/medication(s) ≤ 4 weeks prior to randomization
8. Have primary or secondary immunodeficiency syndromes, history of organ transplant, history of an opportunistic infection, history of disseminated herpes simplex or herpes zoster, have or test positive for human immunodeficiency virus, hepatitis B virus, or active hepatitis C virus
9. Lactating female who is breastfeeding

Test product, dose, and mode of administration:

Etrasimod 3 mg treatment group:

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- Week 1: One etrasimod 2 mg tablet and 1 matching placebo tablet taken orally once daily (qd)
- Week 2 onwards: One etrasimod 2 mg tablet and one etrasimod 1 mg tablet taken orally qd

Note: Subjects who received etrasimod 2 mg in a previous treatment period who are then assigned to etrasimod 3 mg will receive etrasimod 3 mg from the start of treatment.

Etrasimod 2 mg treatment group:

- One etrasimod 2 mg tablet and 1 matching placebo tablet taken orally qd, OR
- One etrasimod 2 mg tablet taken orally qd (if etrasimod 3 mg dose is discontinued)

Reference therapy, dose, and mode of administration:

Placebo treatment group (SS1-P2b, SS2-I, and SS3-M):

- Two matching placebo tablets taken orally qd, OR
- One matching placebo tablet taken orally qd (if etrasimod 3 mg dose is discontinued)

Duration of study:

The overall duration of this study is up to 282 weeks, inclusive of the Screening Period, Treatment Period of up to 274 weeks (Induction, Extension or Maintenance, and LTE Periods), and the 4-Week Follow-Up Period for safety assessment.

SSA-P2: The total duration of this substudy is up to 74 weeks, inclusive of the 28-Day Screening Period, 14-week Induction Period, 52-week Extension Period, and the 4-Week Follow-Up Period.

SS1-P2b: The total duration of this substudy is up to approximately 30 weeks, inclusive of the 40-Day Screening Period, 14-week Induction Period, 6-week Extended Induction (EI) Period, and the 4-Week Follow-Up Period.

SS2-I: The total duration of this substudy is up to approximately 30 weeks, inclusive of the 40-Day Screening Period, 14-week Induction Period, 6-week EI Period, and the 4-Week Follow-Up Period.

SS3-M: The overall duration of this substudy is up to 42 weeks, inclusive of the 38-week Treatment Period and the 4-Week Follow-Up Period.

SS4-E: The overall duration of this substudy is up to 212 weeks, inclusive of the 208-week Treatment Period and the 4-Week Follow-Up Period.

Efficacy Assessments:

Key efficacy assessments in this study include changes in CDAI and SES-CD (centrally read). Efficacy will also be assessed by unweighted daily AP and loose/watery SF symptom scores (electronic diary), Patient-Reported Outcome 2 (PRO2), histopathology (centrally read), biomarkers (eg, C-reactive protein, fecal calprotectin, total lymphocyte count), assessment of extraintestinal manifestations of CD, global histologic disease activity score, and other subject reported outcome measures (Inflammatory Bowel Disease Questionnaire, Crohn's Disease Patient-Reported Outcomes Signs and Symptoms, AP numerical rating scale, Medical Outcomes Study 36 Item Short Form Health Survey, EuroQoL – 5 Dimensions 5-level version (EQ-5D-5L), Work Productivity and Activity Impairment Questionnaire – Crohn's disease, Patient Global Impression of Change, Functional Assessment of Chronic Illness Therapy – Fatigue, and CD-related hospitalizations and surgeries).

Endpoint definitions:

- Endoscopic response: Endoscopic remission or $\geq 50\%$ decrease from baseline in SES-CD
- Endoscopic remission: SES-CD ≤ 4 and at least 2-point reduction from baseline with no sub-score > 1

- Clinical response CDAI: Clinical remission CDAI or ≥ 100 -point decrease from baseline in CDAI
- Clinical remission CDAI: CDAI < 150
- Clinical response PRO2: Clinical remission PRO2 or ≥ 8 -point decrease from baseline in PRO2
- Clinical response CDAI-70: Clinical remission CDAI or ≥ 70 -point decrease from baseline in CDAI
- Clinical remission PRO2: PRO2 < 8
- Corticosteroid-free remission: CDAI < 150 without receiving corticosteroids for ≥ 8 weeks prior to Week 52 (for subjects receiving corticosteroids at baseline)
- Time to remission: Defined as time to onset of clinical remission PRO2 and disease biomarker normalization, such as FCP and/or CRP. Subjects who do not achieve this remission endpoint or discontinue from study, are censored at 7 days after last study drug dose
- Time to response: Defined as time to onset of clinical response PRO2 and disease biomarker normalization, such as FCP and/or CRP. Subjects who do not achieve this response endpoint or discontinue from study, are censored at 7 days after last study drug dose
- Mucosal healing: SES-CD score 0-2
- Histologic response: Proportion of subjects with modified global histologic disease activity score ≤ 4 in those subjects with baseline score > 4

Based on above definitions, subjects in SS1-P2b or SS2-I who meet response criteria at Week 14 (ie, Week 14 responders, defined as subjects who have met at least 1 criterion of endoscopic response, endoscopic remission, clinical response CDAI ≥ 100 improvement, or clinical remission CDAI < 150) will be eligible to enter SS3-M upon completion of the Week 14 Visit. Subjects in SS1-P2b or SS2-I who do not meet response criteria at Week 14 based on the above definitions will be eligible for a 6-week EI Period in SS1-P2b or SS2-I.

SSA-P2

Primary efficacy endpoint:

- Proportion of subjects with endoscopic response

Secondary endpoints:

- Proportion of subjects with clinical remission CDAI
- Change from baseline in SES-CD score
- Change from baseline in CDAI score

Pharmacokinetics

- Etrasimod plasma concentrations at 4 hours postdose and at steady-state trough concentrations ($C_{\text{trough,ss}}$) at selected timepoints

Pharmacodynamics

- Change and percentage change from baseline in ALC
- Change and percent change from baseline in FCP concentration
- Change and percent change from baseline in CRP

SS1-P2b Cohort 1 and Cohort 2

Primary efficacy endpoint:

- Proportion of subjects with endoscopic response at Week 14

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Secondary efficacy endpoints:

- Proportion of subjects with clinical remission CDAI at Week 14
- Proportion of subjects with clinical remission by PRO2 at Week 14

SS2-I

Primary efficacy endpoints:

- Proportion of subjects with endoscopic response at Week 14
- Proportion of subjects with clinical remission CDAI at Week 14

Key secondary efficacy endpoints:

- Proportion of subjects with clinical remission PRO2 at Week 14
- Proportion of subjects with clinical response CDAI at Week 14
- Proportion of subjects with endoscopic response and clinical remission CDAI at Week 14
- Proportion of subjects with endoscopic remission at Week 14
- Change from baseline in CD-PRO/SS at Week 14

SS3-M

Primary efficacy endpoints:

- Proportion of subjects with clinical remission CDAI at Week 52
- Proportion of subjects with endoscopic response at Week 52

Key secondary efficacy endpoints:

- Proportion of subjects with clinical remission CDAI at Week 52 among subjects in clinical remission CDAI at SS3-M baseline
- Proportion of subjects with endoscopic response at Week 52 among subjects in endoscopic response at SS3-M baseline
- Proportion of subjects with corticosteroid free clinical remission CDAI at Week 52 among subjects receiving corticosteroids at SS3-M baseline
- Proportion of subjects with endoscopic remission at Week 52
- Proportion of subjects with clinical remission PRO2 at Week 52
- Proportion of subjects with clinical response or endoscopic response at Week 52

SS4-E

Secondary efficacy endpoints:

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

Pharmacokinetic Assessments:

Plasma concentrations of etrasimod will be assessed at selected time points.

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

Safety Assessments:

Safety will be assessed by vital signs, physical exams including ophthalmic exam with optical coherence tomography, adverse events (AEs), laboratory assessments (eg, hematology, chemistry, coagulation panel, pregnancy test for women of child-bearing potential only), 12-lead

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electrocardiogram (ECG), continuous Holter monitoring, and pulmonary function tests including diffusing capacity of the lungs for carbon monoxide where locally available.

Safety endpoints:

- Incidence of treatment-emergent AEs (TEAEs) and serious AEs (SAEs)
- Incidence and severity of laboratory abnormalities
- Incidence of clinically significant vital sign, ECG, and Holter abnormalities
- Change from baseline in select laboratory values, ECG, and vital signs

Statistical methods:

A description of sample size determination, stratification, testing strategy, statistical analysis methodology for efficacy endpoints, and planned interim analyses are substudy specific and will be provided separately. Safety analyses will be similar across the 5 substudies; therefore, a summary description of safety analyses for all substudies is provided.

Sample size:

SSA-P2: This Phase 2 substudy is to evaluate safety, tolerability, and efficacy in 2 doses of etrasimod with no inferential comparison between groups. With a 1:1 randomization ratio, a sample size of approximately 50 subjects (25 per treatment group) is reasonable to provide numerical description of safety, tolerability, and efficacy at Week 14.

SS1-P2b: Cohort 1 in this substudy is powered to detect a dose-response relationship in the primary endpoint of endoscopic response at Week 14 based on pair-wise comparisons using 2-sample Fisher's exact test. Based on a review of the published literature, . With a 1:1:1 randomization ratio, a total of 150 evaluable subjects (50 per treatment group) in Cohort 1 will be needed to detect a treatment difference between an etrasimod dose and placebo.

In order to ensure high confidence that etrasimod demonstrates efficacy for both endoscopic response and CDAI remission, approximately 135 eligible subjects will be randomized into **Cohort 2** with a 1:1:1 randomization ratio to receive etrasimod 3 mg, etrasimod 2 mg, or matching placebo. With 45 subjects in each group,

SS2-I: The assumptions for sample size and power calculations are preliminarily based on published data of CDAI < 150. Approximately 400 eligible subjects will be randomized into SS2-I with a 3:1 randomization ratio to receive etrasimod (300) or placebo (100). , a total sample size of 400 subjects (300 etrasimod, 100 placebo)

SS3-M: Only Week 14 etrasimod responders enrolling from induction studies will be part of the formal efficacy analyses. This substudy is powered to test hypothesis of 2 primary endpoints in comparison of an etrasimod dose and placebo. For the primary endpoint of clinical remission CDAI < 150 at Week 52, [REDACTED] with a 1:1 randomization ratio, a total of 308 subjects (154 per group) is sufficient [REDACTED] based on a 2-sample Fisher's exact test [REDACTED]. For the other primary endpoint of endoscopic response at Week 52, defined by an SES-CD decrease from baseline of $\geq 50\%$, [REDACTED] the sample size of 308 [REDACTED] to detect a treatment difference [REDACTED] between etrasimod and placebo. [REDACTED]

SS4-E: No formal sample size calculations were performed. Since all subjects will enroll from parent studies SSA-P2 and SS3-M, the maximum number of subjects planned for this study will not exceed the total number of subjects enrolled into these 2 studies. Actual enrollment will depend on the number of subjects who meet eligibility criteria for this study and consent to enroll.

Stratification

SSA-P2, SS1-P2b and SS2-I: Randomization will be stratified by baseline biologic treatment failure status (yes/no) and baseline oral corticosteroid use (yes/no).

SS3-M: Randomization will be stratified by Week 14 endoscopic response status (yes/no), baseline biologic treatment failure status (yes/no), and corticosteroid use (yes/no) at SS3-M baseline.

SS4-E: Subjects will not be stratified.

Testing strategy

SSA-P2: There is no inferential between-group testing specified.

SS1-P2b Cohort 1 and Cohort 2: For Cohort 1, [REDACTED], no multiplicity adjustment. For Cohort 2, there is no formal hypothesis testing.

SS2-I and SS3-M: There are multiple null hypotheses for the comparison of etrasimod and placebo in the primary and key secondary endpoints. [REDACTED]

SS4-E: No formal between group testing will be performed in this study.

Statistical analysis methods for primary and secondary endpoints

SSA-P2: Proportion-based efficacy endpoints will be summarized using frequency counts and percentages and 90% confidence interval (CI). Continuous variables will be summarized using the number of observations, mean, standard deviation, median, minimum, and maximum, and 90% CI of mean by visit on observation basis.

SS1-P2b Cohort 1 and Cohort 2, SS2-I, and SS3-M: All primary and key secondary endpoints are proportion based and will be analyzed using the Mantel-Haenszel weighted method adjusted for randomization stratification factors. The number and percentage of subjects achieving the response and the common risk difference in proportion between treatment groups achieving the response,

along with p-value and the CIs of common risk difference will be reported (CCI SS1-P2b Cohort 1 and Cohort 2 and CCI SS2-I and SS3-M).

SS4-E: All efficacy analyses will be performed using descriptive methods and details will be described in the SAP.

Formal interim analysis

No formal interim analyses for efficacy are planned for substudies SS1-P2b, SS2-I, and SS3-M.

Safety analyses (all substudies)

All safety data will be listed and summarized by treatment group for each substudy and interpreted across substudies as appropriate. All TEAEs will be coded using the Medical Dictionary for Regulatory Activities and tabulated by system organ class and preferred term. Incidence of AEs, SAEs, AEs of special interest, and AEs leading to discontinuation will be summarized and presented in descending order of frequency. Associated laboratory parameters will be grouped and presented together. Individual subject values will be listed, and values outside of the standard reference range will be noted. Analyses of changes from baseline will be produced. The change from baseline for each of the vital signs, ECG parameters, and Holter monitoring (SSA-P2 and SS1-P2b only) will be summarized. Incidence of abnormal vital signs parameters and outlier ECG results will be tabulated.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Explanation
AEM	adverse event monitoring
5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ADR	adverse drug reaction
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AP	abdominal pain
APSF	worst daily abdominal pain and loose/watery stool frequency
AST	aspartate aminotransferase
AV	atrioventricular
AZA	azathioprine
β-hCG	beta-human chorionic gonadotropin
BL	baseline
BP	blood pressure
bpm	beats per minute
BSFS	Bristol Stool Form Scale
CBC	complete blood count
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
<i>C. difficile</i>	<i>Clostridioides difficile</i>
CD-PRO/SS	Crohn's Disease Patient-Reported Outcomes Signs and Symptoms
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Coronavirus disease 2019
CRO	contract research organization
CRF	case report form
CRP	C-reactive protein

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Abbreviation	Explanation
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTSAE	Common Terminology Criteria for Serious Adverse Events
CTIS	Clinical Trials Information System
CYP	cytochrome P450
DE	dose escalation
DILI	drug-induced liver injury
DLCO	diffusing capacity of the lungs for carbon monoxide
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDB	exposure during breast feeding
eDiary	electronic diary
EFD	Extension First Dose
EI	extended induction
EIFD	extended induction first dose
EIMs	extraintestinal manifestations
EDP	exposure during pregnancy
EFD	extension first dose
EMA	European Medicines Agency
EQ-5D-5L	EuroQoL-5 Dimensions 5-level version
ET	Early Termination
ETR	etrasimod
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FA	fluorescein angiogram
FACIT-F	Functional Assessment of Chronic Illness Therapy–Fatigue
FAS	full analysis set
FCP	fecal calprotectin
FDA	Food and Drug Administration

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Abbreviation	Explanation
FEV ₁	forced expiratory volume in 1 second
FOCBP	female of childbearing potential
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
HBcAb	hepatitis B virus core antibody
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HFG	Swiss Human Research Act (Humanforschungsgesetz)
HIV	human immunodeficiency virus
HR	heart rate
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
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IGRA	interferon-gamma release assay
IND	Investigational New Drug
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
JAK	Janus kinase
IUD	intrauterine device
IUS	intrauterine hormone-releasing system

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Abbreviation	Explanation
IV	intravenous
J-GCP	Japan - Good Clinical Practice
LD	last dose
LOR	loss-of-response
LS	least squares
LTE	long-term extension
MCID	minimal clinically important difference
MDR	multi-drug resistance
mFAS	modified full analysis set
MFD	Maintenance First Dose
MI	multiple imputation
MMRM	mixed effects model with repeated measures
MQI	medically qualified individual
MTX	methotrexate
NRI	nonresponder imputation
NRS	numerical rating scale
NSAID	nonsteroidal anti-inflammatory drugs
OCT	optical coherence tomography
PBO	placebo
PD	pharmacodynamic
PE	primary endpoint
PFT	pulmonary function test
PGIC	Patient Global Impression of Change
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PP	per protocol
qd	once daily
QTc	corrected QT interval
QTcF	Fridericia's corrected QT interval
RW	randomized withdrawal
RNA	ribonucleic acid
RSI	reference safety information

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Abbreviation	Explanation
S1P	sphingosine 1-phosphate
S1P _{1,4,5}	sphingosine 1-phosphate receptor 1, 4, 5
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SES-CD	Simple Endoscopic Score in Crohn's disease
SF	stool frequency
SF-36	Medical Outcomes Study 36-Item Short Form Health Survey
SOP	standard operating procedure
SRSD	single reference safety document
TB	tuberculosis
TBL	total bilirubin
TBNK	T Cell, B Cell, and natural killer (cells)
TEAE	treatment-emergent adverse event
TNF α	tumor necrosis factor alpha
TSH	thyroid stimulating hormone
TST	tuberculin skin test
UC	ulcerative colitis
UGT	uridine diphosphate glucuronosyl transferase
ULN	upper limit of normal
UMC	University Medical Center
US	United States
USPI	United States prescribing information
VZV	varicella zoster virus
WBC	white blood cell
W	week
WHO	World Health Organization
WPAI-CD	Work Productivity and Activity Impairment Questionnaire–Crohn's Disease

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1. INTRODUCTION

1.1. Background

1.1.1. Crohn's Disease

Inflammatory bowel disease (IBD) is a broad term that encompasses idiopathic conditions with chronic or recurring immune response and inflammation of the gastrointestinal tract. The two major types of IBD are ulcerative colitis (UC) and Crohn's disease (CD) (CCFA 2014). CD is a chronic, relapsing and remitting, immune-mediated inflammatory condition that may affect the entire gastrointestinal tract and is associated with an increased risk for colon cancer (Kaser 2010, Weimers 2018). CD is distinguished from UC in that it presents as a more severe and widespread inflammation of the gastrointestinal tract and is characterized by chronic inflammation, mucosal and sub-mucosal ulceration and fibrosis, whereas with UC, inflammation is predominately restricted to the mucosal and occasionally the submucosal layer of the colon (Kornbluth 2010, Lichtenstein 2009, Weimers 2018). The transmural tissue damage observed with CD can result in intestinal infections and abscesses, intestinal perforation, strictures, and fistula formation (Lichtenstein 2018a, Lichtenstein 2018b). CD is a heterogeneous disease, and patients may have disease isolated to the colon or the ileum (small intestine) or have ileocolonic disease (Weimers 2018). Fistulas, most commonly perianal, occur in approximately one-third of patients with CD, and fistulizing CD presents distinct treatment challenges (Scharl 2017).

Although CD is primarily a gastrointestinal-specific disease, as a systemic autoimmune disorder, patients can develop a variety of extraintestinal manifestations (EIMs) that take on the same histological features as the underlying disease. While almost every organ system has the potential to be affected by EIMs of IBD, skin is the most commonly affected occurring in 22% to 75% of CD patients (Marzano 2014).

Treatment for patients with CD is generally focused on symptomatic care and mucosal healing with overall goals of inducing and sustaining clinical remission, improving quality of life, and preventing more severe disease manifestations and complications that require hospitalization and surgical intervention (CCFA 2014, Rowe 2017). Treatment of CD includes several major classes of medications: corticosteroids, immunosuppressants (such as methotrexate [MTX] and the thiopurines azathioprine [AZA] and mercaptopurine), biologics (anti-tumor necrosis factor alpha [TNF α] antagonists [infliximab, adalimumab, and certolizumab pegol], interleukin-12 and -23 antagonist [ustekinumab], integrin receptor antagonists [vedolizumab]), and antibiotics (CCF 2017b, Torres 2017). Janus kinase (JAK) inhibitors are being explored for use in CD (upadacitinib and filgotinib) (Olivera 2017, Torres 2017). Though used in the treatment of IBD more broadly, the anti-inflammatory drug 5-aminosalicylic acid (5-ASA) demonstrates a low efficacy preoperatively and at prevention of CD recurrence in the postoperative setting (CCF 2017a, Torres 2017).

CD is considered neither medically nor surgically "curable," with clinical, endoscopic, and surgical recurrence reported in 50%, 80%, and 30% of patients, respectively (Torres 2017). The surgical burden in CD remains high; a meta-analysis showed that the risk that CD patients will require surgery within 5 years of diagnosis is 33.3%, and by 10 years is 46.6%. Furthermore, 25% of CD patients will require additional intestinal surgery within 5 years of their first surgery, further increasing the financial burden and negative impact on a patient's

quality of life (White 2018). There remains a great unmet clinical need for new efficacious and safe treatments for CD, as current therapies often provide only transient or marginal symptomatic relief. The complex and heterogenous nature of the disease further underscores the need for a range of therapies for CD.

Given that immune system dysregulation is a pathophysiological feature of many immune-mediated inflammatory disorders (Reale 2018, Teng 2015), synthetic small molecule sphingosine 1-phosphate (S1P) receptor modulators have the potential to act across a wide range of such diseases. S1P receptor modulators have been shown to reduce inflammation and induce clinical remission in multiple sclerosis (fingolimod, ponesimod, siponimod, ozanimod) (Kappos 2010, Subei 2015), psoriasis (ponesimod) (D'Ambrosio 2016), and UC (ozanimod, etrasimod) (PPD 2018, Sandborn 2016). Therefore, S1P receptor modulators may also reduce inflammation in CD and induce clinical remission.

1.1.2. Etrasimod

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

S1P₁ is a cell surface expressed G protein-coupled receptor that has been shown to regulate lymphocyte migration out of lymphoid tissues (Brinkmann 2010). Synthetic small molecule S1P₁ 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. In theory, a reduction in the number of circulating lymphocytes translates to less pro-inflammatory cytokines release, which mediates tissue damage. Modulation of the S1P/S1P receptor axis is thought to be a potential therapeutic approach to the management of IBDs such as CD (Nielsen 2017); as such, etrasimod is expected to potentially provide therapeutic benefit to patients with CD. Consistent with this hypothesis, a Phase 2 study and 2 Phase 3 studies with etrasimod in adult subjects with moderately to severely active UC demonstrated consistent and clinically meaningful improvements in endpoint measures reflecting cardinal symptoms of UC and objective endoscopic and histologic evidence of colorectal mucosal healing.

A complete summary of the nonclinical and clinical data relevant to etrasimod and its study in human subjects is provided in the current edition of the Investigator's Brochure (IB).

1.2. Benefit-Risk Considerations

This study includes 5 substudies designed to 1) select a dose(s) of etrasimod for continued evaluation in Phase 3 (Substudy A – Phase 2 [SSA-P2] and Substudy 1 – Phase 2b [SS1-P2b Cohort 1 and Cohort 2]); 2) evaluate the efficacy, safety, and tolerability of the selected etrasimod dose(s) compared with placebo during induction (Substudy 2 – Induction [SS2-I]) and maintenance (Substudy 3 – Maintenance [SS3-M]); and 3) evaluate the long-term safety and tolerability of etrasimod (Substudy 4 – Long-Term Extension [SS4-E]) in subjects with moderately to severely active CD.

As of 30 August 2022 (the data cut-off for Edition 10.0 of the IB), etrasimod has been found to be safe and well tolerated in approximately 1838 adult subjects treated at various doses.

The 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 (qd). In a Phase 2 dose-ranging study in UC patients (Study APD334-003), treatment with 2 mg etrasimod qd for 12 weeks led to clinically meaningful and statistically significant endoscopic and symptomatic improvements versus placebo. Sustained beneficial effects of etrasimod were observed for up to 46 weeks in the subsequent open-label extension study (Study APD334-005). In the Phase 3, randomized, double-blind, placebo-controlled UC studies (APD334-301 and APD-334-302) treatment with etrasimod 2 mg resulted in statistically significant and clinically relevant improvements in the primary endpoints (clinical remission at Weeks 12 and 52 and clinical remission at Week 12, respectively) and all key secondary endpoints. Although UC and CD have different pathophysiology including extent and location of disease, they are both antigen- and immune-mediated IBDs and there is evidence that drugs that are effective for the treatment of UC may also be efficacious for the management of CD ([ENTYVIO 2014](#), [HUMIRA 2002](#), [REMICADE 1998](#), [STELARA 2009](#)). Therefore, it is reasonable to hypothesize that etrasimod may offer similar clinical benefits to CD patients with active disease as UC patients, and this clinical investigation is necessary to affirm or reject this hypothesis.

The longer-term safety profile in subjects with UC, with treatment up to 46 weeks (Study APD334-005), is favorable and consistent with that noted in the parent study (Study APD334-003). Serious adverse events (SAEs) in subjects administered etrasimod have been infrequent, with none reported in the 2 mg etrasimod arm of Study APD334-003 compared to 3 SAEs in the 1 mg etrasimod group and 7 SAEs in the placebo group. Of 14 SAEs reported in the open label extension study (Study APD334-005), most were related to worsening of the underlying UC disease. In Phase 3 UC Study APD334-301, 29 subjects had a total of 32 SAEs (etrasimod: 20 [6.9%] subjects; placebo: 9 [6.3%] subjects). Colitis ulcerative and anemia were the most frequently reported SAEs. Colitis ulcerative was reported in 6 (2.1%) subjects in the etrasimod group and 3 (2.1%) subjects in the placebo group and anemia was reported in 2 (0.7%) subjects in the etrasimod group and 1 (0.7%) subject in the placebo group. In Phase 3 Study APD334-302, 8 subjects had a total of 8 SAEs (etrasimod: 6 [2.5%] subjects; placebo: 2 [1.7%] subjects). The most frequently reported SAE was colitis ulcerative (etrasimod: 3 [1.3%] subjects; placebo: 0 subjects).

There was no evidence of noteworthy differences in the rates of adverse events (AEs) or AE profiles between the Japanese, Chinese, and Caucasian subject populations in Phase 1 studies with etrasimod (Studies APD334-109 and ES101001). A single dose of 2 mg etrasimod was generally well tolerated in subjects with mild, moderate, and severe hepatic impairment and normal hepatic function in Study APD334-108.

To date, there have been no clinically significant safety concerns in clinical studies with etrasimod. In Study APD334-003, nervous system disorders were the most frequently reported treatment related AEs (4 subjects [3.9%]) by system organ class in both etrasimod groups; treatment related AEs of dysgeusia, migraine, neurological symptom, and tremor were reported by 1 subject each in the etrasimod groups along with 1 treatment related AE of dizziness reported by 1 subject who received placebo. The most commonly reported, treatment related AEs in the etrasimod group in Study APD334-005 were UC, increased gamma-glutamyl transferase, headache, neutropenia, and decreased appetite, reported in 2 (1.8%) subjects each. In Phase 3 UC Study APD334-301, a total of 287 (66.3%) subjects

experienced at least 1 TEAE, most TEAEs were mild or moderate in severity. Headache and dizziness were the most frequently reported TEAEs in the etrasimod group (> 3% higher proportion of subjects in etrasimod group than placebo group). In Phase 3 UC Study APD334-302, a total of 166 (46.9%) subjects that experienced at least 1 TEAE, most TEAEs were mild or moderate in severity. The most commonly reported TEAE in the etrasimod group (> 2% difference in proportion of subjects between the etrasimod and placebo groups) were headache, nausea, and colitis ulcerative.

However, rare AEs such as macular edema, liver enzyme elevations, and dyspnea have also been reported with the currently licensed S1P receptor modulators fingolimod (GILENYA 2010), siponimod (MAYZENT 2019), and ozanimod (ZEPOSIA 2020).

While there have not been notable safety concerns with vital signs, electrocardiograms (ECGs), Holter monitoring, pulmonary function tests (PFTs), ophthalmoscopy, or laboratory test results with etrasimod, based on the mechanism of action of etrasimod and prior experience with S1P receptor modulators, monitoring for specific safety parameters is planned for this study. This monitoring includes PFTs, cardiac monitoring at first dose and on treatment re-initiation after a defined period of treatment interruption, liver function tests, and ophthalmoscopy with optical coherence tomography (OCT). Based on its mechanism of action, etrasimod is expected to dose-dependently reduce lymphocyte counts. This reduction is reversible, with lymphocyte counts returning to normal levels within 7 days of study drug discontinuation. Thus, serial assessment of white blood cell (WBC) count and differential will be performed to assess the risk for serious and atypical infections and study subjects will be closely monitored by investigators for infections.

S1P receptor modulators are associated with an expected, on-target dose-dependent effect of reducing heart rate (HR) upon first dosing with HR recovery to predose baseline thereafter (Camm 2014). There have been no reported cases of symptomatic bradycardia on first dose and rare first- or second-degree atrioventricular (AV) block found on ECG has been asymptomatic and transient (ie, spontaneous resolution) with etrasimod. The incidence of second-degree atrioventricular (AV) block Type 1 is approximately 1% and the events are transient and limited to Day 1 of dosing. No cases of second-degree AV block Type 1 have occurred after Day 1 or reoccurred with subsequent dosing. Four of the 5 events of etrasimod-related second-degree AV block were asymptomatic, while 1 subject in Study APD334-009 experienced mild and transient symptoms of lightheadedness and palpitations. In all cases there were no associated blood pressure changes or evidence of hemodynamic compromise. There have been no cases of high-degree AV block such as second-degree AV block Type 2 or third-degree AV block (complete heart block) with etrasimod. There has been 1 cardiac SAE (atrial fibrillation) reported (in Study APD334-005) in the etrasimod development program, which was considered by the Investigator not to be related to study drug. In Study APD334-003, the mean transient HR decrease did not exceed 10 beats per minute (bpm) on Day 1 up to 8 hours after dosing, with the mean nadir of HR lowering for 2 mg etrasimod occurring 3 hours after dosing. Therefore, a dose escalation regimen is not necessary for doses up to 2 mg. This study includes an etrasimod 3 mg treatment group (refer to Section 3.3 for a discussion of dose selection). To attenuate the magnitude of first-dose HR reduction with 3 mg etrasimod, subjects randomized to the 3 mg etrasimod group will receive 2 mg etrasimod daily for the first week and 3 mg etrasimod

daily for the remainder of the study. A similar dosing escalation scheme was utilized in a Phase 1 thorough QT study (Study APD334-008), which showed a mean maximum drop in HR of 0.3 bpm with the first dose of etrasimod 3 mg on Day 8 compared to the same day predose baseline.

To protect vulnerable subjects, those with certain cardiac risks (eg, recent myocardial infarction, cardiac conduction delay, recurrent symptomatic bradycardia or syncope) will be excluded from the study. Vital signs will be monitored closely during the study, and direct observation will be performed during the period after the subject receives the first dose of etrasimod or at treatment re-initiation after a defined period of treatment interruption (refer to Section 10.7.8.4 for additional information). In addition to first-dose cardiac monitoring, continuous 24-hour Holter monitoring will be performed during the induction treatment periods in SSA-P2 and SS1-P2b when the etrasimod dose is increased from 2 mg to 3 mg.

As additional safety measures, subjects with elevated liver enzymes, low lymphocyte or neutrophil counts, active severe pulmonary disease or a chronic pulmonary disease requiring intravenous (IV) corticosteroid or hospitalization, and active retinopathy or macular edema will be excluded from the study. An independent Data Monitoring Committee (DMC) will assess for the presence of any dose-limiting toxicities and provide recommendations on study modification, if needed, to ensure the safety of study subjects participating in the trial.

Further description of identified risks, any potential risks, and the reference safety information (RSI) for etrasimod are provided in the current edition of the Investigator's Brochure.

Based on the preclinical and clinical data that have 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 CD in this current Phase 2/3 study.

2. OBJECTIVES

Primary Objectives

Substudy A – Phase 2 (optional substudy under Study Protocol APD334-202EU)

- To evaluate the safety, tolerability, and efficacy of 2 doses of etrasimod as induction therapy in subjects with moderately to severely active CD

Substudy 1 – Phase 2b Cohort 1

- To evaluate the dose-response relationship of 2 doses of etrasimod versus placebo as induction therapy in subjects with moderately to severely active CD
- To select an oral etrasimod dose, based on efficacy and safety, for continued development

Substudy 1 – Phase 2b Cohort 2

- To evaluate the dose-response relationship of 2 doses of etrasimod versus placebo as induction therapy in subjects with moderately to severely active CD

- To select an oral etrasimod dose, based on efficacy and safety, for continued development along with data generated from SS1 Phase 2b Cohort 1

Substudy 2 – Induction (Phase 3)

- To evaluate the efficacy of the selected etrasimod dose versus placebo as induction therapy in subjects with moderately to severely active CD

Substudy 3 – Maintenance (Phase 3)

- To evaluate the efficacy of etrasimod versus placebo as maintenance therapy in subjects with moderately to severely active CD

Substudy 4 – Long-Term Extension

- To evaluate the long-term safety and tolerability of etrasimod in subjects with moderately to severely active CD

Secondary Objectives

Substudy A – Phase 2 (optional substudy under Study Protocol APD334-202EU)

- To evaluate the long-term safety, tolerability, and efficacy of etrasimod in subjects with moderately to severely active CD
- To evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) effects of etrasimod as induction and maintenance therapy, including changes in lymphocytes, C-reactive protein (CRP), and fecal calprotectin (FCP) in subjects with moderately to severely active CD

Substudy 1 – Phase 2b Cohort 1 and Cohort 2

- To evaluate the safety, tolerability, and efficacy of etrasimod in subjects with moderately to severely active CD
- To provide a subset of the target study population, etrasimod responders, to be evaluated in Substudy 3 – Maintenance

Substudy 2 – Induction (Phase 3)

- To evaluate the safety and tolerability of the selected etrasimod Phase 3 dose (3 mg or 2 mg) versus placebo as induction therapy in subjects with moderately to severely active CD
- To provide a subset of the target study population, etrasimod responders, to be evaluated in Substudy 3 – Maintenance

Substudy 3 – Maintenance (Phase 3)

- To evaluate the efficacy of etrasimod on sustained clinical remission and endoscopic response, endoscopic remission, and corticosteroidfree clinical remission in subjects with moderately to severely active CD
- To characterize the safety and tolerability of etrasimod as maintenance therapy in subjects with moderately to severely active CD

Substudy 4 – Long-Term Extension

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

Exploratory Objectives

Substudy 2 – Induction (Phase 3)

- To evaluate the PK and PD effects of etrasimod as induction therapy, including changes in lymphocytes, CRP, and FCP in subjects with moderately to severely active CD

Substudy 3 – Maintenance (Phase 3)

- To evaluate the efficacy and safety of etrasimod in subjects without clinical response to induction therapy
- To evaluate the PK and PD effects of etrasimod as maintenance therapy, including changes in lymphocytes, CRP, and FCP in subjects with moderately to severely active CD

Substudy 4 – Long-Term Extension

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

3. STUDY DESIGN

3.1. Overall Design

This is a Phase 2/3, multicenter, randomized, double-blind, study comprised of 5 substudies designed to evaluate the efficacy, safety, and tolerability of etrasimod as therapy in subjects with moderately to severely active CD who are refractory or intolerant to at least 1 of the current therapies for CD (ie, corticosteroids, immunosuppressants, or biologics, refer to [Appendix 9](#)). Subjects who are refractory or intolerant to corticosteroids and/or immunosuppressants may be either previously exposed to or naïve to biologics. Randomized subjects will remain on stable doses of 5-aminosalicylic acid (5-ASA) compounds, low-dose oral corticosteroids, and/or anti-diarrheal medications as background therapy for CD; however, corticosteroid tapering may be required in subjects who continue treatment beyond the Induction Period.

This study includes 5 substudies:

- SSA-P2: A Phase 2 randomized, double-blind, substudy to assess the safety, tolerability, and efficacy of oral etrasimod therapy in subjects with moderate to severe CD that supports the selection of an induction and maintenance dose(s) for Phase 3
- SS1-P2b Cohort 1 and Cohort 2: A Phase 2b randomized, double-blind, placebo-controlled, dose-ranging induction substudy to evaluate etrasimod as induction therapy and select an induction and maintenance dose(s) for continued evaluation in Phase 3.

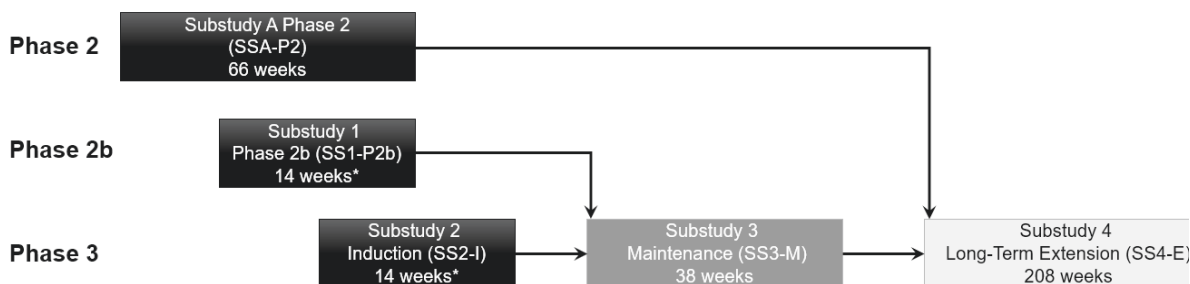
- SS2-I: A Phase 3 randomized, double-blind, placebo-controlled substudy to evaluate etrasimod as induction therapy
- SS3-M: A Phase 3 randomized double-blind, placebo-controlled substudy to evaluate etrasimod as maintenance therapy
- SS4-E: A long-term extension (LTE) substudy for subjects from SSA-P2 and SS3-M who complete at least 52 weeks of treatment

Subjects who discontinue study drug prior to the end of the study will return to the clinic for an Early Termination (ET) Visit within 7 days of the last dose. All study subjects, including those who prematurely discontinue and those who do not continue in SS3-M or SS4-E, will have post-treatment follow-up visits at 2 and 4 weeks ($\pm$ 3 days) after the last dose of study drug as described in Section 9. The overall study duration is up to 282 weeks, inclusive of the Screening Period, Treatment Period of up to 274 weeks, and the 4-Week Follow-Up Period.

For country specific requirements (Canada, Russia, Japan, Switzerland, Netherlands, Israel) see [Appendix 11](#).

An overall schematic diagram of this study is provided in Figure 1. A description of each substudy is provided below.

Figure 1: Schematic Diagram of APD334-202 Study Design



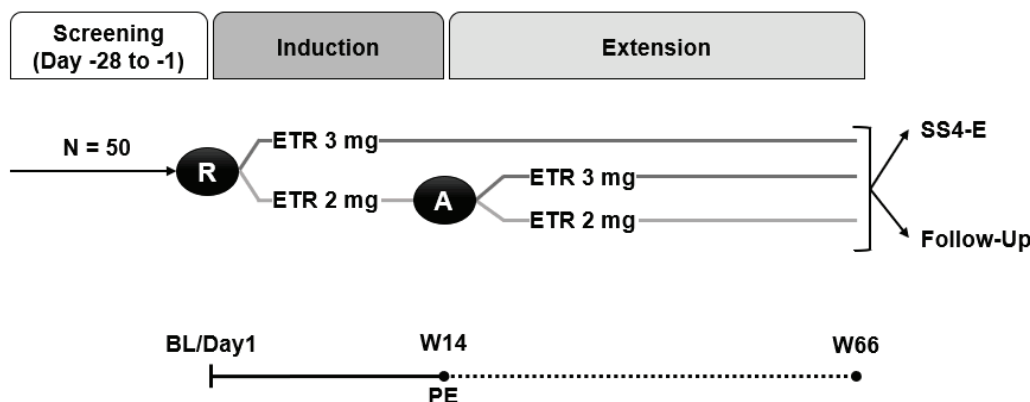
*Subjects in SS1-P2b and SS2-I who do not meet prespecified clinical or endoscopic response criteria (defined in Section 3.1.2) at Week 14 will complete a 6-week Extended Induction Period and may then be eligible for SS3-M. SSA-P2, Substudy A – Phase 2; SS1-P2b, Substudy 1 – Phase 2b; SS2-I, Substudy 2 – Induction; SS3-M, Substudy 3 – Maintenance; SS4-E, Substudy 4 – Long-Term Extension

3.1.1. Substudy A – Phase 2

The Phase 2 substudy will consist of a screening period of up to 28 days (28-Day Screening Period) to determine subject eligibility, a 14-week double-blind induction treatment period (Induction Period), a subsequent 52-week Extension Period (Extension Period), and a 4-Week Follow-Up Period (for subjects who do not continue in another substudy), for a total duration of up to 74 weeks ([Figure 2](#)). SSA-P2 will enroll and treat approximately 50 subjects.

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Figure 2: Substudy A – Phase 2 Schematic Diagram



A, assigned; BL, Baseline; ETR, etrasimod; PE, primary endpoint; R, randomization; SS4-E, Substudy 4 – Long-Term Extension; W, Week

Subjects eligible for this substudy will be randomized in a double-blinded fashion (1:1 ratio) to receive etrasimod 2 mg or 3 mg during the Induction Period. Randomization will be stratified by baseline biologic treatment failure status (yes/no) and baseline oral corticosteroid use (yes/no).

All subjects who complete the Induction Period may enter the Extension Period. Subjects will receive etrasimod 2 mg or 3 mg in the Extension Period according to their Induction Period treatment and clinical response (response criteria defined in Section 3.1.2) as shown in Table 1.

Table 1: Substudy A – Phase 2 Extension Period Treatment Assignment

Induction Period Treatment	Met Criteria for Clinical Response at Week 14	Extension Period Treatment Assignment
2 mg etrasimod	Yes	2 mg etrasimod
	No	2 mg or 3 mg etrasimod (1:1)
3 mg etrasimod	Yes	3 mg etrasimod
	No	3 mg etrasimod

Subjects who achieve clinical response at Week 14 may undergo corticosteroid taper in the Extension Period with the goal of weaning off corticosteroids (Section 6.8.3).

Throughout the Extension Period, subjects will be regularly assessed to monitor the clinical benefit of etrasimod treatment and to evaluate potential lack of efficacy. Subjects who do not show clinical improvement from baseline, as determined by the Investigator (non-EU regions) or defined as a ≥ 70 -point decrease on CDAI (EU region only), by Week 20 will be discontinued from study drug. Subjects who experience unexplained disease worsening, as determined by the Investigator, at any time during the Extension Period may receive short-term, add-on rescue therapy (refer to Section 6.8.4). If subjects show no clinical improvement from rescue therapy, as determined by the Investigator, then they will also be discontinued from study drug.

Subjects who complete 66 weeks of treatment will be eligible to enroll in SS4-E.

3.1.1.1. Subjects Enrolled in Study APD334-202 under Amendment 1.0

Amendment 1.0 of Study APD334-202 contained a 14-week Induction Period in which subjects were randomized (1:1:1) to receive etrasimod 2 mg, etrasimod 3 mg or placebo, followed by a 52-week Extension Period in which subjects were assigned treatment in a similar fashion to the 52-Week Extension Period of SSA-P2. Subjects who have not completed the End of Week 15 Visit will continue with study drug administration and the study visit schedule under Amendment 1.0 until completion of the End of Week 15 Visit, at which time they will be reconsented under Amendment 2.0. These subjects will remain on the same etrasimod dose (ie, dose assigned in the Extension Period of Amendment 1.0) and complete their remaining study visits in the Extension Period of SSA-P2 under Amendment 2.0. Subjects enrolled under Amendment 1.0 who have completed study visits beyond the End of Week 15 Visit will be reconsented under Amendment 2.0 at their next scheduled study visit and will continue in the Extension Period of SSA-P2 for their remaining study visits (ie, subjects will not repeat visits given that the Extension Period visit schedule is the same under Amendment 1.0 as under Amendment 2.0).

3.1.2. Response Criteria for SSA-P2, SS1-P2b, SS2-I, and SS3-M

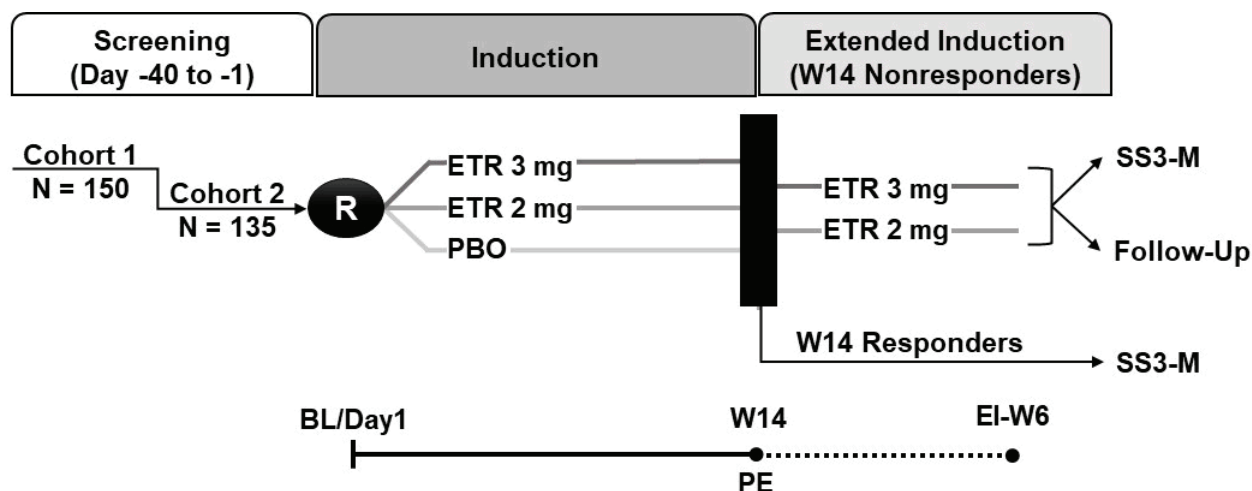
Subjects must meet at least 1 of the following criteria to be considered a responder:

- Clinical response Crohn's Disease Activity Index (CDAI): clinical remission CDAI OR ≥ 100 -point decrease from baseline in CDAI
 - Clinical remission CDAI: CDAI < 150
- Endoscopic response: endoscopic remission OR $\geq 50\%$ decrease from baseline in Simple Endoscopic Score in Crohn's Disease (SES-CD)
 - Endoscopic remission: SES-CD ≤ 4 and at least 2-point reduction from baseline with no subscore > 1

3.1.3. Substudy 1 – Phase 2b

The Phase 2b substudy will consist of a screening period of up to 40 days (40-Day Screening Period) to determine subject eligibility, a 14-week double-blind induction treatment period (Induction Period), a subsequent 6-week Extended Induction (EI) Period for subjects who do not meet response criteria at Week 14 (EI Period), and a 4-Week Follow-up Period (for subjects who do not continue in SS3-M), for a total study duration of up to approximately 30 weeks (Figure 3). Enrollment in SS1-P2b will begin after SSA-P2 has randomized approximately 50 subjects. This study will consist of 2 cohorts that will enroll consecutively. Cohort 1 will enroll and treat approximately 150 subjects. Cohort 2 will enroll and treat approximately 135 subjects. Efficacy and safety data from Cohort 1 and Cohort 2 will be analyzed to select the dose(s) with a favorable benefit/risk profile for continued evaluation in Phase 3 studies.

Figure 3: Substudy 1 – Phase 2b Schematic Diagram



BL, Baseline; EI, Extended Induction; ETR, etrasimod; PBO, placebo; PE, primary endpoint; R, randomization; SS3-M, Substudy 3 – Maintenance; W, Week

Eligible subjects will be randomized in a double-blinded fashion (1:1:1 ratio) to etrasimod 3 mg, etrasimod 2 mg, or matching placebo. Randomization will be stratified by baseline biologic treatment failure status (yes/no) and baseline oral corticosteroid use (yes/no). Subjects who meet response criteria at Week 14 (ie, Week 14 responders; response criteria defined in Section 3.1.2) will be eligible to enter SS3-M upon completion of the Week 14 Visit.

To determine if a proportion of subjects receiving etrasimod 2 mg or 3 mg may be delayed responders and may benefit from extended induction treatment, all subjects who do not meet response criteria at Week 14 will enter a 6-week EI Period for a total of up to 20 weeks induction treatment. In the EI Period, subjects will receive etrasimod 2 mg or 3 mg according to their Induction Period treatment as shown in Table 2. At the end of the EI Period, subjects who show clinical improvement, based on the Investigator's judgement (globally), may be eligible to enter SS3-M (Section 3.1.5); subjects who show no clinical improvement will be discontinued from the study (Section 8.1). For EU region only, subjects with CD worsening, defined as ≥ 100 -point increase in CDAI score from baseline and CDAI ≥ 220 points, will be discontinued from the study, subjects without CD worsening may be eligible for SS3-M (Section 8.1).

Table 2: Substudy 1 – Phase 2b Extended Induction Period Treatment Assignment

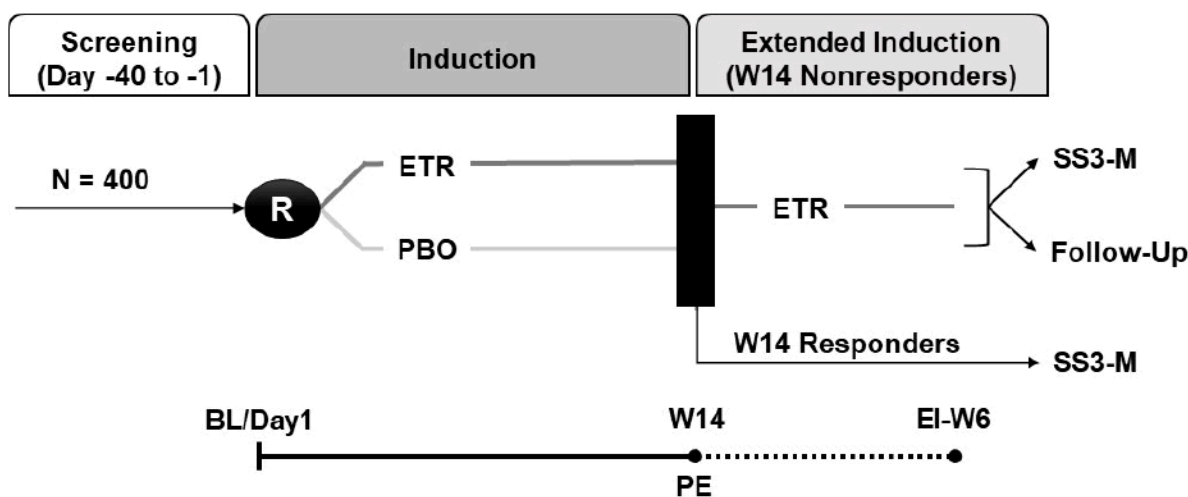
Induction Period Treatment	Extended Induction Period Treatment
Placebo	Etrasimod 2 mg or 3 mg (1:1)
Etrasimod 2 mg	Etrasimod 2 mg
Etrasimod 3 mg	Etrasimod 3 mg

3.1.4. Substudy 2 – Induction

SS2-I is a Phase 3 randomized, double-blind, placebo-controlled substudy that will evaluate the efficacy, safety, and tolerability of etrasimod versus placebo as induction therapy. SS2-I will begin after enrollment in SS1-P2b is completed and a dose(s) is selected for further evaluation in Phase 3.

This substudy will consist of a screening period of up to 40 days (40-Day Screening Period) to determine subject eligibility, a 14-week double-blind induction treatment period (14-Week Treatment Period), a subsequent 6-week EI Period for subjects who do not meet response criteria at Week 14 (EI Period), and a 4-Week Follow-Up Period (for subjects who do not continue in SS3-M) (Figure 4).

Figure 4: Substudy 2 – Induction Schematic Diagram



BL, Baseline; EI, Extended Induction; ETR, etrasimod; PBO, placebo; PE, primary endpoint; R, randomization; SS3-M, Substudy 3 – Maintenance; W, week

Eligible subjects will be randomized in a double-blind fashion (3:1 ratio) to the selected etrasimod dose (2 mg or 3 mg) or placebo treatment. Biologic-experienced subjects may comprise [REDACTED]. Randomization will be stratified by baseline biologic treatment failure status (yes/no) and baseline oral corticosteroid use (yes/no). Subjects who meet response criteria at Week 14 (ie, Week 14 responders; response criteria defined in Section 3.1.2) will be eligible to enter SS3-M upon completion of the Week 14 Visit. To determine if a proportion of subjects receiving etrasimod may be delayed responders and may benefit from extended induction treatment, all subjects who do not meet response criteria at Week 14 will enter a 6-week EI Period for a total of 20 weeks induction

treatment and will receive etrasimod in the EI Period. At the end of the EI Period, subjects who show clinical improvement, based on the Investigator's judgment (globally), may be eligible to enter SS3-M (Section 3.1.5). Subjects who show no clinical improvement will be discontinued from the study (Section 8.1) (non-EU region). For EU region only, subjects with CD worsening, defined as ≥ 100 -point increase in CDAI score from baseline and CDAI ≥ 220 points, will be discontinued from the study; subjects without CD worsening may be eligible for SS3-M (Section 8.1).

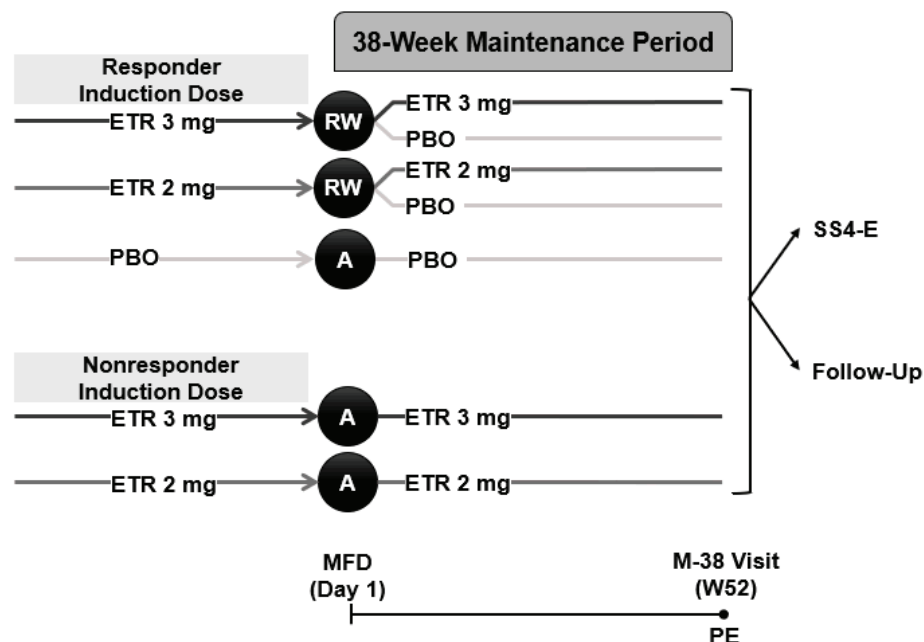
3.1.5. Substudy 3 – Maintenance

SS3-M is a Phase 3 randomized, double-blind, placebo-controlled maintenance substudy (Figure 5). Subjects who complete treatment and meet the study specific criteria in SS1-P2b, SS2-I, or Study APD334-305 (a separate Phase 3 double-blind, placebo-controlled study) may be eligible for SS3-M (refer to Section 4.2.1).

Subjects will be enrolled in the Responder (ie, etrasimod and placebo responders), or Nonresponder Cohort based on the induction treatment (3 mg etrasimod, 2 mg etrasimod, or placebo) they received at the Week 14 or EI-Week 6 Visit and whether or not they met response criteria at Week 14 or EI-Week 6 Visit (refer to Section 3.1.2). The Maintenance First Dose (MFD) Visit is the first visit of SS3-M for all subjects irrespective of cohort and irrespective of whether they completed an EI Period or not. Therefore, the duration of SS3-M is 38 weeks for all subjects.

Subjects who complete this 38-week substudy will have completed at least 52 weeks of treatment and may be eligible to enter SS4-E.

Figure 5: Substudy 3 – Maintenance Schematic Diagram



*All subjects, regardless of cohort and regardless of whether or not they completed an Extended Induction Period, will have a MFD Visit as the first visit of SS3-M. The MFD Visit may be performed on the same day as the last visit of the parent study or substudy but must occur within 7 days of the last visit of the previous treatment period.

A, assigned; ETR, etrasimod; PBO, placebo; PE, primary endpoint; MFD, Maintenance First Dose; RW, randomized withdrawal; SS3-M, Substudy 3 – Maintenance; SS4-E, Substudy 4 – Long-Term Extension

3.1.5.1. Responder Cohort

Subjects who received etrasimod during the Induction or EI Treatment Periods and meet at least 1 response criteria (ie, etrasimod responders; refer to Section 3.1.2 for response criteria) will be randomized (1:1 ratio) in a double-blind fashion to placebo or etrasimod for up to 38 weeks; subjects randomized to etrasimod will receive the same etrasimod dose (2 mg or 3 mg) they received at the last visit of the parent study or substudy. Randomization will be stratified by Week 14 endoscopic response status (yes/no), baseline biologic treatment failure status (yes/no), and corticosteroid use (yes/no) at SS3-M Baseline. Subjects who received placebo during the Induction Treatment Period and meet response criteria (placebo responders) will continue to receive blinded placebo treatment in SS3-M.

Etrasimod and placebo responders who were on corticosteroids at the MFD Visit will undergo corticosteroid taper with the goal of weaning off corticosteroids (Section 6.8.3).

Only etrasimod responders who met response criteria by Week 14 of the Induction Period will be included in the Full Analysis Set (FAS) for the final analyses for SS3-M efficacy endpoints. Etrasimod responders who met response criteria at the EI-Week 6 Visit and placebo responders will be analyzed separately.

Following dose selection, randomization to an etrasimod dose arm may be discontinued and etrasimod responders entering SS3-M would thus be randomized (1:1 ratio) to receive the selected etrasimod dose or matching placebo. The primary analysis for the maintenance will be limited to the comparison between the selected etrasimod dose arm and the matching placebo arm. Subjects randomized to etrasimod in SS3-M prior to dose selection may remain at the same etrasimod dose until the end of the substudy, even if randomization to that dose is discontinued. If randomization to an etrasimod dose arm is discontinued, subjects randomized to that dose will be included in safety analyses but not included in the FAS.

3.1.5.2. Loss-of-Response

All subjects will be regularly monitored for potential symptomatic disease worsening. Following the M-6 (Week 6) Visit, etrasimod and placebo responders who experience sustained disease worsening may be evaluated for potential loss-of-response (LOR) at any scheduled visit during the Maintenance Treatment Period or at any time between scheduled visits (ie, an unscheduled LOR Visit). LOR assessment may not occur prior to the M-6 Visit. Initiation of LOR assessment may begin only if the worsening in abdominal pain (AP) and/or stool frequency (SF) symptom scores over the 7 most recent days compared to SS3-M baseline values have been documented in the subject's daily electronic diary (eDiary).

LOR is defined as an increase in disease activity that satisfies the following criteria:

1. CDAI score ≥ 220 - AND a ≥ 100 -point increase from the MFD Visit
2. Alternative suspected causes for the increased disease activity including viral or bacterial gastroenteritis and *Clostridioides difficile* (*C. difficile*) infection have been ruled out by appropriate stool cultures and other laboratory tests. If a potential other cause is identified, loss of response will not be assessed until a full course of treatment has been completed, or if untreated, the infection would be expected to be resolved based on its natural history. This testing must begin once loss of response is suspected.

If possible, an ileocolonoscopy will be performed prior to the LOR First Dose Visit.

Subjects with confirmed LOR will have a LOR First Dose Visit and receive etrasimod for the remainder of the Maintenance Treatment Period (refer to Section 3.1.5.3). For subsequent visits, these subjects will be considered part of the Nonresponder Cohort.

3.1.5.3. Nonresponder Cohort

Subjects who do not meet response criteria (nonresponders), but showed clinical improvement during the EI Period, will be included in the Nonresponder Cohort and will remain on their EI Period etrasimod dose (2 mg or 3 mg) qd for the 38-week Maintenance Treatment Period. Etrasimod responders who meet LOR criteria and switch to the Nonresponder Cohort will be assigned, in a blinded manner, to receive the etrasimod dose they were on at SS3-M baseline (ie, the etrasimod dose they received at the last visit of the parent induction study). Placebo responders who experience a LOR and switch to the Nonresponder Cohort will receive either etrasimod 2 mg or 3 mg (1:1 ratio). Refer to Section 3.1.5.2 and Section 9.7.3 for LOR criteria.

Subjects in the Nonresponder Cohort may undergo corticosteroid taper at any time during the Maintenance Treatment Period at the Investigator's discretion.

Throughout the Maintenance Treatment Period, subjects will be regularly assessed to monitor the clinical benefit of etrasimod treatment and to evaluate potential lack of efficacy. Subjects who enter SS3-M in the Nonresponder Cohort and show no continued clinical improvement, as determined by the Investigator, by 8 weeks following the MFD Visit will be discontinued from the study drug due to lack of efficacy. Subjects who switch to the Nonresponder Cohort during SS3-M (ie, subjects in the Responder Cohort at the MFD Visit) and show no clinical improvement, as determined by the Investigator, by 14 weeks following the Loss-of-Response First Dose Visit will be discontinued from the study due to lack efficacy, which may occur when the subject is in SS4-E (Section 8.1).

Nonresponders who experience unexplained disease worsening, as determined by the Investigator, at any time may receive short-term, add-on rescue therapy (refer to Section 6.8.4). If subjects show no clinical improvement from rescue therapy, as determined by the Investigator, then they will also be discontinued from study drug.

Following dose selection, subjects entering the Nonresponder Cohort, including those switching from the Etrasimod or Placebo Responder Cohorts, will receive the selected etrasimod dose. Subjects in the Nonresponder Cohort who were assigned the dose not selected prior to dose selection may be switched to the selected etrasimod dose at the next scheduled study visit.

3.1.6. Substudy 4 – Long-Term Extension

SS4-E is an LTE substudy that will evaluate the long-term safety and efficacy of etrasimod in subjects with moderately to severely active CD. Subjects from SS3-M and from SSA-P2 who complete at least 52 and 66 weeks of treatment, respectively, will be eligible to enter this LTE study with a treatment period of up to 208 weeks and a 4-Week Follow-Up Period (Figure 6). Prior to dose selection, subjects who enroll in SS4-E from SS3-M will continue on the etrasimod dose (2 mg or 3 mg) they received at the M-38 Visit of SS3-M and subjects who enroll in SS4-E from SSA-P2 will continue on the etrasimod dose (2 mg or 3 mg) they received at the Week 66 Visit of SSA-P2. Subjects on placebo at SS4-E baseline will be

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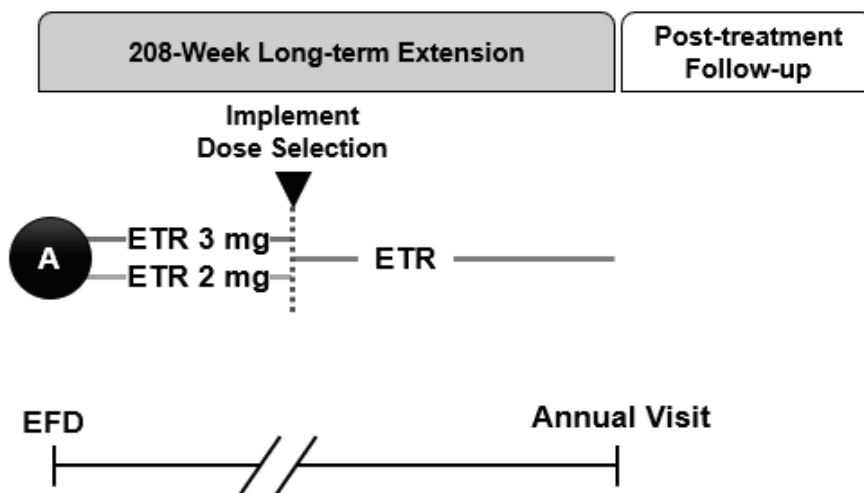
randomized (1:1) to receive etrasimod 2 mg or 3 mg. Following dose selection, an etrasimod dose in SS4-E may be discontinued. If an etrasimod dose is discontinued, subjects entering SS4-E after dose selection will receive the selected etrasimod dose. Subjects already enrolled in SS4-E will be switched to the selected etrasimod dose at their next study visit once it is available.

In SS4-E, starting, stopping, or changing the dose of permitted background treatments for CD will be allowed at the discretion of the Investigator. This includes receiving add-on rescue therapy (refer to Section 6.8.4) for subjects who experience unexplained disease worsening, as determined by the Investigator. Use of rectal and parenteral corticosteroids is also allowed for subjects enrolled in SS4-E (Table 14).

Throughout the LTE Treatment Period, subjects will be regularly assessed to monitor the clinical benefit of etrasimod treatment and to evaluate potential lack of efficacy. Subjects who show no clinical improvement from rescue therapy will be discontinued from study drug.

All subjects (ie, subjects who prematurely discontinue study drug and those who complete the SS4-E treatment period) will have follow-up visits at 2 and 4 weeks after the last dose of study drug during the 4-Week Follow-Up Period.

Figure 6: Substudy 4 – Long-Term Extension Schematic Diagram



A, assigned; EFD, Extension First Dose; ETR, etrasimod

3.2. Discussion and Scientific Rationale for Study Design

This is a Phase 2/3 study designed to evaluate the efficacy, safety, and tolerability of etrasimod as induction and maintenance therapy in subjects with moderately to severely active CD who are refractory or intolerant to at least 1 of the current therapies for CD (ie, corticosteroids, immunosuppressants, or biologics [eg, TNF α antagonists, vedolizumab, ustekinumab]). Subjects who are refractory or intolerant to corticosteroids and/or immunosuppressants may be previously exposed to or naïve to biologics. The study population includes those in different disease stages (eg, patients with early CD that have

failed standard, non-biologic treatment or patients with CD that failed on multiple treatments, including biologics); thus, subjects will be stratified according to baseline biologic treatment failure status (yes/no) and baseline oral corticosteroid use (yes/no) at randomization in all substudies except SS4-E.

As treatment of CD requires chronic therapy, this study consists of 5 substudies so that subjects have the opportunity to continue treatment for up to 282 weeks under 1 protocol. This study design also allows subjects from Phase 2b (SS1-P2b) to continue into a Phase 3 maintenance substudy (SS3-M) for continued Phase 3 evaluation. Allowing Phase 2b subjects to enter a Phase 3 maintenance study will decrease the overall number of subjects required to evaluate the long-term efficacy of etrasimod, compared to a traditional program with separate Phase 3 studies. A similar approach was taken in the pivotal Phase 2/3 operationally seamless study for golimumab leading to FDA approval in 2013 ([Sandborn 2014a](#), [Sandborn 2014b](#), [SIMPONI 2009](#)). In the golimumab program, both Phase 2 and 3 induction treatment responders were eligible for re-randomization in the 54-week Phase 3 maintenance study. Therefore, this study design allows for the collection of long-term safety and efficacy data under 1 protocol and allows subjects to transition between induction and maintenance in a more efficient manner.

The inclusion of key endoscopy and symptom-based endpoints is recommended in studies investigating the effectiveness of novel treatments for CD ([EMA 2018](#)). Primary efficacy endpoints for this study are the proportion of subjects who achieve endoscopic response ($\geq 50\%$ decrease from Baseline in SES-CD score) and clinical remission by CDAI (CAI < 150) at predefined induction and maintenance time points. Endoscopic improvement is considered an essential measure of efficacy because mucosal healing is postulated to be a predictor of longer term disease remission ([Shah 2016](#)). The definition of endoscopic improvement (ie, $\geq 50\%$ decrease in SES-CD) is based on the observations from the Study of Biologic and Immunomodulator Naïve Patients in CD (ie, SONIC trial) that subjects with a $\geq 50\%$ decrease in SES-CD from baseline at Week 26 were identified as those most likely to be in corticosteroid-free clinical remission at Week 50 ([Ferrante 2013](#)). CDAI has been used extensively for primary endpoint efficacy analyses in CD clinical trials. In accordance with EMA guidance, patient-reported outcomes derived from the CDAI (PRO2) will be a key secondary endpoint for this study ([EMA 2018](#)).

The follow-up visits that occur 2 and 4 weeks after the last dose of study drug will provide off-treatment safety information, including the magnitude of and time to lymphocyte recovery.

Rationale for the design of each substudy is provided below.

SSA-P2

This substudy will evaluate the safety, tolerability, and efficacy of 2 doses of etrasimod in subjects with moderately to severely active CD.

Though subjects will be blinded to the actual dose of study drug they will receive in both the Induction and Extension Periods, this substudy does not include a placebo-controlled group during the 14-week Induction Period or during the subsequent 52-week Extension Period given the goals to collect longer-term safety and efficacy data on etrasimod 3 and 2 mg doses

in this subject population. The 14-week Induction Period is expected to provide adequate time to assess if etrasimod provides improvement in endoscopic and clinical symptoms of CD. Week 14 was selected as the timepoint for assessment of the efficacy endpoints based on the observation that drugs with related mechanism of action (ie, lymphocyte regulation/suppression) like natalizumab, vedolizumab (Sandborn 2005, Sandborn 2013, Sands 2014, Vermeire 2017), investigational etrolizumab (Selinger 2018) and investigational ozanimod (Feagan 2017) demonstrated higher rates of clinical and endoscopic responses after at least 12 weeks of treatment. Although circulating and gut specific lymphocytes have variable lifespans, lymphocyte turnover is expected to occur on an ongoing basis and over a 12-week period, in the presence of a lymphocyte suppressing agent, the activated lymphocyte population is expected to diminish and the clinical benefits of treatment with these drugs in a treatment responsive host should be apparent.

Moderate-to-severe CD is a chronic disease that requires long-term therapy; thus, this study contains a 52-week Extension Period to evaluate the long-term safety, tolerability, and efficacy of 2 etrasimod doses. The long-term safety and efficacy results from Study APD334-005 demonstrating a positive benefit-risk ratio for etrasimod 2 mg in subjects with UC supports the long-term evaluation of etrasimod treatment in this Phase 2 study in subjects with CD. To date there is no long-term safety or efficacy data with etrasimod 3 mg. Extension Period treatment reassignment based on a subject's clinical response status at Week 14 will assess whether treatment response can be sustained at either the etrasimod 2 or 3 mg dose for subjects who meet clinical response criteria at Week 14. In addition, the treatment reassignment will evaluate whether some subjects have a delayed response to treatment and therefore require additional time on active drug or if a dose escalation from etrasimod 2 to 3 mg in the Extension Period provides additional therapeutic benefit. Thus, this 66-week Phase 2 study is designed to provide long-term safety, tolerability, and efficacy data in subjects with moderate to severe CD that will support the dose selection analysis for Phase 3, where the primary data informing dose selection is derived from the Induction Period of SS1-P2b.

SS1-P2b

This substudy includes 2 sequential cohorts of identical design and will characterize the efficacy and safety of 2 doses of etrasimod as induction therapy in subjects with moderately to severely active CD and to inform dose selection for Phase 3.

To evaluate the efficacy of etrasimod for CD, this study includes a placebo-controlled group during the 14-week Induction Period. The purpose of the placebo comparison is to determine the treatment effects that are not due to etrasimod itself (ie, the placebo effect). Factors accounting for the placebo effect which may lead to improvement in CD symptoms include increased attention from healthcare providers in the context of a clinical study, aspirations of receiving the active treatment, the expectation of a treatment's benefit because of its novelty, or spontaneous improvement in the CD symptoms as part of the disease course (ie, flares and quiescent states). At study entry, subjects randomized to any treatment group will remain on stable doses of certain background therapy for CD (eg, 5-ASA compounds, oral corticosteroids, and/or anti-diarrheal medications); therefore, even subjects randomized to the placebo treatment during the Induction Period will have concomitant therapies that may be partially effective at controlling CD symptoms. Subjects randomized to receive placebo on

Day 1 who continue in the EI Period (ie, subjects who receive placebo and do not meet response criteria at Week 14) will be randomized (1:1) to receive etrasimod 2 mg or 3 mg qd during the EI Period.

The Induction Period is expected to provide adequate time for separation of endoscopic and symptomatic efficacy effects between etrasimod and placebo as induction therapy. The primary efficacy endpoint is the proportion of subjects who achieve endoscopic response at Week 14 and the secondary endpoint is a symptom-based endpoint that measures the proportion of subjects who achieve clinical remission by CDAI at Week 14. As described above, Week 14 was selected to be the timepoint for assessment of the primary efficacy endpoint based on the observation that drugs with related mechanism of action demonstrated a separation from placebo treatment with higher rates of clinical and endoscopic responses after at least 12 weeks of treatment ([Sandborn 2005](#), [Sandborn 2013](#), [Sands 2014](#), [Vermeire 2017](#)).

Some subjects may need longer time on active drug to achieve clinical response following initial induction therapy (ie, delayed responders). Previous studies in subjects with CD identified a subgroup of delayed responders that benefit from extended induction treatment. For example, in the Phase 3 CD program for ustekinumab, subjects who were considered nonresponders at the end of an 8-week induction received 90 mg subcutaneous ustekinumab for an additional 8 weeks. At Week 16, 50.5% of these subjects achieved response and were considered delayed responders ([Sands 2019](#)). Therefore, SS1-P2b includes a 6-week EI Period for subjects who do not meet response criteria at Week 14. Data from the EI Period will be used for exploratory analyses to assess response/remission rates up to Week 20 and may be used to support dose selection. Subjects who, based on the Investigator's judgement, do not show any clinical improvement at the completion of the EI Period will be discontinued from the study.

CCI

In order to ensure high confidence that etrasimod demonstrates efficacy for both endoscopic response and CDAI remission, data from SS1-P2b Cohort 2 will now be used to further characterize the dose response and ultimately support dose selection for Phase 3 development along with the data generated from SS1-P2b Cohort 1.

SS2-I

SS2-I is a placebo-controlled, double-blind, Phase 3 substudy to evaluate the selected etrasimod dose as induction therapy in subjects with moderately to severely active CD and is similar in design to SS1-P2b. This study will begin after dose selection.

In accordance with regulatory guidance for CD ([EMA 2018](#)), this study has co-primary endpoints of the proportion of subjects with clinical remission and the proportion of subjects with endoscopic response.

While it is anticipated that 14 weeks is the optimal duration length for the induction of clinical remission and endoscopic response, this substudy will also include an EI Period for subjects who do not meet response criteria at Week 14. Data from the EI Period will be used for exploratory analyses to assess response/remission rates for a treatment period of up to 20 weeks. Subjects who, based on the Investigator's judgement, do not show any clinical improvement at the completion of the EI Period will be discontinued from the study.

SS3-M

Evidence from the CD drug development literature spanning several decades reinforces the observation that regardless of the drug's mechanism of action, sustaining or maintaining clinical response/remission in moderately to severely active CD requires the patient to remain on highly effective medical therapy for months, if not years, to continuously attenuate the systemic inflammatory response that mediates disease progression ([Asgharpour 2013](#), [Gonzalez-Lama 2008](#), [Sandborn 2018](#), [Vermeire 2017](#)). This Phase 3 randomized withdrawal substudy is designed to evaluate the efficacy and safety of etrasimod as maintenance therapy in subjects with moderately to severely active CD who completed at least 14 weeks of induction therapy in a parent substudy or study and were identified as etrasimod treatment responders. Subjects who complete treatment in SS1-P2b, SS2-I, or Study APD334-305 regardless of responder status, will be assessed for eligibility in this substudy; however, the primary efficacy population for key efficacy analyses will include only subjects on etrasimod who meet response criteria (etrasimod responders) at Week 14.

The 38-week maintenance treatment period is expected to provide adequate time for separation of endoscopic and symptomatic efficacy effects between etrasimod and placebo as maintenance therapy. Subjects who complete this maintenance study will have had at least 52 weeks of treatment. One year is considered sufficient to demonstrate long-term efficacy ([EMA 2018](#), [FDA 2016](#)).

To evaluate the efficacy of etrasimod as maintenance therapy for CD, this randomized-withdrawal study includes a placebo-controlled group to establish the magnitude of change in endpoints that may occur in the absence of etrasimod. The purpose of the placebo comparison is to determine the long-term treatment effects that are not due to etrasimod itself (ie, the placebo effect). To protect the blind in the parent studies, placebo responders participating in this substudy will continue to receive placebo in a blinded manner but will not be part of formal efficacy analyses. All subjects who receive placebo in this substudy will have the option to receive active drug should they lose response, thereby limiting the ethical concerns of having a placebo group in this 38-week study. Furthermore, at study entry, subjects randomized to any treatment group will remain on stable doses of background therapy for CD (eg, 5-ASA compounds); therefore, even subjects randomized to the placebo treatment will have concomitant therapies that may be partially effective at controlling CD symptoms.

The primary efficacy endpoints are the proportion of subjects in clinical remission at Week 52 and the proportion of subjects who achieve endoscopic response at Week 52. Since this study evaluates etrasimod as long-term therapy, the proportion of subjects with endoscopic remission at Week 52 is a key secondary endpoint.

A goal of maintenance therapy for subjects with CD is the reduction or elimination of corticosteroid use; therefore, etrasimod and placebo responders receiving corticosteroids at baseline who achieved clinical response will undergo mandatory tapering and one of the key secondary endpoints is the proportion of subjects who achieve corticosteroid-free clinical remission at Week 52 among subjects receiving corticosteroids.

SS4-E

As a chronic disease, patients with moderate to severe CD need to remain on highly effective medical therapy for months, if not years, to continuously attenuate the systemic inflammatory response that mediates disease progression (Asgharpour 2013, Gonzalez-Lama 2008, Sandborn 2018, Vermeire 2017). Therefore, this LTE substudy is designed to evaluate the long-term safety and efficacy of etrasimod for up to 5 years in subjects with moderately to severely active CD who are refractory or intolerant to corticosteroids, immunosuppressants, or biologics (eg, TNF α antagonists, vedolizumab, ustekinumab).

To evaluate long-term etrasimod use in a way that more closely resembles real-world management of CD, optimization of background therapy will be allowed and subjects will not be required to stay on stable doses of these therapies during SS4-E (Table 14).

3.3. Rationale for Dose Selection

Phase 2 Substudies SSA-P2 and SS1-P2b

Two doses of etrasimod, 2 mg and 3 mg, will be evaluated in SSA-P2 and SS1-P2b, with the goal of selecting 1 dose for continued evaluation in Phase 3. Etrasimod doses of 2 mg and 3 mg were selected based on information from a single ascending dose study (APD334-001), a multiple ascending dose study (APD334-002), a thorough corrected QT interval (QTc) study (APD334-008), and a single and multiple dose-escalation Study ES101001 conducted in healthy adult subjects, as well as the demonstration of safety and treatment efficacy from a Phase 2 study (APD334-003), including the open-label extension study (APD334-005), in subjects with UC.

In Study APD334-001 in healthy subjects, etrasimod demonstrated only modest declines in peripheral blood lymphocytes at doses up to 1 mg. In contrast, the 3 mg and 5 mg doses induced a clear dose-responsive decline in the absolute number of peripheral blood lymphocytes. In Study APD334-002 up to 21 days of dosing with etrasimod 2 mg or 3 mg was safe and well-tolerated and both doses reduced peripheral lymphocyte counts. In the QTc study, 30 adult subjects received etrasimod 2 mg qd (Days 1-7), then etrasimod 3 mg qd (Days 8-12), and finally etrasimod 4 mg qd (Days 13-14). There were no notable safety findings, and subjects tolerated the doses of etrasimod 2, 3, and 4 mg well. After etrasimod treatment lymphocyte reductions of 46% and 65% for Day 8 and Day 15, respectively, were observed. In the multiple ascending dose periods of Study ES101001, healthy Chinese subjects received etrasimod 1 mg (10 days), etrasimod 2 mg (10 days), or etrasimod 3 mg (etrasimod 2 mg Days 1 - 7 followed by etrasimod 3 mg Days 8 - 14). At steady state of etrasimod 1, 2, and 3 mg, the mean percentage changes from baseline in absolute lymphocyte count (ALC) were -41.22%, -60.70% and -70.33%, respectively. There were no new or significant safety findings during either the single or multiple dosing periods. Together, these Phase 1 studies demonstrated that etrasimod doses up to 4 mg were well-tolerated with no

significant safety findings, and that treatment with etrasimod 2 mg and 3 mg resulted in significant reductions in peripheral lymphocyte counts. Results from Studies APD334-008 and ES101001 suggest that etrasimod 2 mg followed by an increase to 3 mg will provide additional reduction in peripheral lymphocyte counts.

In Study APD334-003, adult subjects with moderately to severely active UC treated with etrasimod 1 mg and 2 mg had notable trends of dose-dependent improvement in symptom, endoscopic and histologic efficacy; however, only 2 mg etrasimod demonstrated statistically significant clinical, endoscopic, and histologic efficacy over placebo. The mean percentage reduction from baseline in total lymphocyte count associated with 2 mg etrasimod in treatment responders was 46%. Treatment benefits were sustained in the majority of subjects with no change in etrasimod's safety profile through Week 46 for subjects continuing on 2 mg etrasimod in the extension Study APD334-005.

Although etrasimod 2 mg demonstrated an improved efficacy over placebo in subjects with moderately to severely active UC, a Phase 2 study of another selective S1P receptor modulator, amiselimod 0.4 mg, associated with a reduction in lymphocyte count of 48% of baseline, did not result in a favorable efficacy over placebo treatment at Week 12 in CD patients (D'Haens 2019). While CD and UC have overlapping features, there are differences in pathophysiology, disease location, and extent of disease that may result in a different optimal dose for the treatment of CD. Therefore, this study will evaluate the treatment effect of etrasimod 2 mg and a higher dose of 3 mg. Based on Phase 1 data in healthy volunteers and Phase 2 data in UC patients, etrasimod 2 mg and 3 mg are expected to be safe and well-tolerated in CD patients.

SS2-I

Selection of an etrasimod dose for continued evaluation in SS2-I will primarily be based on safety and efficacy data from SS1-P2b. Since SS1-P2b is a Phase 2b dose-finding study, conventional analyses of safety, efficacy, and biomarker endpoints will be used to select an etrasimod dose. SSA-P2 will also provide long-term safety, tolerability, and efficacy data to support the dose decision. Provided that both etrasimod 2 mg and 3 mg have a favorable safety profile and no safety signals, then the dose that provides the best benefit to risk profile will be selected for further evaluation in SS2-I.

For safety assessment during the dose selection process, in addition to evaluating the overall rate of SAEs and AEs, special attention will be given to infection AEs, based on the safety profiles of approved drugs for CD ustekinumab and vedolizumab as well as etrasimod data from Study APD334-003. Infection AEs include both opportunistic infections (eg, cryptococcal meningitis and progressive multifocal leukoencephalopathy [PML]) and CD-associated infections (eg, abdominal and intestinal abscesses and infectious gastroenteritis and colitis). AEs and clinically significant changes in safety assessments related to known S1P receptor modulator class effects for fingolimod (CDER 2009, GILENYA 2010) and siponimod (CDER 2018, MAYZENT 2019) will also be closely evaluated. These include sustained lymphopenia ($< 200 \text{ cell/mm}^3$ [$< 0.2 \times 10^9 \text{ cells/L}$]), cardiac AEs (eg, symptomatic and sustained high degree AV blocks associated with first dose administration), ocular AEs (eg, blurred vision and macular edema), respiratory AEs

(eg, unexplained dyspnea, new or worsened obstructive airway disease), and clinically significant abnormalities in liver enzymes.

With regards to efficacy, key efficacy, and biomarker assessments such as SES-CD, CDAI, FCP, and CRP will be evaluated for dose selection. PRO assessments will also be taken into consideration. Since the co-primary endpoints for SS2-I are proportion of subjects with clinical remission and endoscopic response, the greatest weight will be given to CDAI and endoscopic SES-CD endpoints in the dose decision. The selected dose should consistently achieve a minimal clinically important difference (MCID) from placebo across key efficacy endpoints evaluated for dose selection. A statistically significant difference is not required for MCID. The MCID will be based on historical data from approved drugs for moderate to severe CD. For instance, endoscopy data from the most recently approved CD drug ustekinumab demonstrated a 7.2% difference from placebo in the proportion of subjects who achieved endoscopic response following induction therapy; therefore, a similar difference in SS1-P2b could be considered the MCID for the primary endpoint ([Rutgeerts 2018](#)).

Should both doses achieve an MCID for a given efficacy endpoint, then the dose that is markedly better, defined by meeting a clinically meaningful margin, consistently across efficacy endpoints will be selected for further evaluation. The margin for each efficacy endpoint will be dependent on the MCID. For instance, if the MCID in the example above is 7.2%, then the margin between etrasimod 2 and 3 mg could be 3.6%, or half the MCID, for the 3 mg dose to be considered markedly better. Overall, the dose that demonstrates the most consistent clinically meaningful benefit across efficacy endpoints will be selected for further evaluation.

SS3-M

Since subjects from SS1-P2b are eligible to enroll in SS3-M, 2 doses of etrasimod, 3 mg and 2 mg, were selected for evaluation in SS3-M based on safety and efficacy data from the etrasimod clinical studies described above and based on the safety and efficacy objectives for the development of etrasimod in CD in this study. Safety and efficacy data from SSA-P2 and SS1-P2b will be used to assess if continued evaluation of 2 etrasimod maintenance doses is warranted for subjects who enroll from Phase 3 induction studies SS2-I and Study APD334-305. In addition, long-term data from SSA-P2, which has a 66-week treatment period, will support whether to discontinue an etrasimod treatment arm in SS3-M.

SS4-E

Subjects who may benefit from continued treatment will have the opportunity to receive either etrasimod 3 mg or 2 mg during SS4-E. The use of both etrasimod doses in this study to evaluate the long-term safety profile of etrasimod is supported by the previously described Phase 1 and Phase 2 clinical data. Safety and efficacy data from the Phase 2 substudies SSA-P2 and SS1-P2b may support discontinuation of an etrasimod dose.

3.4. End of Study

Primary Completion: The date on which the last subject was examined or received an intervention to collect final data for the primary endpoint. For the overall study, this date is defined as when the last subject has completed assessments for M-38 Visit (or ET Visit) in SS3-M.

End of Study (End of Trial): The end of the study is defined as the date of the last visit of the last subject in the trial globally.

4. STUDY POPULATION

4.1. Eligibility Criteria for Substudy A – Phase 2, Substudy 1 – Phase 2b and Substudy 2 – Phase 3

4.1.1. Inclusion Criteria for Substudy A – Phase 2, Substudy 1 – Phase 2b, Substudy 2 – Phase 3

Subjects must meet ALL of the following inclusion criteria to be eligible for enrollment into SSA, SS1 and SS2:

1. Subjects 18 to 80 years of age, inclusive, at the time of consent
2. Ability to provide written informed consent and to be compliant with the schedules of protocol assessments
3. Have CD for ≥ 3 months prior to randomization, involving the ileum and/or colon, at a minimum; diagnosis may be confirmed at any time in the past by endoscopy and histopathology. The screening endoscopy and histopathology reports may serve as source documents for subjects who do not have diagnostic endoscopy reports in their medical chart
4. Have moderately to severely active CD at **Screening**, defined as:
 - b. CDAI score ≥ 220 and ≤ 450 , AND
 - c. Unweighted average worst daily AP score ≥ 2 (using a 4-point scale; ie, 0 [none] to 3 [severe]) OR unweighted average daily loose/watery SF (Bristol Stool Form Scale [BSFS] type 6 or 7) score ≥ 4 , AND
 - d. SES-CD of ≥ 6 or SES-CD ≥ 4 for subjects with isolated ileal disease
5. Demonstrated inadequate response, loss of response to, or intolerance to ≥ 1 of the following therapies for the treatment of CD (refer to [Appendix 9](#), see [Appendix 11](#) for Israel specific criteria):
 - b. Oral corticosteroids (eg, prednisone [or its equivalent] or budesonide)
 - c. Immunosuppressants (eg, AZA, 6-mercaptopurine [6-MP], or MTX)
 - d. TNF α antagonists (eg, infliximab, adalimumab, certolizumab pegol, or biosimilars)
 - e. Integrin receptor antagonist (eg, vedolizumab)
 - f. Interleukin-12/-23 antagonist (eg, ustekinumab)
6. Females of childbearing potential (FOCBP) must be nonpregnant evidenced by a negative serum beta-human chorionic gonadotropin (β -hCG) pregnancy test at Screening and negative urine dipstick pregnancy test at Day 1
7. Females must meet either a or b of the following criteria and males must meet criterion c to qualify for the study:
 - b. 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 and confirmed by follicle-stimulating hormone (FSH) within postmenopausal range according to local standards

- Permanent sterilization procedure, such as hysterectomy, bilateral salpingectomy, or bilateral oophorectomy
- c. A female who is of childbearing potential must agree to using a highly effective contraception method during treatment and for 4 weeks following treatment that can achieve a failure rate of less than 1% per year when used consistently and correctly. The following are considered highly effective birth control methods:
 - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal, or transdermal
 - Progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injected, or implanted
 - Intrauterine device (IUD)
 - Intrauterine hormone-releasing system (IUS)
 - Bilateral tubal occlusion
 - Vasectomized partner, provided that partner is the sole sexual partner of the FOCBP 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 drug). 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
- d. A male must agree to using condoms during treatment and for 4 weeks following treatment

Definitions:

Inadequate response (primary non-response): Signs and symptoms of persistently active disease despite completing an induction regimen at dosage per product label or institutional standard of care.

Loss of response (secondary non-response): Recurrence of signs and symptoms of active disease despite being on a maintenance regimen per institutional standard of care following prior clinical benefit. Discontinuation despite clinical benefit does not qualify as having failed or being intolerant to therapy.

Intolerance: Significant toxicities and/or tolerability issues that led to a reduction in dose or discontinuation of the medication.

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4.1.2. Exclusion Criteria for Substudy A – Phase 2, Substudy 1 – Phase 2b and Substudy 2 – Phase 3

Subjects will be excluded from the study if they meet any of the following exclusion criteria:

1. History of inadequate response (ie, primary non-response) to agents from ≥ 2 classes of biologics marketed for the treatment of CD (ie, TNF α antagonists, interleukin-12/-23 antagonist, and integrin receptor antagonist, refer to [Appendix 9](#))
2. Have stopped, started, or changed the dosage of oral 5-ASA compounds ≤ 2 weeks prior to randomization or do not intend to maintain the same dose during the study
3. Have stopped, started, or changed the dosage of oral corticosteroids (prednisone ≤ 20 mg/day or its equivalent, budesonide ≤ 9 mg/day) ≤ 2 weeks prior to randomization
4. Have a confirmed ALC < 800 cells/mm³ ($< 0.8 \times 10^9$ cells/L) at Screening or confirmed absolute neutrophil count < 1000 cells/mm³ ($< 1.0 \times 10^9$ cells/L) at Screening
5. Have confirmed aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $> 2 \times$ upper limit of normal (ULN) and total bilirubin $> 1.5 \times$ ULN (unless consistent with a history of Gilbert's Syndrome) at Screening
6. Used any of the following therapies within the timeframes prior to randomization indicated in Table 3

Table 3: Medication and Treatment Restrictions Prior to Randomization

Time Frame	Therapies
Within 2 weeks	AZA, 6-MP, MTX, adalimumab or biosimilars (unless there is documentation of an undetectable biologic level), antibiotics (eg, metronidazole, ciprofloxacin) used for the treatment of CD
Within 4 weeks	Infliximab, certolizumab, vedolizumab, ustekinumab or biosimilars (unless there is documentation of an undetectable or subtherapeutic biologic trough level according to the American Gastroenterological Association 2017 Guidelines for Therapeutic Drug Monitoring (Feuerstein 2017), or in the Investigator's opinion, if target trough concentrations have not been proposed), therapeutic apheresis, total parenteral nutrition, IV corticosteroids, or medications that are known to be moderate or strong inhibitors or inducers that inhibit or induce at least 2 of the following: CYP2C8, CYP2C9, and CYP3A4 (eg, fluconazole [inhibitor]), enzalutamide or rifampin (inducer)
Within 8 weeks	6-Thioguanine, systemic lymphocyte suppressive therapy (eg, cyclosporine, mycophenolate mofetil), or IV immunoglobulin
Within 12 weeks	Any investigational agent or device
Within 48 weeks	Mesenchymal stem cell transplant (eg, Prochymal)
Any time prior to randomization	S1P receptor modulators (eg, ozanimod, fingolimod, siponimod), $\alpha 4\beta 1$ -integrin receptor antagonist (eg, natalizumab), lymphocyte-depleting therapies (eg, rituximab, cyclophosphamide, bone marrow transplantation, total body irradiation)

6-MP, 6-mercaptopurine; AZA, azathioprine; CD, Crohn's disease; CYP, cytochrome P450; IV, intravenous; MTX, methotrexate; S1P, sphingosine 1-phosphate; UGT, uridine diphosphate glucuronosyl transferase

7. Have a known hypersensitivity to etrasimod or any of the excipients
8. Have UC, indeterminate colitis, microscopic colitis, ischemic colitis, radiation colitis, diverticular disease-associated colitis, toxic megacolon, or active infectious colitis or test positive for *C. difficile* toxin at Screening. NOTE: Subjects with *C. difficile* colitis who have been treated with documented evidence of *C. difficile* toxin clearance ≥ 2 weeks prior to randomization and are symptomatically stable, in the opinion of the Investigator, are eligible for enrollment
9. Have functional or post-operative short-bowel syndrome or any associated complications that may require surgery or interfere with efficacy assessments (eg, intestinal stricture with obstructive symptoms, colonic stenoses that are not passable with an adult colonoscope, active perianal/intra-abdominal abscess, active fistula [except for perianal fistula], fulminant colitis)
10. Had surgical treatment for intra-abdominal abscesses ≤ 8 weeks prior to randomization or surgical treatment for perianal abscesses ≤ 4 weeks prior to randomization
11. Had intestinal resection ≤ 24 weeks prior to randomization or other intra-abdominal surgeries ≤ 12 weeks prior to randomization. Subjects who have undergone previous colonic resection or ileocelectomy must have > 25 cm of colon remaining
12. Have an ileostomy or a colostomy
13. Have a serious infection requiring IV antibiotic(s)/medication(s) ≤ 4 weeks prior to randomization
14. Have any of the following conditions or risk factors:
 - b. Primary or secondary immunodeficiency syndromes (eg, hereditary immunodeficiency syndrome, acquired immunodeficiency syndrome [AIDS])
 - c. History of organ transplant (except corneal transplant)
 - d. History of an opportunistic infection (eg, cryptococcal meningitis, PML)
 - e. History of disseminated herpes simplex or herpes zoster or ≥ 2 episodes of herpes zoster
 - f. Known to have or test positive for human immunodeficiency virus (HIV; positive HIV antibody), hepatitis B virus (HBV; positive hepatitis B surface antigen or core immunoglobulin (Ig) M antibody), or active hepatitis C virus (HCV; positive hepatitis C antibody with detectable HCV RNA)

NOTE: If the Investigator suspects false positive hepatitis serology results, such as an antibody pattern indicating acute hepatitis infection but no corresponding elevated liver enzymes and no signs or symptoms of liver disease, an infectious disease expert may be consulted. If the infectious disease expert finds no evidence of acute or chronic hepatitis infection and considers the serology results false positive and not clinically relevant, the Investigator may document (in source data and in the electronic case report form [eCRF]) that the serology results are considered false positive and may randomize the subject

- g. History of active or latent tuberculosis (TB) (refer to [Appendix 2](#) for details of TB screening requirements, interpretation of test results, and specific requirements for subjects residing in countries identified by the World Health Organization [WHO])

as having a high burden of TB or multi-drug resistance [MDR] TB). The following is the EXCEPTION to this exclusion criterion

- Subjects with treated latent TB or latent TB diagnosed at Screening who have received ≥ 4 weeks of TB prophylaxis treatment as defined by local country guidelines (or WHO guidelines) prior to randomization (and will complete TB prophylaxis treatment course during the study), ruled out for active TB, and have not had recent close contact with a person with active TB. It is the responsibility of the Investigator to verify the adequacy of TB prophylaxis treatment and provide appropriate documentation

15. Received a live or live-attenuated vaccine (except the influenza vaccine) ≤ 4 weeks prior to randomization

16. Have not received zoster vaccination for prevention of herpes zoster (shingles) (recombinant zoster vaccine or live zoster vaccine) if clinically indicated, prior to randomization, unless the subject has a documented positive varicella zoster virus (VZV) IgG status

NOTE: VZV IgG status documentation and vaccination requirements are applicable only to subjects residing in countries where the vaccine is approved/licensed and locally available. VZV vaccination should only be administered per product labeling to individuals within the appropriate age range and immune system status (refer to indication and usage and contraindications sections of the product label)

17. Subjects with high risk for colorectal cancer (eg, family history, CD duration, disease involving $\geq 30\%$ of the colon), who have not had a surveillance colonoscopy ≤ 12 months prior to randomization to rule out polyps, colorectal dysplasia/neoplasia. In the absence of a recent history of surveillance colonoscopy, this may be done as part of the screening colonoscopy. Any visualized adenomatous polyps must be removed, and any suspicious lesions must be confirmed free of dysplasia and/or malignancy prior to baseline

18. History of malignancy of any organ system, treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases (Note: other than localized cutaneous basal or squamous cell carcinoma that has been excised or resolved, or carcinoma in situ of the uterine cervix that has been treated with no evidence of recurrence)

19. Have active epilepsy

20. Have any of the following conditions or receiving treatments that may affect cardiovascular function:

- b. Myocardial infarction, unstable angina, stroke/transient ischemic attack, decompensated heart failure requiring hospitalization or Class III/IV heart failure ≤ 6 months prior to randomization
- c. Second-degree or third-degree AV block, sick sinus syndrome without a functional pacemaker, or periods of asystole for > 3 seconds without an implanted cardiac defibrillator
- d. Recurrent symptomatic bradycardia or recurrent cardiogenic syncope
- e. Screening and Day 1 pre-randomization vital signs (taken in the sitting position) with a HR < 50 bpm AND systolic blood pressure (BP) < 90 mm Hg OR diastolic

BP < 55 mm Hg. Vital signs may be repeated up to 3 times during a visit to confirm abnormal readings

- f. Screening and Day 1 pre-randomization ECG with PR interval ≥ 220 ms or Fridericia's corrected QT interval (QTcF) ≥ 450 ms in males or ≥ 470 ms in females
- g. Start, stop, or change in dosage of any anti-arrhythmic drugs (Class I to IV) within 1 week before treatment initiation

21. Have active retinopathy or macular edema

22. Have active severe pulmonary disease (eg, chronic obstructive pulmonary disease, pulmonary fibrosis) or have a chronic pulmonary disease requiring IV corticosteroid or hospitalization ≤ 12 months prior to screening

23. Have forced expiratory volume in 1 second (FEV₁) or forced vital capacity (FVC) < 70% of predicted values at Screening

24. Lactating female who is breastfeeding

25. Any acute illnesses or medical conditions including cognitive impairment and alcohol/drug abuse/dependence, or signs/symptoms suspicious for a serious disease that, in the Investigator's opinion, could put the subject at increased risk for safety event(s) or interfere with protocol-specified procedures or adherence with study drug

Note: A confirmed result means there have been 2 consecutive assessments showing similar findings.

If a subject fails ≥ 1 screening laboratory criteria, the laboratory assessment(s) may be repeated once at the discretion of the Investigator, and the subject may be enrolled if the laboratory criteria are then met, provided that laboratory assessments are completed within the Screening Period. Any screening laboratory assessments repeated beyond 1 time will need to be discussed with the Medical Monitor before proceeding.

4.2. Eligibility Criteria for Substudy 3 – Maintenance

4.2.1. Inclusion Criteria for Substudy 3 – Maintenance

Subjects must meet ALL of the following inclusion criteria to be eligible for enrollment into SS3-M:

1. Ability to provide written informed consent and to be compliant with the schedule of protocol assessments
2. Subject must have completed the Week 14 assessment of SS1-P2b, SS2-I, or Study APD334-305 and have 14-week CDAI and SES-CD scores assessed and have met the responder criteria (see [Section 3.1.2](#))
3. Subjects who entered the EI Period of SS1-P2b, SS2-I, or Study APD334-305 must have completed the EI-Week 6 Visit and demonstrate a meaningful improvement from Baseline (Day 1) in CDAI based on the Investigator's judgement (globally) or demonstrate no worsening of CD, defined as ≥ 100 -point increase in CDAI score from baseline and CDAI ≥ 220 points (EU-region).

4. FOCBP must be nonpregnant evidenced by a negative urine β -hCG pregnancy test at the MFD Visit
5. Females and males must continue to meet contraception criterion described above in Inclusion Criterion 7 for SS1-P2b or SS2-I

4.2.2. Exclusion Criteria for Substudy 3 – Maintenance

Subjects will be excluded from SS3-M if they meet any of the following exclusion criteria:

1. Do not intend to maintain the same dose of oral 5-ASA compounds during the study
2. Required rescue therapy or surgical procedures (based on institutional standard of care) for the treatment of CD during the parent induction study due to worsening of disease
3. Have or suspected of having adenomatous polyps visualized on ileocolonoscopy that were not removed or confirmed free of dysplasia and/or malignancy
4. Have any acute illnesses or medical conditions including cognitive impairment and alcohol/drug abuse/dependence, or signs/symptoms suspicious for a serious disease that, in the Investigator's opinion, could put the subject at increased risk for safety event(s), could interfere with participation in the study according to the study protocol, or with the ability of the subject to cooperate and comply with the study procedures
5. Have started, stopped, or changed dosage of Class I-IV anti-arrhythmic drugs within 1 week of the MFD Visit

4.3. Eligibility Criteria for Substudy 4 – Long-Term Extension

4.3.1. Inclusion Criteria for Substudy 4 – Long-Term Extension

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

1. Ability to provide written informed consent and to be compliant with the schedule of protocol assessments
2. Subject must have completed the M-38 Visit of SS3-M or the Week 66 Visit of SSA-P2
3. FOCBP must be nonpregnant evidenced by a negative urine β -hCG pregnancy test at the Extension First Dose (EFD) Visit
4. Females and males must continue to meet contraception criterion described above in Inclusion Criterion 7 for SSA-P2, SS1-P2b, or SS2-I

4.3.2. Exclusion Criteria for Substudy 4 – Long-Term Extension

Subjects will be excluded from the study if they meet any of the following exclusion criteria:

1. Required surgical procedures (based on institutional standard of care) for the treatment of CD during the parent study due to worsening of disease
2. Have or suspected of having adenomatous polyps visualized on ileocolonoscopy that were not removed or confirmed free of dysplasia and/or malignancy
3. Have started, stopped, or changed dosage of Class I-IV anti arrhythmic drugs within 1 week of the EFD Visit

5. SUBJECT RESTRICTIONS

Prohibited concomitant therapy and procedures are described in Section 6.8.5. Additionally, subjects in ALL substudies are restricted from the following:

- Poppy seeds: Consumption of poppy seeds within 48 hours prior to drug screen may cause a positive drug screen. Subjects who report that they have consumed poppy seeds within 48 hours of the screening visit of SSA-P2, SS1-P2b, or SS2-I should not be screened. They may return 48 hours after the last poppy seed consumption for screening. Poppy seeds should not be eaten between screening and baseline (Week 0/Day 1)
- St John's wort: Subjects should be instructed to abstain from consuming herbal remedies containing St John's wort during the study as these may interfere with the metabolism of etrasimod

6. STUDY DRUG

6.1. Study Drugs Administered

6.1.1. Substudy A – Phase 2 Study Drugs

Study drug in the Phase 2 substudy (SSA-P2) are listed in Table 4.

Table 4: Study Drugs for Substudy A – Phase 2

Study Drug	Dose	Mode of Administration	Frequency	Formulation
Etrasimod	3 mg ^a	Oral	qd	Tablet
Etrasimod	2 mg	Oral	qd	Tablet

^a Subjects randomized to receive etrasimod 3 mg in the Induction Period will receive 2 mg qd for the first week of treatment and 3 mg qd for the remainder of the treatment period. This dose escalation regimen will not be required for subjects who are assigned etrasimod 3 mg in the Extension Period.
qd, once daily

6.1.2. Substudy 1 – Phase 2b Study Drugs

Study drugs in the Phase 2b substudy (SS1-P2b) are listed in Table 5.

Table 5: Study Drugs for Substudy 1 – Phase 2b

Study Drug	Dose	Mode of Administration	Frequency	Formulation
Etrasimod	3 mg ^a	Oral	qd	Tablet
Etrasimod	2 mg	Oral	qd	Tablet
Placebo	NA	Oral	qd	Tablet

a. Subjects randomized to receive etrasimod 3 mg will receive 2 mg qd for the first week of treatment and 3 mg qd for the remainder of the treatment period.
NA, not applicable; qd, once daily

6.1.3. Substudy 2 – Induction Study Drugs

Study drugs in SS2-I are listed in Table 6.

Table 6: Study Drugs for Substudy 2 – Induction

Study Drugs	Dose	Mode of Administration	Frequency	Formulation
Etrasimod	Selected Phase 3 dose ^a	Oral	qd	Tablet
Placebo	NA	Oral	qd	Tablet

a If the selected Phase 3 dose is 3 mg, subjects in SS2-I randomized to etrasimod will receive 2 mg qd for the first week of treatment and 3 mg qd for the remainder of the treatment period.
NA, not applicable; qd, once daily; SS2-I, Substudy 2 – Induction

6.1.4. Substudy 3 – Maintenance Study Drugs

Study drugs in SS3-M are listed in Table 7.

Table 7: Study Drugs for Substudy 3 – Maintenance

Study Drug	Dose	Mode of Administration	Frequency	Formulation
Etrasimod	3 mg ^a	Oral	qd	Tablet
Etrasimod	2 mg	Oral	qd	Tablet
Placebo	NA	Oral	qd	Tablet

a Responders assigned to placebo in SS3-M who switch to the Nonresponder Cohort due to loss-of-response and are assigned to etrasimod 3 mg will receive etrasimod 2 mg qd for the first week of treatment and 3 mg qd for the remainder of the treatment period. All other subjects assigned to etrasimod 3 mg will receive etrasimod 3 mg from the start of the SS3-M treatment period.
NA, not applicable; qd, once daily; SS3-M, Substudy 3 – Maintenance

6.1.5. Substudy 4 – Long-Term Extension Study Drugs

Study drug in SS4-E is listed in [Table 8](#).

Table 8: Study Drug for Substudy 4 – Long-Term Extension

Study Drug	Dose	Mode of Administration	Frequency	Formulation
Before Dose Selection				
Etrasimod	3 mg ^a	Oral	qd	Tablet
Etrasimod	2 mg	Oral	qd	Tablet
After Dose Selection				
Etrasimod	Selected Phase 3 dose ^a	Oral	qd	Tablet

^a Subjects assigned to etrasimod 3 mg who received placebo in SS3-M will receive etrasimod 2 mg qd for the first week of treatment in SS4-E followed by etrasimod 3 mg qd for the remainder of the SS4-E treatment period. All other subjects assigned to etrasimod 3 mg will receive etrasimod 3 mg from the start of the SS4-E treatment period.
qd, once daily; SS3-M, Substudy 3 – Maintenance; SS4-E, Substudy 4 – Extension

6.2. Identity of Study Drugs

6.2.1. Etrasimod

The active pharmaceutical ingredient in etrasimod tablets is APD334 L-arginine (the L-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 (pH = 8.9) at 30°C. APD334 L-arginine is manufactured, packaged, tested, and released in compliance with current Good Manufacturing Practice.

Etrasimod tablet drug product is a blue, round, biconvex, plain, immediate-release, film-coated tablet. Etrasimod tablets are composed of APD334 L-arginine active pharmaceutical ingredient and excipients (microcrystalline cellulose, mannitol, sodium starch glycolate, magnesium stearate, and Opadry® II Blue 85F90951) and is supplied in the dosage strength (based on etrasimod free acid content) of 1 and 2 mg. The etrasimod drug product is manufactured, packaged, tested, and released in compliance with current Good Manufacturing Practice.

6.2.2. Placebo

The placebo tablet formulation is composed of excipients (microcrystalline cellulose, mannitol, sodium starch glycolate, magnesium stearate, and Opadry® II Blue 85F90951). The placebo tablet is a blue, round, biconvex, plain, film-coated tablet. The placebo drug product is manufactured, packaged, tested, and released in compliance with current Good Manufacturing Practice.

6.3. Dosage and Administration

During the treatment period for each substudy, subjects will self-administer study drug qd, according to the dosages below, with water (either with or without food) at approximately the same time each day, preferably in the morning. If subjects are assigned 2 tablets, subjects will self-administer 1 tablet from Bottle 1 and 1 tablet from Bottle 2 and both tablets should be taken together. If subjects are assigned 1 tablet, subjects will self-administer 1 tablet from 1 bottle.

On study visit days when first-dose cardiac monitoring and 24-hour Holter monitoring are conducted and/or PK samples are collected (refer to Schedules of Assessments in [Appendix 1](#)), study drug should be withheld until all predose assessments and procedures have been completed. The time of PK sample collection and subsequent dosing should be documented.

6.3.1. Substudy A – Phase 2 Dosage and Administration

Induction Period

Study drug dosage and administration for the 14-week Induction Period of SSA-P2 are summarized in Table 9.

Table 9: Study Drug Dosage and Administration for Substudy A – Phase 2

Induction Treatment Group	Week 1 of Induction Treatment Period in SSA-P2	Beyond Week 1 of Induction Treatment Period in SSA-P2
Etrasimod 3 mg	One etrasimod 2 mg tablet qd and one matching placebo tablet qd	One etrasimod 2 mg tablet qd and one etrasimod 1 mg tablet qd
Etrasimod 2 mg	One etrasimod 2 mg tablet qd and one matching placebo tablet qd	One etrasimod 2 mg tablet qd and one matching placebo tablet qd

qd, once daily; SSA-P2, Substudy A – Phase 2

Extension Period

During the 52-week Extension Period, subjects will receive etrasimod 2 mg or 3 mg qd according to their Induction Period treatment assignment as described in [Table 1](#). All subjects will receive the assigned dose (refer to [Table 1](#)) of etrasimod from the beginning of the Extension Period.

6.3.2. Substudy 1 – Phase 2b Dosage and Administration

Induction Period

Study drug dosage and administration for the 14-week Induction Period of SS1-P2b are summarized in Table 10.

Table 10: Study Drug Dosage and Administration for Substudy 1 – Phase 2b Induction

Treatment Group	SS1-P2b Treatment Period Dosage and Administration	
	Week 1 of SS1-P2b Induction Treatment Period	Beyond Week 1 of SS1-P2b Induction Treatment Period
Etrasimod 3 mg	One etrasimod 2 mg tablet qd and one matching placebo tablet qd	One etrasimod 2 mg tablet qd and one etrasimod 1 mg tablet qd
Etrasimod 2 mg	One etrasimod 2 mg tablet qd and one matching placebo tablet qd	One etrasimod 2 mg tablet qd and one matching placebo tablet qd
Placebo	Two matching placebo tablets qd	Two matching placebo tablets qd

qd, once daily; SS1-P2b, Substudy 1 – Phase 2b

Extended Induction Period

During the EI Period, subjects will receive etrasimod 2 mg or 3 mg qd, according to their Induction Period treatment assignment as described in Table 2. Subjects who received placebo during the Induction Period and are assigned to receive etrasimod 3 mg during the EI Period will receive etrasimod 2 mg qd for the first week and etrasimod 3 mg qd for the remainder of the EI Period. All other subjects will receive their assigned dose of etrasimod throughout the EI Period as indicated in Table 10.

6.3.3. Substudy 2 – Induction Dosage and Administration

Study drug dosage and administration for the 14-week treatment period of SS2-I are summarized in Table 11. During the EI Period, subjects will receive the selected etrasimod dose.

Table 11: Study Drug Dosage and Administration for Substudy 2 – Induction

Treatment Group	SS2-I Treatment Period Dosage and Administration
Etrasimod selected Phase 3 dose (3 mg or 2 mg)	<u>Etrasimod 3 mg</u> Week 1: One etrasimod 2 mg tablet qd and one matching placebo tablet qd Beyond Week 1 of SS2-I Treatment Period: One etrasimod 2 mg tablet qd and one etrasimod 1 mg tablet qd OR <u>Etrasimod 2 mg</u> One etrasimod 2 mg tablet qd and one matching placebo tablet qd ^a
Placebo	Two matching placebo tablets qd ^b

a If the etrasimod 3 mg dose is discontinued, the 2 mg dose may consist of 1 etrasimod 2 mg tablet (ie, no matching placebo).

b If the etrasimod 3 mg dose is discontinued, the placebo dose may consist of 1 matching placebo tablet.
qd, once daily; SS2-I, Substudy 2 – Induction

6.3.4. Substudy 3 – Maintenance Dosage and Administration

Study drug dosage and administration for the treatment period of SS3-M are summarized in Table 12.

Table 12: Study Drug Dosage and Administration for Substudy 3 – Maintenance

Treatment Group ^a	SS3-M Treatment Period Dosage and Administration
Etrasimod 3 mg	One etrasimod 2 mg qd and one etrasimod 1 mg tablet qd
Etrasimod 2 mg	One etrasimod 2 mg tablet qd and one matching placebo tablet qd ^b
Placebo	Two matching placebo tablets qd ^c

a. Subjects enrolling after dose selection assigned to the Etrasimod Responder Cohort will receive the selected etrasimod dose, either etrasimod 2 mg or 3 mg.

b. If the etrasimod 3 mg dose is discontinued after dose selection, the etrasimod 2 mg dose may consist of 1 etrasimod 2 mg tablet (ie, no matching placebo) for subjects enrolling in SS3-M from SS2-I.

c. If the etrasimod 3 mg dose is discontinued after dose selection, the placebo dose may consist of 1 matching placebo tablet for subjects enrolling in SS3-M from SS2-I.
qd, once daily; SS3-M, Substudy 3 – Maintenance

6.3.5. Substudy 4 – Long-Term Extension Dosage and Administration

Study drug dosage and administration for the treatment period of SS4-E are summarized in Table 13. If an etrasimod dose is discontinued following dose selection, subjects will be switched to the selected etrasimod dose at the next study visit once it is available. Subjects should continue to take the dose assigned to them prior to dose selection until they are switched by the site.

Table 13: Study Drug Dosage and Administration for Substudy 4 – Long-Term Extension

Treatment Group ^a	SS4-E Treatment Period Dosage and Administration
Etrasimod 3 mg	One etrasimod 2 mg tablet qd and one etrasimod 1 mg tablet qd ^b
Etrasimod 2 mg	One etrasimod 2 mg tablet qd and one matching placebo tablet qd ^c

a If an etrasimod dose is discontinued following dose selection, subjects enrolling in SS4-E will receive the selected etrasimod dose and subjects already enrolled in SS4-E will be switched to the selected etrasimod dose at the next study visit once it is available.

b Subjects who completed the M-38 Visit of SS3-M on placebo and are assigned to the 3 mg dose should receive one etrasimod 2 mg tablet qd and one matching placebo tablet qd for the first week of the SS4-E Treatment period followed by 1 etrasimod 2 mg tablet qd and 1 etrasimod 1 mg tablet qd for the remainder of the treatment period.

c If the etrasimod 3 mg dose is discontinued after dose selection, subjects may receive one etrasimod 2 mg tablet qd (ie, no matching placebo tablet).
qd, once daily; SS3-M, Substudy 3 – Maintenance; SS4-E, Substudy 4 – Long-Term Extension

6.3.6. 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 tablets, he/she should be instructed not to take additional tablets on the same day but to take the next dose at the regular time on the following day.

Subjects should be instructed to contact the Investigator if they miss more than 2 consecutive doses.

6.3.7. Dose Interruptions

Temporary withholding of study drug, if deemed necessary by the Investigator, is permitted for up to 6 days without obtaining prior approval from the Medical Monitor. If study drug interruption ≥ 7 days is required for a medical reason, the Investigator must contact the Medical Monitor as soon as this is anticipated.

Subjects who do not take the study drug for ≥ 2 consecutive days within the first week of treatment or for ≥ 7 consecutive days after the first week of treatment for all substudies must contact the Investigator to discuss treatment re-initiation and are required to return to the study site before taking their next dose of study drug. The subject must take the next dose of study drug at the study site, and the in-clinic cardiac monitoring as outlined in Section 10.7.8.4 should be performed.

6.4. Method of Assigning Subjects to Treatment

Subjects will be centrally assigned to study drug using an Interactive Response Technology (IRT) as described below for each substudy. Before the study is initiated, the log in information and directions for the IRT will be provided to each study site.

6.4.1. Substudy A – Phase 2

Subjects will be randomized in a double-blinded fashion (1:1 ratio) to etrasimod 3 mg or etrasimod 2 mg in the Induction Period via stratified randomization. Randomization will be stratified by baseline biologic treatment failure status (yes/no) and baseline oral corticosteroid use (yes/no).

At the start of the Extension Period, subjects will receive etrasimod 2 mg or 3 mg, according to their Induction Period treatment assignment and clinical response status at Week 14, as described in [Table 1](#) (Section 3.1.1).

Each subject will be dispensed blinded study drug at study visits according to the Schedule of Assessments ([Appendix 1](#); [Table 29](#)).

6.4.2. Substudy 1 – Phase 2b

Subjects in both Cohorts 1 and 2 of SS1-P2b will be randomized (1:1:1) to etrasimod 3 mg, etrasimod 2 mg, or matching placebo in the Induction Period via stratified randomization. Randomization will be stratified by baseline biologic treatment failure status (yes/no) and baseline oral corticosteroid use (yes/no).

At the start of the EI Period, subjects will receive etrasimod 2 mg or 3 mg, according to their Induction Period treatment assignment at Week 14, as described in [Table 2](#) (Section 3.1.2).

Each subject will be dispensed blinded study drug at study visits according to the Schedule of Assessments ([Appendix 1](#); [Table 30](#)).

6.4.3. Substudy 2 – Induction

Subjects in SS2-I will be randomized (3:1 ratio) to the selected etrasimod dose or placebo treatment via stratified randomization. Randomization will be stratified by baseline biologic treatment failure status (yes/no) and baseline oral corticosteroid use (yes/no).

At the start of the EI Period, subjects will receive the selected etrasimod dose (2 mg or 3 mg).

Each subject will be dispensed blinded study drug at study visits according to the Schedule of Assessments ([Appendix 1](#); [Table 31](#)).

6.4.4. Substudy 3 – Maintenance

Responder Cohort

Subjects who received etrasimod 2 mg during an Induction or EI Period and meet response criteria as described in Section 3.1.2 (etrasimod responders) will be randomized (1:1 ratio) in a double-blinded fashion to placebo or etrasimod 2 mg. Similarly subjects who received etrasimod 3 mg during Induction or EI Period and meet response criteria will be randomized (1:1) to receive placebo or etrasimod 3 mg. Randomization will be stratified by Week 14 endoscopic response status (yes/no), baseline biologic treatment failure status (yes/no), and corticosteroid use (yes/no) at SS3-M baseline. Following dose selection, randomization to an

etrasimod dose arm may be discontinued and etrasimod responders entering SS3-M would thus be randomized (1:1 ratio) to receive the selected etrasimod dose or matching placebo. Subjects randomized to etrasimod in SS3-M prior to dose selection would remain at the same etrasimod dose until the end of the substudy, even if randomization to that dose is discontinued.

Subjects who received placebo during the Induction Period and meet response criteria (placebo responder) and enroll in SS3-M will continue blinded placebo treatment.

If an etrasimod responder experiences confirmed LOR during the Maintenance Treatment Period, the subject will switch to the Nonresponder Cohort and receive the etrasimod dose they received at SS3-M baseline. Placebo responders who experience a LOR and switch to the Nonresponder Cohort will receive either etrasimod 2 mg or 3 mg (1:1 ratio). If randomization to an etrasimod dose arm is discontinued following dose selection, subjects from the Responder Cohort entering the Nonresponder Cohort will receive the selected etrasimod dose.

Nonresponder Cohort

Subjects who completed the induction treatment period and do not meet response criteria, regardless of Induction Period treatment assignment, will continue to receive the etrasimod dose they received during the EI Period of SS1-P2b, SS2-I, or Study APD334-305. If an etrasimod dose arm is discontinued following dose selection, enrolled subjects receiving the discontinued dose will be switched to the selected etrasimod dose at the next study visit and subjects entering the Nonresponder Cohort of SS3-M will receive the selected etrasimod dose.

6.4.5. Substudy 4 – Long-Term Extension

Prior to dose selection, subjects on etrasimod at SS4-E baseline will remain on the etrasimod dose received at the last study visit of SSA-P2 or SS3-M. Subjects on placebo at SS4-E baseline will be randomized (1:1) to receive etrasimod 2 mg or 3 mg.

After dose selection, a treatment arm may be discontinued and enrolled subjects receiving the discontinued dose will be switched to the selected etrasimod dose at the next study visit and subjects entering SS4-E will receive the selected etrasimod dose.

6.5. Selection and Timing of Dose for Each Subject

If the dose according to Section 6.3 consists of 2 tablets, subjects will self-administer 1 tablet from Bottle 1 and 1 tablet from Bottle 2 for a total of 2 tablets qd (with water, either with or without food); both tablets should be taken together at approximately the same time each day, preferably in the morning. If the dose according to Section 6.3 consists of 1 tablet, subjects will self-administer 1 tablet from 1 bottle qd (with water, either with or without food) at approximately the same time each day, preferably in the morning. On study visit days when first dose- cardiac monitoring and 24-hour Holter monitoring are conducted and/or PK samples are collected (refer to Schedules of Assessments in [Appendix 1](#)), study drug should be withheld until all predose assessments and procedures have been completed.

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6.6. Blinding

SSA-P2, SS1-P2b, SS2-I, and SS3-M are double-blind substudies with limited access to the randomization code. Although subjects in the EI Period of SS1-P2b or SS2-I will receive active drug, they will be blinded to the actual dose (etrasimod 2 mg or 3 mg) being administered. Similarly subjects in SSA-P2 and the Nonresponder Cohort of SS3-M will be blinded to the administered dose. Prior to dose selection, all subjects enrolled in SS4-E will be blinded to the actual dose being administered but are unblinded to the study drug itself as there is no placebo group in this substudy. After dose selection, subjects in SS4-E may be unblinded to their current dose of study drug, however, a subject's treatment in previous substudies or Study APD334-305 will remain blinded until the unblinding of data from those studies.

The etrasimod and placebo tablets, bottles, and kits 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 IRT will hold treatment codes and kit or bottle numbers for study drug.

To minimize the risk of unintentional unblinding of treatment assignment, study staff, including Investigators and study coordinators, should not disclose HR data collected after treatment initiation or re-initiation during the cardiac monitoring periods to study subjects. If there are AEs associated with changes in HR during the treatment period, then Investigators may discuss the relevant measurement with subjects as needed for appropriate AE inquiry and/or management. Trends in HR changes should not be discussed among study staff unless this is required to provide appropriate medical care to study subjects. Additionally, site staff including Investigators will be blinded to the following laboratory results during the double-blind, placebo-controlled substudies SS1-P2b, SS2-I, and SS3-M: CRP, FCP, WBC differential (percentage and absolute number), and T Cell, B Cell, and natural killer cell (TBNK) panel cell counts (refer to Section 10.7.8.2).

Treatment assignments should remain blinded unless that knowledge is necessary to determine a subject's 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. Subject safety must always be the first consideration in making such a determination. The IRT 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.

6.7. Treatment Compliance

The Investigator is responsible for ensuring that subjects are correctly instructed on how to take the study drug and that each subject is fully compliant with the assigned regimen. The study drug 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 7.4.

Subject compliance will be based on tablet count per bottle. Tablet counts per bottle < 80% or > 120% of the expected value between visits should be documented as a protocol deviation.

6.8. Concomitant Therapy

The allowed and prohibited concomitant therapies described in this section apply to ALL substudies, unless noted otherwise.

6.8.1. Required Concomitant Therapy

Not applicable.

6.8.2. Allowed Concomitant Therapy

Permitted medications for the treatment of CD are described in Section 6.8.2.1. Concomitant medications for medical conditions other than CD are permitted as clinically indicated, subject to specific protocol requirements outlined in Section 4.

All medications (over the counter and prescribed) that are taken by subjects and all procedures that are performed during the Screening Period through the safety reporting period must be recorded in the eCRF along with

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant therapy.

6.8.2.1. Permitted Medications for the Treatment of Crohn's Disease

Medications for the treatment of CD permitted during this study are presented by substudy in [Table 14](#).

If a subject experiences unexplained disease worsening, as determined by the Investigator, while participating in SSA-P2 Induction Period, SS1-P2b, SS2-I, or SS3-M Responder Cohort and requires initiation of a new therapy or increase in corticosteroids for CD above the baseline level, the subject should discontinue study drug, enter the Follow-up Period and appropriate treatment should be given at the discretion of the Investigator.

Oral corticosteroid rescue therapy is permitted in the Extension Period of SSA-P2, SS3-M (Nonresponder Cohort), and SS4-E (refer to Section 6.8.3.1).

During the SS4-E, changes to permitted background treatment will be allowed at the discretion of the Investigator. Use of rectal and parenteral corticosteroids will also be allowed for subjects enrolled in SS4-E.

Table 14: Medications for the Treatment of Crohn's Disease Permitted by Substudy

Substudy	Oral 5-ASA Compounds	Anti-Diarrheal Medications	Oral Corticosteroids	Oral Corticosteroid Rescue Therapy	Rectal and Parenteral Corticosteroids
SSA-P2 Induction Period	Allowed; MUST remain at stable dose unless change required due to AE	Allowed; MUST remain at stable dose unless change required due to AE	Allowed; MUST remain at stable dose	Not allowed	Not allowed
SSA-P2 Extension Period			Allowed; MAY undergo taper (refer to Section 6.8.3)	Allowed; refer to Section 6.8.4	
SS1-P2b			Allowed; MUST remain at stable dose	Not allowed	
SS2-I					
SS3-M Etrasimod and Placebo Responder Cohort			Allowed; MUST undergo taper (refer to Section 6.8.3)		
SS3-M Nonresponder Cohort			Allowed; MAY undergo taper (refer to Section 6.8.3)	Allowed; refer to Section 6.8.4	
SS4-E	Start, stop, or change in dose allowed	Start, stop, or change in dose allowed	Start, stop, or change in dose allowed	Allowed; refer to Section 6.8.4	Allowed

5-ASA, 5-aminosalicylic acid; AE, adverse event; SSA-P2, Substudy A – Phase 2; SS1-P2b, Substudy 1 – Phase 2b; SS2-I, Substudy 2 – Induction; SS3-M, Substudy 3 – Maintenance; SS4-E, Substudy 4 – Long-Term Extension

Oral and Rectal 5-Aminosalicylic Acid Compounds

Oral 5-ASA compounds are permitted, provided that the subject will have been on a stable dose for > 2 weeks prior to randomization in SSA-P2, SS1-P2b, SS2-I, or SS3-M and remains on the same dose, unless a change in dose is required due to AEs, while participating in these substudies. Rectal 5-ASA compounds are only permitted for subjects enrolled in the SS3-M Nonresponder Cohort, and SS4-E.

Oral Corticosteroids

Oral corticosteroids (eg, prednisone at a stable dose ≤ 20 mg/day [or its equivalent], budesonide at a stable dose ≤ 9 mg/day, or beclomethasone ≤ 5 mg/day) are permitted, provided that the subject will have been on a stable dose for > 2 weeks prior to randomization in SSA-P2, SS1-P2b, or SS2-I and remains on a stable dose during the Induction and EI Periods of these substudies. However, the SS3-M Responder Cohort must undergo corticosteroid tapering, as described in Section 6.8.3. Subjects who enter the SSA-P2 Extension Period or SS3-M nonresponders may also undergo corticosteroid taper, at the Investigator's discretion (refer to Section 6.8.3).

Anti-Diarrheal Medications

Anti-diarrheal medications are also permitted during participation in SSA-P2, SS1-P2b, SS2-I, and SS3-M provided that the dose remains stable through the Week 66 Visit of SSA-P2 or M-38 Visit of SS3-M, unless dose reduction or discontinuation is required due to clinical improvement or an AE.

6.8.3. Corticosteroid Taper in Substudy A – Phase 2 Extension Period and Substudy 3 – Maintenance

In SSA-P2, corticosteroid taper should begin after Week 14 for subjects who achieve clinical response at Week 14 and at any time during the Extension Period, at the Investigator's discretion, in other subjects.

During participation in SS3-M (Responder Cohort only), corticosteroid taper is mandatory starting at the MFD Visit. Subjects in the Nonresponder Cohort of SS3-M may undergo corticosteroid taper at any time at the Investigator's discretion.

6.8.3.1. Corticosteroid Tapering Procedure

The recommended tapering schedule for corticosteroid tapering is as follows:

- b. 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
- c. Dose ≤ 10 mg/day prednisone or equivalent: Taper daily dose by 2.5 mg/week until 0 mg/day
- d. Budesonide: Taper daily dose by 3 mg every 3 weeks until 0 mg/day
- e. Beclomethasone: Taper daily dose by 5 mg every other day until 0 mg/day

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

6.8.4. Rescue Therapy in Substudy A – Phase 2 Extension Period, Substudy 3 – Maintenance (Nonresponder Cohort Only), and Substudy 4 – Long-Term Extension

Oral corticosteroids (a maximum of 1 mg/kg prednisone, or equivalent, or budesonide up to 9 mg/day) may be administered as rescue therapy during the SSA-P2 Extension Period, SS3-M (Nonresponder Cohort only), and SS4-E. Subjects who receive oral corticosteroid rescue therapy should be tapered off steroids within 12 weeks of starting such therapy. If subjects are unable to taper, show no improvement within 12 weeks of initiating rescue therapy, or relapse within 2 months of initiating taper, they should be considered treatment failures and should be discontinued from the study.

6.8.5. Prohibited Concomitant Therapy and Procedures

The following therapies are prohibited during the study:

- Immunosuppressants (eg, AZA, 6MP, or MTX)
- TNF α antagonists or biosimilars, vedolizumab, risankizumab or ustekinumab
- JAK inhibitors (eg, upadacitinib)

- Antibiotics (eg, metronidazole, ciprofloxacin) used specifically for the treatment of CD
- Therapeutic apheresis
- 6-Thioguanine, systemic lymphocyte suppressive therapy (eg, cyclosporine, mycophenolate mofetil)
- Rectal or IV corticosteroids for the treatment of CD (except for in SS4-E)
- IV Ig
- Mesenchymal stem cell transplant (eg, Prochymal)
- S1P receptor modulators (eg, fingolimod, siponimod, ozanimod)
- $\alpha 4 \beta 1$ integrin receptor antagonist (eg, natalizumab)
- Lymphocyte depleting therapies (eg, rituximab, cyclophosphamide, bone marrow transplantation, or total body irradiation)
- Class Ia (eg, quinidine, procainamide) and Class III (eg, sotalol, amiodarone) antiarrhythmic drugs
- Moderate/strong inhibitors or inducers that inhibit or induce at least 2 of the following: CYP2C8, CYP2C9, and CYP3A4 (eg, fluconazole [inhibitor]), enzalutamide or rifampin (inducer).
- Live attenuated vaccines (except the influenza vaccine) during study drug and for 4 weeks after the last dose of study drug
- Chronic nonsteroidal anti-inflammatory drug (NSAID) use. (Note: Occasional use of NSAIDs [eg, for treatment of headache, arthritis, myalgias, or menstrual cramps] and aspirin up to 325 mg/day is permitted.)
- Any investigational drug other than the study drug

Start, stop, or change in dosage of any anti-arrhythmic drugs (Class I to IV) within 1 week before or after treatment initiation or reinitiation following dose interruption of a duration requiring in-clinic cardiac monitoring.

Subjects who discontinue study medication and/or enter the 4-Week Follow-Up Period will no longer need to abstain from the medications that were prohibited during the treatment periods, including receiving rescue medication, unless noted otherwise (eg, live attenuated vaccines for 4 weeks after the last dose of study drug).

For concomitant procedures:

- Subjects should not undergo major elective surgery while on study drug
- Subjects may not donate blood during the study and for 30 days after the last dose of study drug
- Subjects may not donate sperm, or oocytes during the study and for 30 days after the last dose of study drug

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7. STUDY DRUG MATERIALS MANAGEMENT

7.1. Packaging and Labeling

Study drug will be provided in induction-sealed, high-density polyethylene bottles with child-resistant screw caps. Each bottle will be labeled as required per country requirement.

Study drug will be dispensed to subjects as a kit containing 2 bottles, labeled as Bottle 1 and Bottle 2. Subjects will be instructed to take 1 tablet each from Bottle 1 and Bottle 2 together qd as described in Section 6.3.

If the etrasimod 3 mg dose is discontinued, subjects who enroll in SS2-I may be dispensed study drug in bottles (ie, not as a kit) for the entirety of their study participation (ie, in SS2-I, SS3-M, and SS4-E) and will be instructed to take 1 tablet from 1 bottle as described in Section 6.3. After dose selection if the etrasimod 3 mg dose is discontinued, subjects entering SS4-E or SS3-M may be dispensed study drug as a bottle, not as a kit. SS4-E subjects whose next study visit is between the EFD Visit and the Last Annual Visit at the time of dose selection will be dispensed study drug as a bottle, not as a kit, at their next study visit once it is available.

7.2. Storage and Handling

Bottles should be stored between 15°C to 25°C (59°F to 77°F).

7.3. Preparation

No preparation by study site personnel is required.

7.4. Accountability

Subjects will be instructed to record tablet self-administration daily in an eDiary that will be reviewed at each treatment visit by study site staff. At each in person visit, previously dispensed study drug tablets will be collected by the Investigator or qualified staff to assess subject compliance.

The Investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of study drug tablets. 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 study drug tablets.

7.5. Retention and Disposal

All study drug 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 drug, the Investigator will contact the sponsor (or contract research organization [CRO]) for approval of such action. Final reconciliation will be performed at study completion.

8. REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

8.1. Criteria for Discontinuation of Study Drug

The criteria for discontinuation of study drug apply to ALL substudies, unless noted otherwise.

Study drug **must** be discontinued in the following instances:

- Unacceptable AE or AE that, in the judgment of the Investigator, is considered to not be in the best interest of the subject to continue study drug, including:
 - New onset of malignancy
 - New onset mental status change without alternate etiology
 - Suspected drug induced liver injury as defined by the 2009 FDA Guidance for Industry (FDA 2009) as described in Section 10.7.8.1
 - Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 laboratory abnormalities (eg, anemia, platelet counts) considered related to study drug by the Investigator. An algorithm for the management of AEs (both clinical AEs and clinically significant laboratory abnormalities), including guidance on discontinuation of study drug, based on CTCAE severity grade is provided in Appendix 7
 - Persistent ALC < 200 cells/ μ L, as described in Section 10.7.8.2
- Subjects in SS1-P2b, SS2-I, or SS3-M Responder Cohort who require initiation of a new therapy for CD or increase in oral corticosteroids for CD above the baseline level (Section 6.8.2.1)
- Insufficient efficacy as determined by the Investigator (eg, no clinical improvement after 14 weeks of treatment in the Nonresponder Cohort in SS3-M)
- Subject is considered a treatment failure (eg, subject is unable to taper rescue therapy or relapses within 2 months of initiating taper of rescue therapy)
- Subject request to discontinue for any reason
- Pregnancy during the study (Section 10.7.10)
- Diagnosis of active TB
- A subject receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with treatment regimen
- Termination of the study by the sponsor or at the request of a regulatory agency or an Institutional Review Board (IRB) or Independent Ethics Committee (IEC)

Study drug may be discontinued for subject noncompliance. A subject may elect to discontinue study participation at any time for any reason without prejudice to their future medical care by the physician or at the institution.

When possible, all follow-up procedures specified in Section 9.4.4, 9.5.4, 9.6.5, 9.7.4, and 9.8.3 should be performed. 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 medical record.

Subjects who discontinue treatment prematurely, should be instructed to return for an ET Visit within 7 days of when the last dose of study drug was taken (refer to the Schedules of Assessments in [Appendix 1](#)) and before initiation of any new treatments to complete all of the ET assessments.

If a subject discontinues due to pregnancy, they are not required to complete the endoscopy.

If the ET Visit is within 6 weeks of the last endoscopy and biopsy, these procedures do not need to be repeated.

8.2. Lost to Follow-Up

A subject will be considered lost to follow-up if the subject repeatedly fails to return for scheduled visits and cannot 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 known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record

If the above methods do not succeed in reaching the subject, he/she will be considered to have withdrawn from the study.

8.3. Premature Termination of the Study or a Study Site

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 AEs 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 the Investigator if the study is placed on hold or if the sponsor decides to discontinue the study. Health authorities and IRBs/IECs 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
- Noncompliance with the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP)

9. STUDY PERIODS

In the event that a need for decentralized study procedures arises some visits may be conducted by telehealth, home health, or mobile visits. as specified in the Schedule of Assessments for each substudy, only if permitted by local guidelines and regulations. Patients will be made aware of the potential for virtual/home visits and will be consented to this possibility at the time of screening into the study if permitted by local guidelines and regulations.

9.1. Telehealth Visits

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

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

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

9.2. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits. Home health visits include a healthcare provider (eg, the study investigator or a designee physician who is medically qualified) conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. The following may be performed during a home health visit (see the schedule of assessments):

- Review and record study drug(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact.

- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

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

9.3. Mobile Visits

In the event that an in-person visit is not feasible at the site, a mobile visit may be performed by a licensed healthcare professional at an alternate site approved by the investigator (see the schedule of assessments).

9.4. Study Periods for Substudy A – Phase 2

9.4.1. Substudy A – Phase 2 Screening

Subjects must sign the informed consent before any study-specific procedure can be performed (refer to Section 10.1).

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

Screening procedures must be completed within 28 days prior to Day 1 (Appendix 1; Table 29). In the event of unexpected circumstances (eg, COVID-19 pandemic) and it is necessary for the subject to be randomized > 28 days from the signing of the informed consent form, the Medical Monitor should be consulted to see whether repeat testing is needed. Rescreening procedures are described in Section 10.2.1.

Subjects with a screening visit or Day 1 pre-randomization 12-lead ECG showing a second- or third-degree AV block, sick sinus syndrome without a functional pacemaker, periods of asystole > 3 seconds without an implanted cardiac defibrillator, PR interval ≥ 220 ms, or QTcF ≥ 450 ms (men) or QTcF ≥ 470 ms (women) are not eligible for rescreening.

Subjects with *C. difficile* colitis who have been treated may be rescreened, provided they have documented evidence of *C. difficile* toxin clearance ≥ 2 weeks prior to randomization.

9.4.2. Substudy A – Phase 2 Randomization and Induction Period

9.4.2.1. Substudy A – Phase 2 Induction Period: Day 1 (Pre-Randomization)

At the Day 1 visit, prior to randomization, inclusion and exclusion criteria must be evaluated again. To this end, vital signs including HR and BP must be measured first, followed by 12-lead ECG. Vital signs may be repeated up to 3 times to confirm abnormal readings.

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

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

- 12-lead ECG showing a second or third-degree AV block, periods of asystole > 3 seconds, PR interval ≥ 220 ms, or QTcF ≥ 450 ms (males) or QTcF ≥ 470 ms (females)

All pre-dose 12-lead ECGs should be obtained prior to blood sample collection. Subjects should fast for 9 to 12 hours (drinking water only) before the blood sample collection for the lipid panel.

FOCBP will have a urine pregnancy test prior to randomization.

Subjects who continue to meet all inclusion criteria and no exclusion criteria will be randomized as outlined in Section 6.4.1.

9.4.2.2. Substudy A – Phase 2 Induction Period: Day 1 (Post-Randomization)

Randomization may occur on Day 1 after all eligibility criteria have been confirmed.

A blood sample for PK assessment is to be taken before administration of the first dose of study drug.

Cardiac monitoring will take place under direct observation during the period after the first dose of study drug is administered on Day 1. Day 1 pre-randomization vital signs (resting HR, BP, body temperature, and respiratory rate) will be used as baseline measurements for cardiac monitoring. Refer to Section 10.7.8.4 for detailed guidance on cardiac monitoring following administration of the first dose and subject discharge criteria postdose.

Refer to guidance regarding disclosure of HR data discussed in Section 6.6.

A blood sample for PK assessment is to be taken 4 hours (± 15 minutes) postdose after the ECG on Day 1.

9.4.2.3. Substudy A – Phase 2 Induction Period Study Visits After Day 1

After the Baseline (Day 1) Visit, a visit window of ± 1 day is permitted for the Week 1 Visit and a visit window of ± 3 days is permitted for the other study visits during the Induction Period.

Negative pregnancy test results must be documented for all FOCBP prior to dosing at all applicable study visits. At study visits where PK samples are collected, blood sample collections should be performed prior to dosing. At the Week 14 Visit, subjects should fast for 9 to 12 hours (drinking water only) before the blood sample collection for the lipid panel.

Subjects who discontinue treatment during the Induction Period prematurely should have an Early Termination (ET) Visit (Section 9.4.5), followed by the 2 follow-up visits in the Follow-Up Period (Section 9.4.4), and are not eligible to participate in the Extension Period.

9.4.3. Substudy A – Phase 2 Extension Period

9.4.3.1. Week 15 Visit

At the Week 15 visit, subjects will be assigned to an Extension Period treatment group (etrasimod 3 mg or 2 mg) as described in Table 1. Clinical response will be determined by the pre-defined criteria in Section 3.1.2. A visit window of ± 3 days is permitted for the Week 15 Visit.

9.4.3.2. Other Extension Period Study Visits

After the Week 15 study visit, a visit window of ± 3 days is permitted for the End of Week 15 visit and a visit window of ± 7 days is permitted for the other study visits during the Extension Period.

Negative pregnancy test results must be documented for all FOCBP prior to dosing at all applicable study visits. At study visits where PK samples are collected, blood sample collections should be performed prior to dosing. At the Week 66 visit, subjects should fast for 9 to 12 hours (drinking water only) before the blood sample collection for the lipid panel.

Subjects in the Extension Period who do not show clinical improvement from baseline by Week 20, as determined by the Investigator (Non-EU regions) or defined as a ≥ 70 -point decrease on CDAI (EU region only), will be discontinued from study. Subjects who experience unexplained disease worsening, as determined by the Investigator, at any time during the Extension Period may receive short-term, add-on rescue therapy (refer to Section 6.8.4). If subjects show no clinical improvement from rescue therapy, as determined by the Investigator, then they will also be discontinued from the study drug.

Subjects who complete the Extension Period will be eligible to enter SS4-E after completion of the Week 66 Visit.

Subjects who discontinue treatment prematurely should have an ET Visit (Section 9.4.5) followed by the 2 follow-up visits in the Follow-Up Period (Section 9.4.4).

9.4.4. Substudy A – Phase 2 Follow-Up

Subjects who do not enroll in SS4-E will have follow-up visits for safety assessment 14 days (± 3 days) and 28 days (± 3 days) after the last dose of study drug.

All AEs should be recorded for 30 days after last dose of study drug (refer to Section 10.7.9.2.2).

9.4.5. Substudy A – Phase 2 Early Termination

Subjects who discontinue study drug prior to the end of the 52-week Extension Period will return to the clinic for an ET visit. The ET visit assessments are detailed in the Schedules of Assessments (Appendix 1; Table 29). The ET visit should occur within 7 days of last dose and before initiation of any new treatments. Site staff will work with subjects who withdraw early to obtain as much follow-up data as possible. If ophthalmology, OCT, PFT, and diffusing capacity of the lungs for carbon monoxide (DLCO) assessments were performed within 2 weeks of the ET Visit, these assessments do not need to be repeated.

9.5. Study Periods for Substudy 1 – Phase 2b

9.5.1. Substudy 1 – Phase 2b Screening

Subjects must sign the informed consent before any study-specific procedure can be performed (Section 10.1).

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

Screening procedures must be completed within 40 days prior to Day 1 ([Appendix 1; Table 30](#)). The Screening period may be extended on a case-by-case basis to accommodate reasonable delays in specific screening assessments (eg, PFTs, OCT, labs) due to testing availability. The Medical Monitor must be consulted prior to extension in each case. Rescreening procedures are described in Section [10.2.1](#).

Subjects with a Screening Visit or Day 1 pre-randomization 12-lead ECG showing a second- or third-degree AV block, sick sinus syndrome without a functional pacemaker, periods of asystole > 3 seconds without an implanted cardiac defibrillator, PR interval ≥ 220 ms, or QTcF ≥ 450 ms (men) or QTcF ≥ 470 ms (women) are not eligible for rescreening.

Subjects with *C. difficile* colitis who have been treated may be rescreened, provided they have documented evidence of *C. difficile* toxin clearance ≥ 2 weeks prior to randomization.

9.5.2. Substudy 1 – Phase 2b Randomization and Induction Period

Study procedures described in this section apply to both Cohorts 1 and 2, unless stated otherwise.

9.5.2.1. Substudy 1 – Phase 2b Induction Period: Day 1 (Pre-Randomization)

At the Day 1 Visit, prior to randomization, inclusion and exclusion criteria must be evaluated again. To this end, vital signs including HR and BP must be measured first, followed by 12-lead ECG. Vital signs may be repeated up to 3 times to confirm abnormal readings.

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

- Sitting vital sign assessment: HR < 50 bpm AND systolic BP < 90 mm Hg OR diastolic BP < 55 mm Hg
- 12lead ECG showing a second or third-degree AV block, periods of asystole > 3 seconds, PR interval ≥ 220 ms, or QTcF ≥ 450 ms (males) or QTcF ≥ 470 ms (females)

All pre-dose 12-lead ECGs should be obtained prior to blood sample collection. Subjects should fast for 9 to 12 hours (drinking water only) before the blood sample collection for the lipid panel.

FOCBP will have a urine pregnancy test prior to randomization.

Subjects who continue to meet all inclusion criteria and no exclusion criteria will be randomized as outlined in Section [6.4.2](#).

9.5.2.2. Substudy 1 – Phase 2b Induction Period: Day 1 (Post-Randomization)

Randomization may occur on Day 1 after all eligibility criteria have been confirmed.

A blood sample for PK assessment is to be taken before administration of the first dose of study drug.

Cardiac monitoring will take place under direct observation during the period after the first dose of study drug is administered on Day 1. Day 1 pre-randomization vital signs (resting HR, BP, body temperature, and respiratory rate) will be used as baseline measurements for

cardiac monitoring. Refer to Section 10.7.8.4 for detailed guidance on cardiac monitoring following administration of the first dose and subject discharge criteria postdose.

Refer to guidance regarding disclosure of HR data discussed in Section 6.6.

A blood sample for PK assessment is to be taken 4 hours ($\pm$ 15 minutes) postdose after the ECG on Day 1.

9.5.2.3. Substudy 1 – Phase 2b Induction Period Study Visits After Day 1

After the Baseline (Day 1) Visit, a visit window of $\pm$ 1 day is permitted for the Week 1 Visit and a visit window of $\pm$ 3 days is permitted for the other study visits during the Induction Period.

Negative pregnancy test results must be documented for all FOCBP prior to dosing at all applicable study visits. At study visits where PK samples are collected, blood sample collections should be performed prior to dosing. At the Week 14 Visit, subjects should fast for 9 to 12 hours (drinking water only) before the blood sample collection for the lipid panel.

Subjects who complete the Induction Period and meet response criteria (Section 3.1.2) may enter SS3-M. Subjects who do not meet response criteria may enter the SS1-P2b EI Period. Subjects who prematurely discontinue treatment during the Induction Period should have an ET Visit (Section 9.5.5) followed by the 2 follow-up visits in the Follow-Up Period (Section 9.5.4).

9.5.3. Substudy 1 – Phase 2b Extended Induction Period

9.5.3.1. Substudy 1 – Phase 2b Extended Induction First Dose Visit

Subjects who completed Week 14 of the Induction Period and do not meet response criteria (Section 3.1.2) will be assigned to an EI Period treatment group (etrasimod 3 mg or 2 mg) as described in Table 2 (Section 3.1). The Extended Induction First Dose (EIFD) Visit is the first visit of the EI Period and should occur within 1 week ($\pm$ 3 days) of the Week 14 Visit but may be performed on the same day as the Week 14 Visit. First-dose cardiac monitoring will be performed at the EIFD Visit as described for the Induction Period (Section 9.5.2.2).

9.5.3.2. Substudy 1 – Phase 2b Extended Induction Period Study Week 1 and Week 6 Visits

A visit window of $\pm$ 3 days is permitted for the EI Week 1 and EI Week 6 Visits.

Negative pregnancy test results must be documented for all FOCBP prior to dosing at all applicable study visits. At study visits where PK samples are collected, blood sample collections should be performed prior to dosing. At the EI Week 6 Visit, subjects should fast for 9 to 12 hours (drinking water only) before the blood sample collection for the lipid panel.

Subjects who complete the EI Period may enter SS3-M after completion of the EI Week 6 Visit, provided that all eligibility criteria for SS3-M are met.

Subjects in the EI Period who do not show clinical improvement by the EI Week 6 Visit, as determined by the Investigator or defined as a $\geq$ 70-point decrease in CDAI (EU region only), will be discontinued from this study due to a lack of efficacy.

Subjects who discontinue treatment prematurely should have an ET Visit (Section 9.5.5) followed by the 2 follow-up visits in the Follow-Up Period (Section 9.5.4).

9.5.4. Substudy 1 – Phase 2b Follow-Up

Subjects who do not enroll in SS3-M will have follow-up visits for safety assessment 14 days (± 3 days) and 28 days (± 3 days) after the last dose of study drug.

All AEs should be recorded for 30 days after last dose of study drug (Section 10.7.9.2.2).

9.5.5. Substudy 1 – Phase 2b Early Termination

Subjects who discontinue study drug prior to the end of SS1-P2b will return to the clinic for an ET Visit. The ET Visit assessments are detailed in the Schedule of Assessments (Appendix 1; Table 30). The ET Visit should occur within 7 days of last dose and before initiation of any new treatments. Site staff will work with subjects who withdraw early to obtain as much follow-up data as possible. If ophthalmology, OCT, PFT, and DLCO assessments were performed within 2 weeks of ET Visit, these assessments do not need to be repeated.

9.6. Study Periods for Substudy 2 – Induction

9.6.1. Substudy 2 – Induction Screening

Subjects must sign the informed consent before any study-specific procedure can be performed (Section 10.1).

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

Screening procedures must be completed within 40 days prior to Day 1 (Appendix 1; Table 31). The Screening period may be extended on a case-by-case basis to accommodate reasonable delays in specific screening assessments (eg, PFTs, OCT, labs) due to testing availability. The Medical Monitor must be consulted prior to extension in each case. Rescreening procedures are described in Section 10.2.1.

Subjects with a Screening Visit or Day 1 pre-randomization 12-lead ECG showing a second- or third-degree AV block, sick sinus syndrome without a functional pacemaker, periods of asystole > 3 seconds without an implanted cardiac defibrillator, PR interval ≥ 220 ms, or QTcF ≥ 450 ms (men) or QTcF ≥ 470 ms (women) are not eligible for rescreening.

Subjects with *C. difficile* colitis who have been treated may be rescreened, provided they have documented evidence of *C. difficile* toxin clearance ≥ 2 weeks prior to randomization.

9.6.2. Substudy 2 – Induction Randomization and Treatment Period

9.6.2.1. Substudy 2 – Induction Day 1 (Pre-Randomization)

At the Day 1 Visit, prior to randomization, inclusion and exclusion criteria must be evaluated again. To this end, vital signs including HR and BP must be measured first, followed by 12-lead ECG. Vital signs may be repeated up to 3 times to confirm abnormal readings.

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

- Sitting vital sign assessment: HR < 50 bpm AND systolic BP < 90 mm Hg OR diastolic BP < 55 mm Hg
- 12-lead ECG showing a second or third-degree AV block, periods of asystole > 3 seconds, PR interval $\geq$ 220 ms, or QTcF $\geq$ 450 ms (males) or QTcF $\geq$ 470 ms (females)

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

FOCBP will have a urine pregnancy test prior to randomization.

Subjects who continue to meet all inclusion criteria and no exclusion criteria will be randomized as outlined in Section 6.4.3.

9.6.2.2. Substudy 2 – Induction Day 1 (Post-Randomization)

Randomization may occur on Day 1 after all eligibility criteria have been confirmed.

A blood sample for PK assessment is to be taken before administration of the first dose of study drug.

Cardiac monitoring will take place under direct observation during the period after the first dose of study drug is administered on Day 1. Day 1 pre-randomization vital signs (resting HR, BP, body temperature, and respiratory rate) will be used as baseline measurements for cardiac monitoring. Refer to Section 10.7.8.4 for detailed guidance on cardiac monitoring following administration of the first dose and subject discharge criteria postdose.

Refer to guidance regarding disclosure of HR data discussed in Section 6.6.

A blood sample for PK assessment is to be taken 4 hours ($\pm$ 15 minutes) postdose after the ECG on Day 1.

9.6.3. Substudy 2 – Induction Period Study Visits After Day 1

After the Baseline (Day 1) Visit, a visit window of $\pm$ 1 day is permitted for the Week 1 Visit and a visit window of $\pm$ 3 days is permitted for the other study visits during the Induction Period. The Week 1 Visit will be required only if etrasimod 3 mg is the selected Phase 3 dose.

Negative pregnancy test results must be documented for all FOCBP prior to dosing at all applicable study visits. At study visits where PK samples are collected, blood sample collections should be performed prior to dosing.

Subjects who complete the Induction Period and meet response criteria (Section 3.1.2) may enter SS3-M. Subjects who do not meet response criteria may enter the EI Period. Subjects who prematurely discontinue treatment during the Induction Period should have an ET Visit (Section 9.6.6) followed by the 2 follow-up visits in the Follow-Up Period (Section 9.6.5).

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9.6.4. Substudy 2 – Induction Extended Induction Period

9.6.4.1. Substudy 2 – Induction Extended Induction First Dose Visit

Subjects who completed Week 14 of the Induction Period and do not meet response criteria (Section 3.1.2) will enter the EI Period and receive the selected etrasimod dose (etrasimod 3 mg or 2 mg). The EIFD Visit is the first visit of the EI Period and should occur within 1 week (± 3 days) of the Week 14 Visit but may be performed on the same day as the Week 14 Visit. First-dose cardiac monitoring will be performed at the EIFD Visit as described for the Induction Period (Section 9.6.2.2).

9.6.4.2. Substudy 2 – Induction Extended Induction Period Study Visits After Extended Induction First Dose Visit

If etrasimod 3 mg is the selected dose, an EI Week 1 Visit will be required. A visit window of ± 3 days is permitted for the EI Week 1 and EI Week 6 Visits.

Negative pregnancy test results must be documented for all FOCBP prior to dosing at all applicable study visits. At study visits where PK samples are collected, blood sample collections should be performed prior to dosing.

Subjects who complete the EI Period may enter SS3-M upon completion of the EI Week 6 Visit, provided that all eligibility criteria for SS3-M are met.

Subjects in the EI Period who do not show clinical improvement by the EI Week 6 Visit, as determined by the Investigator or defined as a ≥ 70 -point decrease on CDAI (EU region only), will be discontinued from this study due to a lack of efficacy.

Subjects who discontinue treatment prematurely should have an ET Visit (Section 9.6.6) followed by the 2 follow-up visits in the Follow-Up Period (Section 9.6.5).

9.6.5. Substudy 2 – Induction Follow-Up

Subjects who do not enroll in SS3-M will have follow-up visits for safety assessment 14 days (± 3 days) and 28 days (± 3 days) after the last dose of study drug.

All AEs should be recorded for 30 days after last dose of study drug (Section 10.7.9.2.2).

9.6.6. Substudy 2 – Induction Early Termination

Subjects who discontinue study drug prior to the end of SS2-I will return to the clinic for an ET Visit. The ET Visit assessments are detailed in the Schedule of Assessments (Appendix 1; Table 31). The ET Visit should occur within 7 days of last dose and before initiation of any new treatments. Site staff will work with subjects who withdraw early to obtain as much follow-up data as possible. If ophthalmology, OCT, PFT, and DLCO assessments were performed within 2 weeks of ET Visit, these assessments do not need to be repeated.

9.7. Study Periods for Substudy 3 – Maintenance

The Schedule of Assessments for SS3-M can be found in Appendix 1, Table 32.

9.7.1. Substudy 3 – Maintenance First Dose Visit

At the MFD Visit, the first visit of SS3-M for all subjects, subjects who meet all inclusion criteria and no exclusion criteria for SS3-M will be enrolled as outlined in Section 6.4.4.

Subjects will be enrolled in the Responder Cohort or Nonresponder Cohort based on whether they achieved the response criteria described in Section 3.1.2.

The MFD Visit may be performed on the same day as the last visit of the parent induction study or substudy but must occur no later than 7 days after the Week 14 or EI-Week 6 Visit.

The subject should NOT take his or her double-blinded study drug from the parent substudy or study (ie, SS1-P2b, SS2-I, or Study APD334-305) at the MFD Visit.

The first-dose cardiac monitoring procedure will not be performed at the MFD Visit because no subjects who received placebo at their last visit of the parent induction study or substudy will be randomized to etrasimod in this substudy (ie, all subjects assigned to etrasimod treatment at the MFD Visit will have received etrasimod at their last visit prior to the MFD Visit).

9.7.2. Substudy 3 – Maintenance Treatment Period Study Visits after First Dose Visit

A visit window of ± 3 days is permitted for the M-6 Visit and a visit window of ± 7 days is permitted for the other study visits during the 38-week Maintenance Treatment Period.

Negative pregnancy test results must be documented for all FOCBP prior to dosing at all applicable study visits as specified in the schedule of activities. At study visits where PK samples are collected, blood sample collections must be performed prior to dosing.

Nonresponders who experience unexplained disease worsening, as determined by the Investigator, at any time may receive short-term, add-on rescue therapy (refer to Section 6.8.4). If subjects show no clinical improvement from rescue therapy, as determined by the Investigator, then they will also be discontinued from study drug.

Subjects who prematurely discontinue treatment during the Maintenance Treatment Period should have an ET Visit (Section 9.7.5) followed by the 2 follow-up visits in the Follow-Up Period (Section 9.7.4).

9.7.3. Substudy 3 – Maintenance Responder Cohort Loss-of-Response Assessment

Subjects in the SS3-M Responder Cohort will be regularly monitored for potential symptomatic worsening. Following the M-6 Visit, subjects who experience sustained disease worsening may be assessed for LOR at any scheduled visit during the Maintenance Treatment Period or any time between scheduled visits (ie, an unscheduled LOR Visit) as indicated in the Schedule of Assessments (Appendix 1; Table 32). LOR assessment may not occur prior to the M-6 Visit. Initiation of LOR assessment may begin only if the sustained worsening in AP and/or SF symptom scores over the 7 most recent days compared to SS3-M baseline values have been documented in the subject's daily eDiary.

LOR is defined as an increase in disease activity that satisfies the following criteria:

1. CDAI score ≥ 220 - AND a ≥ 100 -point increase from the MFD Visit
2. Alternative suspected causes for the increased disease activity including viral or bacterial gastroenteritis and *C. difficile* infection have been ruled out by appropriate stool cultures and other laboratory tests. If a potential other cause is identified, loss of response will not be assessed until a full course of treatment has been completed, or if untreated, the infection

would be expected to be resolved based on its natural history. This testing must begin once loss of response is suspected

If evaluation determines that the subject meets the LOR criteria, the subject may switch to the Nonresponder Cohort and receive etrasimod for the remaining duration of the SS3-M Treatment Period. Repeat LOR Visits are permitted; however, visits should be at least 1 week apart so that there is no overlap in diary assessments.

If possible, an ileocolonoscopy will be performed prior to the LOR First Dose Visit.

Subjects who meet the LOR criteria will return to the clinic for a LOR First-Dose Visit that may occur at an unscheduled visit or at a scheduled Maintenance Treatment Period Visit. Subjects with a confirmed LOR will subsequently be considered part of the Nonresponder Cohort and receive etrasimod according to Section 6.4.4. First-dose cardiac monitoring will be performed at the LOR First-Dose Visit as described in Section 10.7.8.4. Subjects where possible will have an ileocolonoscopy prior to switching to the Nonresponder Cohort if the LOR Visit occurs > 6 weeks after the Week 14 Visit of the parent induction study or substudy. Prior to dose selection or if the selected dose in Phase 3 is etrasimod 3 mg and dose escalation is required, subjects will return for a second, unscheduled visit approximately 1 week later (LOR Dose Escalation Visit).

Subjects should continue with the visit schedule as indicated in the Schedule of Assessments (Appendix 1; Table 32), but repeat assessments are not required if the LOR or LOR Dose Escalation Visit occurs on the same day as a scheduled visit in the Maintenance Treatment Period.

Subjects who switch to the Nonresponder Cohort and do not show clinical improvement, as determined by the Investigator, by 14 weeks after the LOR First Dose Visit in SS3-M will be discontinued from the study due to lack efficacy.

9.7.4. Substudy 3 – Maintenance Follow-Up

Subjects who do not enroll in SS4-E will have follow-up visits for safety assessment 14 days (± 3 days) and 28 days (± 3 days) after the last dose of study drug (Appendix 1; Table 32).

All AEs should be recorded for 30 days after last dose of study drug (Section 10.7.9.2.2).

9.7.5. Substudy 3 – Maintenance Early Termination Visit

Subjects who discontinue study drug prior to the end of the SS3-M treatment period will return to the clinic for an ET Visit. ET Visit assessments are detailed in the Schedule of Assessments (Appendix 1; Table 32). If the subject has discontinued study drug, the ET Visit should occur within 7 days of last dose and before initiation of any new treatments. Site staff will work with subjects who withdraw early to obtain as much follow-up data as possible. If ophthalmology, OCT, PFT, and DLCO assessments were performed within 2 weeks of ET Visit, these assessments do not need to be repeated.

9.8. Study Periods for Substudy 4 – Long-Term Extension

The Schedule of Assessments for SS4-E can be found in Appendix 1, Table 33.

9.8.1. Substudy 4 – Long-Term Extension First Dose Visit

At the EFD Visit, subjects who meet all SS4-E inclusion criteria and no exclusion criteria will be enrolled as outlined in Section 6.4.5.

The EFD Visit may be performed on the same day as the Week 66 Visit of SSA-P2 or the M-38 Visit of SS3-M but must occur no later than 14 days after the last visit of the parent substudy.

The subject should NOT take his or her double-blinded study drug from the parent substudy (SSA-P2 or SS3-M) at the EFD Visit of the Long-Term Extension substudy.

Subjects from the SS3-M Responder Cohort who enroll in SS4-E may be receiving etrasimod for the first time in the study; therefore, first-dose cardiac monitoring will be performed for these subjects only as described below.

9.8.1.1. Extension First Dose Visit Predose (Substudy 3 – Maintenance Responder Cohort Only)

At the EFD Visit, vital signs including HR and BP followed by 12-lead ECG must be measured before study drug administration. Vital signs may be repeated up to 3 times to confirm abnormal readings.

Subjects with the following must not receive study drug and should be discontinued from the study:

- Sitting vital sign assessment: HR < 50 bpm AND systolic BP < 90 mm Hg OR diastolic BP < 55 mm Hg
- 12-lead ECG showing a second or third-degree AV block, periods of asystole > 3 seconds, PR interval $\geq$ 220 ms, or QTcF $\geq$ 450 ms (males) or QTcF $\geq$ 470 ms (females)

FOCBP will have a urine pregnancy test prior to study drug administration.

9.8.1.2. Extension First Dose Visit Postdose (Substudy 3 – Maintenance Responder Cohort Only)

Cardiac monitoring will take place under direct observation during the period after the first dose of study drug is administered at the EFD Visit. The SS4-E baseline predose vital signs (resting HR, BP, body temperature, and respiratory rate) will be used as baseline measurements for cardiac monitoring. Refer to Section 10.7.8.4 for detailed guidance on cardiac monitoring following administration of the first dose and subject discharge criteria postdose.

Refer to guidance regarding disclosure of HR data discussed in Section 6.6.

9.8.2. Substudy 4 – Long-Term Extension Treatment Period Visits

A visit window of $\pm$ 3 days is permitted for the E-1 Visit and a visit window of $\pm$ 7 days is permitted for the other study visits during SS4-E treatment period.

The E-1 Visit will be required only for subjects from the SS3-M Responder Cohort prior to dose selection or if etrasimod 3 mg is the selected Phase 3 dose. The E-1 Visit should occur within 1 week ($\pm$ 3 days) following the EFD Visit.

Subjects will have assessments performed at each study visit as listed in the Schedule of Assessments ([Appendix 1](#); [Table 33](#)).

Negative pregnancy test results must be documented for all FOCBP prior to dosing at all applicable study visits.

Throughout the LTE Treatment Period, subjects will be regularly assessed to monitor the clinical benefit of etrasimod treatment and to evaluate potential lack of efficacy. Subjects who experience unexplained disease worsening, as determined by the Investigator, may receive add-on rescue therapy (refer to [Section 6.8.4](#)). Subjects who show no clinical improvement from rescue therapy will be discontinued from study drug.

Subjects who discontinue treatment prematurely should have an ET Visit ([Section 9.8.4](#)) followed by the 2 follow-up visits in the Follow-Up Period ([Section 9.8.3](#)).

9.8.3. Substudy 4 – Long-Term Extension Follow-Up/End of Study

All subjects will have follow-up visits for safety assessment 14 days (± 3 days) and 28 days (± 3 days) after the last dose of study drug ([Appendix 1](#); [Table 33](#)).

All AEs should be recorded for 30 days after last dose of study drug ([Section 10.7.9.2.2](#)).

9.8.4. Substudy 4 – Long-Term Extension Early Termination Visit

If a subject ends study participation prior to Week 208 of the LTE Treatment Period, the ET Visit and 2- and 4-Week Follow-Up Visits should be performed. If the subject has discontinued study drug, the ET Visit should occur within 7 days of last dose and before initiation of any new treatments. Site staff will work with subjects who withdraw early to obtain as much follow-up data as possible. If ophthalmology, OCT, PFT, and DLCO assessments were performed within 2 weeks of ET Visit, these assessments do not need to be repeated.

10. STUDY ASSESSMENTS AND PROCEDURES

10.1. Subject Informed Consent

The Investigator, or a person designated by the Investigator, will obtain written informed consent from each subject before any study-specific activity is performed (refer to [Section 12.3](#) for additional details).

10.2. Screening and Eligibility for Substudy A – Phase 2, Substudy 1 – Phase 2b, and Substudy 2 – Induction

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

Screening procedures must be completed within 28 days for SSA and 40 days for SS1 and SS2 prior to receiving the first dose of study drug ([Appendix 1](#); [Table 29](#), [Table 30](#) and [Table 31](#)).

10.2.1. Rescreening

If a subject fails screening, 1 rescreening attempt during a new Screening Period may be made at the Investigator's discretion. Additional screening attempts beyond the first

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rescreening attempt should be approved by the Medical Monitor prior to rescreening. Each subject must be reconsented prior to each screening attempt.

For subjects who are being rescreened, the following tests or procedures will not need to be repeated if the re-screen is within 3 months of the original screening date provided that the results or findings from these tests or procedures met the screening eligibility criteria. These tests and procedures are physical examination, 12-lead ECG, infectious disease serology, TB screening and TB questionnaire, ophthalmoscopy and OCT, PFT and DLCO. For stool studies, the time frame requirement is within 6 weeks of the original screening date.

10.2.2. Demography and Other Subject Characteristics

Demographics including year of birth, sex at birth, Hispanic ethnicity, and race, as described by the subject, will be collected at Screening.

10.2.3. Social History

At Screening, a social history including current tobacco and alcohol usage will be collected. Duration of tobacco and alcohol use (year start and end) will also be recorded.

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

10.2.4. Prior and Ongoing Therapies

All medications and procedures conducted within 30 days prior to the first dose will be recorded at Screening. Updates to medications or procedures prior to dosing at the Day 1 Visit should be made as needed.

Prior therapies related to the treatment of CD will be collected during screening including name of therapy, dosage, dosing frequency, route of administration, start and stop dates (month and year), side effects or intolerance, and patient perception of disease control on the therapy. In addition, documentation should also include the rationale for prior treatment failure.

10.2.5. Medical History/Crohn's Disease History

A complete medical history of each subject will be collected and documented during screening to determine subject eligibility. The history should include recent blood donations (within 30 days), illnesses, hospitalizations, and participation in other investigational drug studies.

A detailed history of the subject's CD, including date of diagnosis, disease severity, hospitalizations, EIMs, and presence and location of fistula will be collected. In addition, CD medical history should include smoking status, duration, disease localization (ileum/colon/both), disease activity, prior treatment, and complications associated with CD treatments.

10.2.6. Pregnancy Testing

A serum pregnancy test for β -hCG will be performed on FOCP to determine eligibility. Post-screening urine pregnancy tests (β -hCG) should be performed predose, as indicated in the Schedules of Assessments ([Appendix 1](#); [Table 29](#), [Table 30](#), and [Table 31](#)). In non-visit months, a monthly home pregnancy test should be performed in countries where allowed per

local regulations and any positive result immediately reported to the study site. If not allowed per local regulations, this pregnancy test will be performed on site during an unscheduled visit. If at any time a subject in the study cannot come into the study site for a visit, a home pregnancy test must be performed, and any positive result should be immediately reported to the study site.

If at any point there is a case of a positive urine β -hCG test, the subject will have study drug interrupted and a serum sample will be submitted to the central laboratory for β -hCG testing. If the serum test confirms positive, the subject will be discontinued from the study drug and all the necessary follow-up will be conducted as per Section 10.7.10. If the serum test is negative, the subject may resume study drug.

Negative pregnancy test results must be documented for all FOCBP 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. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy however, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to confirm postmenopausal state.

10.2.7. Tuberculosis Screening

TB screening will be done at Screening and annually (eg, Weeks 52, 104, 156, 208, 260) via a central laboratory interferon-gamma release assay (IGRA) (eg, QuantiFERON-TB PLUS or equivalent assay) in all subjects except those with a history of active or latent TB. Refer to [Appendix 2](#) for details of TB screening, interpretation of test results, and specific requirements including administration of a TB screening questionnaire to subjects residing in countries identified by WHO as having a high burden of TB or MDR TB.

10.2.8. Varicella Zoster Virus Antibody Screening

Subjects who have not received zoster vaccination for the prevention of herpes zoster (shingles) (recombinant zoster vaccine or live zoster vaccine), if clinically indicated, prior to randomization may be excluded from the study, unless the subject has documented positive VZV IgG status. The requirement for zoster vaccination and VZV IgG screening is applicable only to subjects residing in countries where the vaccine is approved/licensed and locally available. The zoster vaccine should only be administered to individuals within the appropriate age range and immune system status, in a manner consistent with product labeling (as described in the indications and usage and contraindications sections of the product label).

CDC recommends inactivated, recombinant zoster vaccine over live zoster vaccine for the prevention of herpes zoster (shingles) and related complications ([CDC 2018](#)). The administration of the 2-dose inactivated, recombinant zoster vaccine is not contraindicated in individuals with immunosuppression due to disease or therapy. If a subject cannot receive the zoster vaccine because it is not approved/licensed or locally available, or not clinically indicated, as determined by the investigator, then testing for VZV IgG antibody titer will not be performed.

10.2.9. Ileocolonoscopy

Planned time points for the ileocolonoscopy are provided in the Schedules of Assessments ([Appendix 1](#)). The first video ileocolonoscopy should be performed at least 5 days before the Day 1 (Baseline) Visit to obtain central reading for eligibility assessment. Ileocolonoscopy to determine study eligibility should be performed after most other screening assessments are completed and results are available. At the other study visits, where video ileocolonoscopy will be performed (including the ET Visit, if applicable), the procedure should be performed on the day of the visit or no more than 5 days prior to the visit date ([Appendix 1](#)).

A repeat video ileocolonoscopy is NOT required if the ET Visit occurs within 6 weeks after Baseline/Day 1 or Week 14 Visit of SSA-P2, SS1-P2b, or SS2-I or within 6 weeks after Week 52 Visit of SSA-P2. No additional ileocolonoscopy is required if a subject's ET Visit occurs after the M-38 Visit.

To ensure quality data and standardization, the same endoscopist should be used throughout the study wherever possible. Endoscopy images will be obtained during each endoscopy and will be sent for central reading. 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 centrally read SES-CD score will be used for eligibility determination as well as determination of efficacy endpoints; however, treatment decisions will be made by the treating Investigator. Any endoscopy report and any photographs and/or video recordings taken during the procedure per local custom should be filed in subject's medical record.

10.2.10. Ileocolonoscopy Biopsy Collection

Biopsies will be obtained at each endoscopy to support assessment of the histopathology and, where permitted, for the assessment of exploratory biomarkers. The original location of biopsy specimens acquired at Screening must be clearly indicated. Detailed instructions for endoscopic biopsies (eg, number of biopsies, anatomic site, normal or inflamed mucosa) will be provided in the laboratory manual.

Biopsy samples will be processed and scored [eg, Robarts Histopathology Index, global histologic disease activity ([Novak 2017](#))] by a central laboratory. Histopathological scores and biomarker results will not be made available to study sites.

If additional biopsy samples are needed (eg, missing histological diagnosis of CD at screening, safety concerns, or suspicious findings during colonoscopy), additional biopsies should be collected and analyzed locally. Any documentation must be available prior randomization.

10.3. Eligibility Assessments for Substudy 3 – Maintenance

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

10.3.1. Ongoing Therapies

Updates to medications or procedures prior to dosing at the MFD Visit should be made as needed to the appropriate eCRF.

10.3.2. Pregnancy Testing

A urine pregnancy test for β -hCG will be performed on FOCBP to determine eligibility. Following the MFD Visit, urine pregnancy tests (β -hCG) should be performed predose as indicated in the Schedule of Assessments ([Appendix 1](#); [Table 32](#)). In non-visit months after the Week 20 Visit, a monthly home pregnancy test should be performed in countries where allowed per local regulation and any positive result immediately reported to the study site. If not allowed per local regulations, this pregnancy test will be performed on site during an unscheduled visit. If a subject at any time in the study cannot come into the study site for a visit, a pregnancy test must be performed at home and any positive result should be immediately reported to the study site.

If at any point there is a case of a positive urine β -hCG test, the subject will have study drug interrupted and a serum sample will be submitted to the central laboratory for β -hCG testing. If the serum test confirms positive, the subject will be discontinued from the study drug and all the necessary follow-up will be conducted as per Section [10.7.10](#). If the serum test is negative, the subject may resume study drug.

Negative pregnancy test results must be documented for all FOCBP prior to dosing at applicable study visits.

10.4. Eligibility Assessments for Substudy 4 – Long-Term Extension

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

10.4.1. Ongoing Therapies

Updates to medications or procedures prior to dosing at the Day 1 Visit should be made as needed to the appropriate eCRF.

10.4.2. Pregnancy Testing

A urine pregnancy test for β hCG- will be performed on FOCBP to determine eligibility. Following the EFD Visit, urine pregnancy tests (β hCG-) should be performed predose as indicated in the Schedule of Assessments ([Appendix 1](#); [Table 33](#)). In non-visit months, a monthly home pregnancy test should be performed in countries where allowed per local regulation and any positive result immediately reported to the study site. If not allowed per local regulations, this pregnancy test will be performed on site during an unscheduled visit. If a subject at any time in the study cannot come into the study site for a visit, a pregnancy test must be performed at home.

If at any point there is a case of a positive urine β -hCG test, the subject will have study drug interrupted and a serum sample will be submitted to the central laboratory for β -hCG testing. If the serum test confirms positive, the subject will be discontinued from the study drug and all the necessary follow-up will be conducted as per Section [10.7.10](#). If the serum test is negative, the subject may resume study drug.

Negative pregnancy test results must be documented for all FOCBP prior to dosing at applicable study visits.

10.5. Efficacy Assessments

The efficacy assessments detailed below apply to ALL substudies, unless stated otherwise. Planned time points for all efficacy assessments are provided in the Schedules of Assessments ([Appendix 1](#)).

10.5.1. Simple Endoscopic Score in Crohn's Disease

The SES-CD is an endoscopic grading system that consists of a composite score based on 4 components: the size of mucosal ulcers, the extent of the ulcerated surface, the endoscopic extension, and the presence of stenosis. Each of the four SES-CD components are assessed in the 5 segments of the ileum and colon: ileum, right, transverse, left, and rectum. The SES-CD is the sum of the individual scores of each of the components across the 5 segments. The SES-CD variables and scoring are included in [Appendix 3](#).

Planned time points for the ileocolonoscopy for SES-CD are provided in the Schedules of Assessments for each substudy ([Appendix 1](#)). For subjects in the SS3-M Responder Cohort that experience a LOR and switch to the Nonresponder Cohort, an ileocolonoscopy for SES-CD should occur 52 weeks after the Nonresponder First Dose Visit instead of at the M-38 Visit.

10.5.2. Crohn's Disease Activity Index and Patient-Reported Outcome 2

The CDAI consists of 8 variables. Two of these, the AP and general well-being, are subjective and related to the disease, and each is weighted according to its ability to be predictive of disease activity. SF, hematocrit value, use of anti-diarrheal medications, body weight, assessment for EIMs of CD, and presence/absence of an abdominal mass are also needed for the CDAI calculation. The total score ranges from zero to over 600. The CDAI variables and weighting factors are listed in [Table 35](#) in [Appendix 4](#).

The CDAI to qualify for randomization in SSA-P2, SS1-P2b, and SS2-I will be evaluated during the Screening Period. Subject-reported components of the CDAI (SF, AP, general well-being, whether the subject experienced a fever greater than 100°F [37.8°C] and if the subject took any anti-diarrheal medications) will be collected daily in an eDiary using data from the most recent 7-day period prior to the first day of bowel preparation for the screening ileocolonoscopy (refer to [Section 10.2.9](#)). The remaining components of the CDAI will be collected by the site, and the score will be calculated electronically.

Beginning on Day 1, for visits without endoscopy, the CDAI will be calculated using the 7-day period prior to the day of the visit. For visits when an endoscopy occurs, the CDAI will be calculated from the most recent 7-day period prior to the first day of bowel preparation for ileocolonoscopy. A minimum of 3 days of non-missing data at a visit is required to calculate or derive the CDAI for the visit. A detailed description of CDAI missing data handling, calculation, or derivation will be specified in the Statistical Analysis Plan (SAP).

In addition to the CDAI score, 2 variables of the CDAI, the daily AP and SF scores, are used (without the CDAI weighting factor) to determine study eligibility and as an efficacy endpoint. Loose/watery stool for the loose/watery SF score is defined as Type 6 ("fluffy pieces with ragged edges, a mushy stool") or Type 7 ("watery, no solid pieces, entirely

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liquid”) on the Bristol Stool Form Scale (refer to [Appendix 5](#)). The reported score for diarrhea is the average over 7 days of the number of loose/watery stools per day. The reported score for AP is the average worst daily AP score over 7 days. A minimum of 3 days of non-missing data is required to calculate the AP and SF scores.

The PRO2 is a patient-reported outcome based on the SF and AP components of the CDAI ([Khanna 2015](#)). The CDAI weighting factors for the SF and AP variables will be used to calculate the PRO2.

Planned time points for the CDAI assessments are provided in the Schedules of Assessments for each substudy ([Appendix 1](#)).

10.5.3. Extraintestinal Manifestations

During the physical examinations (Section [10.7.2](#)), specific systems (such as eyes, skin, and joints) will be examined for EIMs for CD.

10.5.4. Biomarkers

Collection of samples for biomarker assessments, in particular those associated with inflammation and lymphocyte trafficking, is also part of this study. The following samples for biomarker assessments are required and will be collected from all subjects in this study as specified in the Schedules of Assessments for each substudy ([Appendix 1](#)).

- Blood
- Stool
- Endoscopic tissue

Blood, stool, and tissue samples will be analyzed by the central or specialty laboratory. Details for collection, processing, and storage will be provided in the Laboratory Manual. Residual samples will be stored and may be used for additional analyses if the subject has granted consent where allowed by the regulatory authorities and local ethics committees.

In addition to the efficacy assessment biomarkers described in this section, exploratory biomarker analyses will be performed in SSA-P2 and SS1-P2b as described in Section [10.11](#).

10.5.4.1. C-Reactive Protein

CRP is an acute phase protein expressed by hepatocytes in response to inflammatory cytokines. Serum CRP will be assessed using a high sensitivity (hs)-CRP assay. For subjects who enroll into the double-blind, placebo-controlled substudies SS1-P2b, SS2-I, or SS3-M, Investigators will be blinded to the hs-CRP results during the treatment period and until after the EFD Visit of SS4-E.

10.5.4.2. Lymphocyte Count

Etrasimod is believed to modulate lymphocyte trafficking resulting in a reduction of peripheral lymphocyte count (inclusive of B cell and T cell subsets); thus, lymphocytes that are usually recruited to sites of inflammation where tissue destruction occurs are sequestered in the lymph nodes. Lymphocyte count will be determined based on the WBC and the WBC differential. TBNK cell counts will also be assessed. To prevent unintentional unblinding of treatment assignment, post-randomization WBC differentials and TBNK panel cell counts

will not be released to the Investigator until after the EFD Visit EXCEPT with the emergence of advanced immunosuppression which may require treatment interruption and closer monitoring for infections by the Investigators (Section 10.7.8.2). During the time when the Investigator is blinded to lymphocyte counts, lymphocyte and TBNK panel cell counts will be monitored by a

Medical Monitor (not providing direct medical oversight of study conduct), who will provide instructions to the site Investigator when actions are required as specified by the study protocol (Section 10.7.8.2).

10.5.4.3. Fecal Calprotectin

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

10.6. Pharmacokinetic Assessments

Blood samples for analysis of etrasimod will be collected from all subjects who received ≥ 1 dose of study drug (etrasimod or placebo) at the timepoints described in [Appendix 1](#).

Subjects should be instructed to document the time of their last dose prior to the study visit (Section 7.4) and the time must be recorded in the eCRF. The time of administration of study drug during the study visits where PK samples are obtained must also be recorded in the source along with the time of each PK sample.

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

No urine samples will be collected for PK analysis.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

10.7. Safety Assessments

The safety assessments described in this section apply to ALL substudies, unless stated otherwise. Planned time points for all safety assessments are provided in the Schedules of Assessments ([Appendix 1](#)).

10.7.1. Vital Signs

Resting vital signs measurements will be made in the seated position and include HR, BP, body temperature, and respiratory rate. Vital signs will be measured prior to any blood draws that occur at the same study visit or overlapping time point. Planned time points for vital signs assessments are provided in the Schedules of Assessments for each substudy ([Appendix 1](#)).

To minimize the risk of unintentional unblinding of treatment assignment, refer to guidance regarding disclosure of HR data discussed in Section 6.6.

10.7.2. Physical Examinations

Full physical examination includes the following assessments:

- General inspection, including height (Screening only) and weight
- Head/ears/eyes/nose/throat examination
- Neck
- Cardiac examination
- Visual acuity test
- Auscultation of lungs
- Abdominal examination (liver, spleen, and lower abdomen)
- Neurological assessment
- Musculoskeletal assessment to include lower extremity edema evaluation
- Dermatologic assessment
- Perianal inspection and palpation for the presence and number of fistulas (open vs closed) and active drainage

Planned time points for physical examinations are provided in the Schedules of Assessments for each substudy ([Appendix 1](#)). For visits where a full physical examination is not required, symptom-directed physical examination should assess clinically significant changes from prior study visits including the baseline physical examination or any new signs or symptoms. Symptom-directed physical examination may be performed at the Investigator's discretion at any time during the study. In addition to symptom-directed physical examination, assessment at each study visit should include, at a minimum, measurement of weight and a physical examination that assesses the presence of abdominal mass and physical signs consistent with all of the following EIMS of IBD: arthritis/arthralgias, iritis/uveitis, erythema nodosum, pyoderma gangrenosum, aphthous stomatitis, anal fissure, anal abscess, anal fistula and other types of fistulas. The presence of a draining anal fistula (per the CDAI) will trigger a specific fistula assessment at this visit and at each subsequent visit until the fistula has been closed for 2 consecutive study visits. Findings will be documented in the eCRF.

10.7.3. Electrocardiography

All ECGs will be recorded from a 12-lead ECG machine. Every attempt should be made to ensure the subject ECG readings are obtained using the same machine throughout the study.

All ECGs will be recorded with subjects in supine position. Planned time points for ECG are provided in the Schedules of Assessments for each substudy ([Appendix 1](#)).

Intervals to be provided on the confirmed read for each safety ECG are: RR, PR, QRS, QT, and QTcF. If an ECG shows a new onset QTc interval above 500 ms (CTCAE Grade 3) during the treatment period, a repeat ECG is warranted, and, if this abnormal finding is

confirmed and is considered related to study drug, then study drug must be interrupted. Effective diagnostic and therapeutic strategies should be employed.

Reversible causes of prolonged QTc interval (eg, electrolyte abnormalities like hypokalemia and hypomagnesemia), should be corrected as clinically indicated. When evaluating a subject with new onset QTc interval above 500 ms, referral to a physician experienced in treating cardiac conduction disorders should be considered. If treatment is interrupted, re-initiation of study drug can only be considered if the QTcF interval is < 450 ms (males) or < 470 ms (females), the prolonged QTc interval is not considered related to study drug, the individual risk-benefit is favorable (as determined by the Investigator, in agreement with the cardiologist), and after discussion with the Medical Monitor. If, after re-initiation, the QTc interval is again prolonged above 500 ms, then study drug must be discontinued.

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

Specific guidance on ECG following the first dose of study drug is provided in Section 10.7.8.4.

10.7.4. Continuous Holter Monitoring

Continuous 24-hour Holter monitoring will be performed in SSA-P2 and SS1-P2b according to the Schedules of Assessments (Appendix 1; Table 29 and Table 30). On the indicated study days, the Holter monitor will be placed on the subject at the study site, and continuous Holter monitoring will begin at least 15 minutes predose. Once all study assessments for the visit are completed, subjects will be released from the study site with the Holter monitor in place, and continuous monitoring will be performed until at least 24 hours postdose. Subjects will remove the Holter monitor at home and may return the device at the next scheduled study visit.

Additional details about Holter monitoring procedure will be provided in the Holter Manual.

10.7.5. Clinical Laboratory Assessments

Details regarding clinical laboratory sample collection, preparation, and shipment are provided in the laboratory manual by the central laboratory. All laboratory assessments required by the protocol will be performed by a central laboratory unless otherwise stated (eg, issues with sample transport to the central laboratory, or samples being canceled by the central laboratory) or warranted due to special circumstances (eg, inability to ship to central laboratory due to COVID-19 restrictions or other emergencies). Refer to Table 15 for the list of clinical laboratory tests to be performed and the Schedules of Assessments for each substudy (Appendix 1) for timing and frequency for each test.

Clinical safety laboratory tests should be completed predose. Subjects should fast for 9 to 12 hours (drinking water only) before study visits that include blood sample collection for the lipid panel (applies only to subjects in substudies SSA-P2 and SS1-P2b). The Investigator must review the laboratory report, document the review, and record any clinically relevant changes on the AE section of the eCRF (results of the WBC differential and ALC will be reviewed and monitored as described in Section 10.7.8.2). The laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal (ie, those that are AEs) during participation in the study or within 30 days after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator. If such values do not return to normal or baseline, or otherwise resolve to a value that is not clinically significant within a reasonable period of time, as judged by the Investigator, the etiology should be identified, and the Medical Monitor should be notified. In cases when laboratory values from non-protocol-specified assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the Investigator (eg, AE or dose modification), then the results must be recorded in the eCRF.

Information on the grading and management of laboratory abnormalities according to assessed severity is provided in [Appendix 6](#) and [Appendix 7](#).

See [Appendix 10](#) for suggested actions and follow-up assessments in the event of potential DILI.

Table 15: Clinical Laboratory Tests

<u>Infectious Disease</u> HIV, Hepatitis B surface antigen, IgM anti-hepatitis B core (if reactive, reflex to HBV DNA quantification), HCV antibody (if reactive, reflex to HCV DNA quantification), TB ^a , VZV IgG (only if the zoster vaccine is clinically indicated for a subject, as determined by the investigator, and the vaccine is approved/licensed and locally available in the country of residence)		<u>Drugs of Abuse</u> Amphetamine, barbiturates, benzodiazepines, cocaine, methadone, methamphetamine, methylenedioxymethamphetamine, opiate, oxycodone, phencyclidine
<u>Pregnancy and Postmenopausal Status Testing</u> Serum pregnancy test for β -hCG (Screening; FOCBP only) Urine β -hCG (FOCBP only) FSH (Screening; postmenopausal women only)		<u>Coagulation</u> International normalized ratio (INR) Activated partial thromboplastin time
<u>Urinalysis</u> Appearance Bilirubin Color Glucose Ketones Microscopic examination of sediment	Nitrite Occult blood pH Protein Specific gravity Urobilinogen	<u>Hematology</u> Hematocrit Hemoglobin Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular volume Platelet count Red blood cell count White blood cell count with differential ^b TBNK panel cell counts ^b
<u>Serum Chemistry</u> Albumin Alkaline phosphatase		Potassium Sodium

Table 15: Clinical Laboratory Tests

Alanine aminotransferase	Total bilirubin
Aspartate aminotransferase	Direct bilirubin
Bicarbonate	Total protein
Blood urea nitrogen	Thyroid-stimulating hormone
C-reactive protein (hs-CRP)	Total cholesterol
Calcium	LDL cholesterol
Chloride	HDL cholesterol
Creatinine	Triglycerides
Creatine kinase	Uric acid
Glucose	
<u>Stool Sample^c</u>	
Fecal calprotectin ^d	
Ova and parasites, bacterial culture, and <i>C. difficile</i>	
<u>Exploratory biomarkers</u>	
Immunophenotyping	
Proteomics	
RNA transcriptomics	
Fecal microbiome	
Genomic DNA (optional)	

a. TB screening will be done at Screening and annually via a central laboratory IGRA (eg, QuantiFERON-TB PLUS or equivalent assay) in all subjects except those with a history of active or latent TB.

b. Results of the white blood cell count with differential and TBNK panel cell counts will be assessed by an unblinded Medical Monitor during SSA-P2, SS1-P2b, SS2-I, and SS3-M and through the EFD Visit of SS4-E as described in Section 10.7.8.2. Investigators will remain blinded to the results during this time.

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

d. Fecal calprotectin should also be obtained at any time during the study when subjects have new or worsened Crohn's disease symptoms suggestive of disease relapse or progression. Investigators will remain blinded to the results.

β-hCG, beta-human chorionic gonadotropin; *C. difficile*, *Clostridioides difficile*; FOCBP, female of child-bearing potential; FSH, follicle-stimulating hormone; HCV, hepatitis C virus; HIV, human immunodeficiency virus; hs-CRP, high-sensitivity C-reactive protein; IgG, immunoglobulin G; IgM, immunoglobulin M; IGRA, interferon-gamma release assay; SSA-P2, Substudy A - Phase 2; SS1-P2b, Substudy 1 – Phase 2b; SS2-I, Substudy 2 – Induction; SS3-M, Substudy 3 – Maintenance; SS4-E, Substudy 4 – Long-Term Extension; TB, tuberculosis; TBNK, T Cell, B Cell, and natural killer cells; VZV, varicella zoster vaccine

10.7.6. Pulmonary Function Test

Subjects with known active severe pulmonary disease (eg, chronic obstructive pulmonary disease or pulmonary fibrosis) or chronic pulmonary disease requiring IV corticosteroid treatment or hospitalization ≤ 12 months prior to Screening, or during Screening will be excluded from the study. Subjects with FEV₁ or FVC < 70% of predicted values at Screening will also be excluded from the study.

PFTs will be performed according to the Schedules of Assessments for each substudy (Appendix 1) and include FEV₁, FVC, and forced expiratory flow at 25% to 75% measurements. Where locally available, DLCO measurements will also be performed (sites

where DLCO is not available should consult the sponsor or sponsor's delegate). Because carbon monoxide binds readily to hemoglobin, the diffusion capacity needs to be corrected for hemoglobin in order to reflect an altered lung gas transport rather than altered hemoglobin. All DLCO values will be corrected for hemoglobin concentration (ie, hemoglobin-adjusted diffusion capacity) in the study.

PFTs and DLCO will be conducted in all subjects in a manner consistent with 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](#)).

Patient respiratory history will be collected at the Screening Visit, and any condition that might affect the outcome of PFT testing, including infection, respiratory symptoms, occupational exposures (including asbestos) and cigarette smoking, will be collected before every PFT and recorded in the eCRF. Furthermore, any issues with patient effort or compliance with the test procedure should be explicitly recorded in the eCRF. This information is important to determine whether PFT abnormalities may be the result of poor effort or compliance with test procedure. Smoking status will be collected and recorded in the eCRF each time a PFT assessment is conducted.

The window to perform PFTs and DLCO is ± 7 days for all post-screening visits. In addition, subjects reporting any respiratory symptoms (eg, dyspnea, shortness of breath, chest tightness, or wheezing) should be seen at an unscheduled visit for clinical assessment and full PFT assessment, preferably on the same day. Additional guidance on clinical monitoring of pulmonary function is provided in Section [10.7.8.5](#).

10.7.7. Ophthalmoscopy and Optical Coherence

A complete ophthalmoscopy and OCT assessment will be performed according to the Schedules of Assessments for each substudy ([Appendix 1](#)). A standard visual acuity chart should be used for the visual acuity assessment. The OCT machine used should preferably not be changed during the study to allow for comparison of central foveal thickness measurements within each subject across time points.

Screening Visit:

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

- Ophthalmologic history
- Best corrected visual acuity measurement (autorefraction, using Snellen chart internationally)
- Ophthalmoscopy (may include contact lens biomicroscopy to examine the macula and optic disc). A dilated fundus exam should be performed in all subjects at the Screening Visit and as needed at subsequent visits in subjects with significant abnormalities identified on the screening exam
- Measurement of central foveal thickness by OCT (recorded in micrometers; required for all subjects regardless of the results of visual acuity or ophthalmoscopy)

- Retinal photographs should be taken
- Slit lamp examination should be performed to establish uveitis disease status (yes/no). Uveitis should be characterized and graded using the Standardization of Uveitis Nomenclature criteria. Subjects with active uveitis without macular edema at Screening are eligible to enroll in the study. Refer to Section 10.7.8.6 for guidelines for follow-up examination of subjects with active uveitis
- If there is a suspicion of macular edema by ophthalmoscopy and increased central foveal thickness by OCT, then a fluorescein angiogram (FA) may be performed (at the discretion of the ophthalmologist). Subjects with diagnosed macular edema at Screening should be deemed a screening failure and should not be randomized
- Ophthalmic findings should be recorded

Scheduled post-screening visits:

At the scheduled ophthalmology visit, the eye examination will include

- Ophthalmic history
- Best corrected visual acuity measurement
- Ophthalmoscopy (may include contact lens biomicroscopy to examine the macula and optic disc)
- Measurement of central foveal thickness by OCT
- Retinal photographs should be taken
- FA should be considered for subjects with uveitis findings on ophthalmic exam

The window to perform ophthalmology assessment and OCT is ± 7 days for all scheduled post-screening visits. Subjects experiencing unexpected ophthalmic symptoms without a known suspected etiology or experiencing a relevant ophthalmic AE may need to have repeat ophthalmoscopy and OCT testing performed. Guidance on clinical monitoring of ophthalmic symptoms is provided in Section 10.7.8.6.

10.7.8. Safety Monitoring Guidance

10.7.8.1. Drug-Induced Liver Injury

An increase of serum AST or ALT to $> 3 \times$ ULN for subjects with normal baseline measures or 2-fold increases above baseline values for subjects with elevated baseline values should be followed by repeat testing, within 48 to 72 hours, of all 4 of the usual serum measures (ALT, AST, alkaline phosphatase, and total bilirubin [TBL]) to confirm the abnormalities and to determine if they are increasing or decreasing. There also should be inquiry made about symptoms. If symptoms persist or repeat testing shows AST or ALT $> 3 \times$ ULN for subjects with normal baseline measures or 2-fold increases above baseline values for subjects with elevated baseline values, it is appropriate to initiate close observation to determine whether the abnormalities are improving or worsening (eg, repeat liver enzyme and serum bilirubin tests 2 or 3 times weekly). Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is

asymptomatic. It is essential to gather additional clinical and laboratory information necessary for differential diagnosis of the cause.

It is important to observe the time course of the AST or ALT elevation, and to seek alternative causes of the liver injury, such as acute viral hepatitis A, B, C, D, or E; concomitant use of a hepatotoxic drug or exposure to hepatotoxins; autoimmune or alcoholic hepatitis; biliary tract disorders; and circulatory problems of hypotension or right heart congestive failure that may cause ischemic or hypoxic hepatopathy. As appropriate, obtain additional tests to evaluate liver function (eg, international normalized ratio [INR], direct bilirubin). It is also prudent to assess the subject for previously existing liver disease, such as chronic hepatitis C or nonalcoholic steatohepatitis (NASH), that may or may not have been recognized before exposure to study drug.

There is no published consensus on exactly when to stop a drug in the face of laboratory abnormalities and the decision may be affected by the clinical status of the patient and many other factors. The following can be considered a basic guide. When there is no alternative etiology for persistently elevated liver enzymes, discontinuation of study drug should be considered, consistent with the FDA Guidance ([FDA 2009](#)), if:

- ALT or AST $> 8 \times$ ULN
- ALT or AST $> 5 \times$ ULN for more than 2 weeks
- ALT or AST $> 3 \times$ ULN **and** (TBL $> 2 \times$ ULN **or** INR > 1.5) if baseline was normal (or ALT or AST $> 3 \times$ baseline **and** [TBL $> 2 \times$ baseline **or** INR > 1.5] if baseline was abnormally elevated)
- ALT or AST $> 3 \times$ ULN if baseline was normal (or ALT or AST $> 3 \times$ baseline if baseline was abnormally elevated) with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($> 5\%$)

Information on the grading and management of laboratory abnormalities according to assessed severity is provided in [Appendix 6](#) and [Appendix 7](#). Information on potential DILI is provided in [Appendix 10](#).

10.7.8.2. Lymphocyte Counts and Infections

Etrasimod prevents lymphocyte egress from lymphoid tissues, resulting in a reduction in peripheral lymphocyte count and lymphocyte availability for recruitment to sites of inflammation. To minimize the risk of unintentional unblinding of treatment assignment, site staff including Investigators will be blinded to the WBC differential (percentage and absolute number) and TBNK panel cell counts during SSA-P2, SS1-P2b, SS2-I, and SS3-M. While the sites are blinded to WBC differential and TBNK panel cell counts, these laboratory results will be assessed by an unblinded Medical Monitor (not involved in any other aspects of study conduct or data analysis). Investigators should minimize review of WBC differential results obtained by other health care providers caring for study subjects when review of those data is not required to ensure the safety of study subjects.

If the ALC is confirmed below the 200 cells/ μ L limit, study drug should be interrupted and should not be reinitiated if the ALC remains below this threshold. If the Investigator is

blinded to lymphocyte counts (ie, through the EFD Visit), the unblinded Medical Monitor will notify the Investigator and provide instructions on additional actions that the investigator may need to take. When there is at least 1 measurement of $ALC < 200$ cells/ μ L, blinded values may be released to treating physicians and Investigators as deemed medically necessary to monitor the risk of infection and/or aid in diagnostic work-up as clinically indicated, and/or as a tool to assess the effectiveness of therapeutic interventions for an infection. Investigators will repeat complete blood count with differentials weekly until $ALC > 500$ cells/ μ L.

Re-initiation of the study drug can only be considered when $ALC > 500$ cells/ μ L.

Refer to Section 10.7.8.3 for information on monitoring for signs and symptoms of infections and diagnostic work-up and treatment of infections.

10.7.8.3. Guidance on Monitoring Subjects for Infections

Low lymphocyte counts with the use of other S1P receptor modulators in patients with multiple sclerosis have been associated with serious and atypical infections ([GILENYA 2010](#), [MAYZENT 2019](#)). To date, there have been no reports of PML with the use of etrasimod in clinical studies. Nevertheless, Investigators should remain vigilant in monitoring for signs and symptoms of serious and atypical infections during the study and after discontinuation of study drug (ie, the 28-day post-treatment period).

If a subject exhibits signs and symptoms suspicious for PML, study drug must be interrupted and cannot be restarted until diagnostic evaluation is completed and PML has been excluded. The Medical Monitor should be informed of any suspected cases of PML. Refer to [Appendix 8](#) for PML signs and symptoms and case evaluation algorithm. In the evaluation and management of treatment-emergent infections, the Investigator may consult with infectious disease or relevant experts, as needed.

All radiologic images (eg, magnetic resonance imaging, computer tomography, X-rays) and diagnostic laboratory test results performed by local laboratories/facilities should be retained as source documents by study sites and made available upon request by the Sponsor for central adjudication as needed. All infections that develop during the study will be reported as AEs on the respective eCRF pages.

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

Cardiac monitoring following treatment initiation applies to the first dose administered at the following visits:

- SSA-P2, SS1-P2b and SS2-I Day 1 Visits
- EIFD Visits of SS1-P2b and SS2-I
- EFD Visit of SS4-E for subjects entering from SS3-M Responder Cohort
- SS3-M Nonresponder First-Dose Visit for subjects who experience loss-of-response during the maintenance treatment

Pre-randomization (ie, Baseline) vital signs (resting HR, BP, body temperature, and respiratory rate) will be used as the baseline measurements. The lowest predose HR

measurement will be used for comparison to the postdose measurement. Subjects should receive the first dose of study drug before 12:00 PM (noon).

To minimize the risk of unintentional unblinding of treatment assignment, refer to guidance regarding disclosure of HR data discussed in Section 6.6.

First Dose Heart Rate Monitoring

In-clinic cardiac monitoring, of at least 4 hours following the first dose will include the following (Table 16):

- Full baseline vital signs (HR, BP, body temperature, and respiratory rate) and 12-lead ECG will be assessed pre-randomization (ie, baseline)
- After the first dose of study drug, subjects must remain under direct observation in the clinic for at least 4 hours
- At Hours 1, 2, and 3 ($\pm$ 15 minutes) postdose, the HR and BP will be assessed with the subject in the seated position, with the time recorded. If the subject has a HR < 50 bpm, or if cardiovascular symptoms develop, the subject should remain closely monitored, including 12-lead ECGs as clinically indicated, until the Hour 4 discharge assessment
- At the Hour 4 ($\pm$ 15 minutes) discharge assessment, HR and BP will be assessed with the subject in the seated position and a 12-lead ECG in the supine position will also be performed. Subjects may be discharged from the clinic after the 4-hour assessment if they meet the criteria described in Table 17. 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, and/or syncope) associated with reduction of the HR together with clinically relevant 12-lead ECG changes at any time during the 4-hour monitoring period should be discontinued from study drug (Table 18)

Table 16: Procedures to be Performed During the Cardiac Monitoring Period

Procedure	Predose	Hours 1, 2, and 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 $\pm$ 15 minutes of the scheduled time.

^b Heart rate is based on vital signs.

ECG, electrocardiogram

Table 17: Discharge Criteria After Cardiac Monitoring

Subjects will be released from the clinical site after dosing (but no sooner than 4 hours postdose) when they fulfill the following discharge criteria:
Heart rate $\geq$ 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; bpm, beats per minute

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 a 12-lead ECG may be performed, as clinically indicated, until the subject meets the discharge criteria (Table 17)
- The Medical Monitor should be contacted if the subject does not meet the discharge criteria after $\geq$ 4 hours of extended cardiac monitoring
- Any subject who requires extended monitoring after the first dose must return the next day for the second dose and will be re-monitored as for the first dose. These subjects will be discontinued from study drug if they do not meet the discharge criteria at 4 hours after the second dose. Extended cardiac monitoring should be continued until the subject meets the discharge criteria (Table 17)
- Subjects experiencing a symptomatic event (eg, chest pain, dizziness, palpitations, lightheadedness, shortness of breath, and/or syncope) at any time during the 4-hour monitoring period that is not associated with either a reduction in HR or clinically relevant change in 12-lead ECG, may be discharged provided they meet the discharge criteria (Table 17), and deemed appropriate by the Investigator; however, these subjects must return the next day for the second dose and will be re-monitored as for the first dose. These subjects should be discontinued from treatment if they do not meet the discharge criteria at 4 hours after the second dose and extended cardiac monitoring should be continued until the subject meets the discharge criteria (Table 17)

Study Drug Discontinuation Related to Postdose Cardiac Monitoring

A complete list of reasons for study drug discontinuation is provided in Section 8.1. Reasons for study drug discontinuation specific to postdose cardiac monitoring are provided in Table 18. The Medical Monitor should be contacted before discontinuing a subject from study drug.

Table 18: Discontinuation of Study Drug Related to Post-Dose Cardiac Monitoring

Reasons for Study Drug Discontinuation Related to Post-dose Cardiac Monitoring ^a
Subjects who have a cardiovascular treatment-related symptomatic event (eg, chest pain, dizziness, palpitations, lightheadedness, shortness of breath, and/or syncope) associated with reduction of the HR or associated with clinically relevant 12-lead ECG changes at any time during the 4-hour monitoring period after the first or second dose (as applicable).
Subjects who have not met the discharge criteria after the first dose after ≥ 4 hours of extended monitoring, or after the second dose by 4 hours postdose.

^a All treatment discontinuations should be discussed with the Medical Monitor.
ECG, electrocardiogram; HR, heart rate

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Additional Cardiac Monitoring for Subjects With Concomitant Beta-Blocker Medication or Other Bradycardia-Inducing Medications (EU Regions Only)

Additional cardiac monitoring is only required for subjects receiving concomitant betablocker medication or other bradycardia-inducing medications (anti-arrhythmic drugs in Class Ib, eg, lidocaine, mexiletine; Class II, eg, metoprolol, propranolol, atenolol; or Class IV, eg, verapamil, diltiazem) who met criteria for extended monitoring on Day 1 or any prior first dose heart rate monitoring. This additional monitoring will occur on the day of (blinded) dose escalation to etrasimod 3 mg:

- SSA-P2 Week 1 and Week 15
- SS1-P2b Week 1 and extended induction Week 1 (EI-W1) visit
- SS2-I Week 1 and EI-W1 visit
- SS3-M loss-of-response dose-escalation visit
- SS4-E E1 visit

Additional cardiac monitoring will be the same as the procedures listed for the first dose heart rate monitoring and in [Table 16](#) and [Table 17](#). Subjects experiencing a clinically relevant treatment-related symptomatic event should be discontinued from study drug as described for first dose heart rate monitoring and in [Table 18](#).

Continuous 24-Hour Holter Monitoring

Continuous 24-hour Holter monitoring will be performed from at least 15 minutes predose until at least 24 hours postdose in SSA-P2 and SS1-P2b according to the Schedule of Assessments ([Appendix 1](#); [Table 29](#) and [Table 30](#)).

Cardiac Monitoring Upon Treatment Re-Initiation Following Dose Interruption

The requirement for cardiac monitoring upon treatment re-initiation following dose interruption described in this section applies to all substudies. The procedure for first dose cardiac monitoring as outlined should be performed any time a subject misses study drug for ≥ 2 consecutive days within the first week of treatment during SSA-P2, SS1-P2b, SS2-I, and SS4-E (SS3-M, Responder Cohort only) or within the first week of treatment during the EI Periods of SS1-P2b and SS2-I. After the first week of treatment, the procedure for first dose cardiac monitoring should be performed and discussed with the Medical Monitor any time a subject misses study drug for ≥ 7 consecutive days. Holter monitoring will not be performed after treatment re-initiation.

10.7.8.5. Pulmonary Function Monitoring

Based on changes in pulmonary function observed with the use of S1P receptor modulators fingolimod and siponimod, approved for relapsing multiple sclerosis ([GILENYA 2010](#), [MAYZENT 2019](#)), pulmonary function will be assessed in this study. PFTs will be performed according to the Schedules of Assessments ([Appendix 1](#)).

Subjects experiencing clinically significant dyspnea or other respiratory AEs, may need to have additional PFT testing as clinically indicated. Severity of respiratory AEs should be

categorized using the CTCAE scale described in [Appendix 6](#). Investigators should consider interruption of study drug when there is a clinically significant respiratory AE considered related to study drug that leads to limitations in instrumental or self-care activities of daily living. The decision to interrupt study drug should be discussed with the Medical Monitor. Subjects should be promptly referred to a pulmonologist for further evaluation and treatment. The pulmonologist should be provided with a standard referral letter explaining the reason for the referral along with information about the investigational drug. Clinically significant respiratory AEs should be followed until there is stability, improvement, or resolution.

Re-initiation of study drug can only be considered if the respiratory AE has improved, stabilized, and/or resolved, and is not considered related to study drug; the individual risk-benefit is favorable (as determined by the investigator, in agreement with the pulmonologist); and after discussion with the Medical Monitor.

10.7.8.6. Ophthalmic Symptom Monitoring

Subjects experiencing unexpected ophthalmic symptoms, including blurred vision, decreased visual acuity, or other clinically significant ocular AEs, without a known/suspected etiology may need to have repeat ophthalmoscopy and OCT testing performed. If there is evidence of new onset macular edema considered related to study drug, then study drug should be interrupted as appropriate and the subject should be monitored closely with the appropriate diagnostic and clinical work-up.

Unscheduled ophthalmology visits in case of any visual complaint:

If, during the study, there are complaints of decreased vision or identification of worsening visual acuity (equal to or more than 2 lines on a standard eye chart using best corrected vision) then an unscheduled ophthalmic examination should be performed.

At an unscheduled ophthalmology visit, the eye examination will include

- Best corrected visual acuity measurement
- Ophthalmoscopy (may include contact lens biomicroscopy to examine the macula and optic disc)
- OCT for all subjects to investigate a suspected diagnosis of macular edema

NOTE: For both scheduled and unscheduled visits, in case of suspected macular edema based on the ophthalmoscopy or a relevant increase of central foveal thickness, then a FA may be performed.

If a subject with or without previous history of uveitis presents with active uveitis without macular edema (as per OCT and/or FA) during the study, the subject may stay on study drug and will receive treatment at the discretion of the local ophthalmologist. If systemic immunosuppressive treatment (other than corticosteroids) is planned for the treatment of uveitis, study drug should be interrupted prior to initiating treatment.

Subjects with active uveitis must have a follow-up ophthalmic examination at 1 month after uveitis diagnosis, and then every 3 months up to the end of the study or until symptoms have stabilized.

Subjects with a diagnosis of macular edema considered related to study drug during the study must interrupt the study drug. These subjects must be followed up monthly with ophthalmologic evaluations until such time as resolution is confirmed or no further improvement is expected by the ophthalmologist (based on a follow-up period of no less than 3 months). These evaluations will include repeat best-corrected visual acuity, fundus examination, and OCT. FA may also be performed at the discretion of the ophthalmologist. If the subject does not show definite signs of improvement on examination by specialist testing (eg, OCT and/or FA) 6 to 8 weeks after interruption of study drug, then therapy for macular edema should be initiated in conjunction with treatment from an ophthalmologist experienced in the management of this condition.

For subjects diagnosed with macular edema, copies of the colored OCT and FA images (if conducted) should be kept by the investigative site as source documents. These documents may need to be submitted for review by an independent panel.

10.7.9. Adverse Events

10.7.9.1. Definitions

10.7.9.1.1. Adverse Event

An AE is any untoward medical occurrence that does not necessarily have a causal relationship with this treatment. An AE 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.

AEs can include, but are not limited to, 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

Additional guidance on the management of AEs according to assessed severity is provided in [Appendix 7](#).

10.7.9.1.2. Serious Adverse Event

An AE should be classified as a serious AE (SAE) if it meets one of the following criteria:

Fatal:	The AE resulted in death.
Life-threatening:	The AE placed the subject at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE 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 AE 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 study drug before conception or during pregnancy.
Medically significant:	The AE 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.

Additionally, in this study, any diagnosis of PML will be considered an SAE.

10.7.9.1.3. 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 AE is at least a reasonable possibility (ie, the relationship cannot be ruled out).

10.7.9.1.4. Events of Special Interest

Potential events of special interest including, but not limited to, those in Section 10.7.8, may be identified based on the mechanism of action of etrasimod and prior experience with other agents acting via a similar mechanism. In addition to appropriate reporting of these events as an AE or SAE, supplementary detailed information may be collected.

10.7.9.1.5. Severity

The severity of each AE will be assessed at the onset by a nurse/or physician. When recording the outcome of the AE the maximum severity of the AE experienced will also be recorded. The severity of each AE will be graded according to the CTCAE:

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.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care activities of daily life (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 AE.
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Additional information on CTCAE grading of AEs is provided in [Appendix 6](#).

10.7.9.1.6. Relationship

The Investigator is obligated to assess the relationship between the study drug and each occurrence of each AE. The AE relationship to study drug must be characterized as one of the following categories:

Not Related (Unrelated = flag 'no' on the AEM Report form)	The AE does not follow a reasonable temporal sequence from administration of the drug, does not abate upon discontinuation of the drug, does not follow a known or hypothesized cause-effect relationship, and (if applicable) does not reappear when the drug is reintroduced, furthermore, there may exist a clear alternative medical explanation (eg, underlying disease state) or association with study procedure or study conduct.
Unlikely Related (Unrelated = flag 'no' on the AEM report form)	The temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
Probably Related (Related = flag 'yes' on the AEM Report form)	The AE follows a reasonable temporal sequence from administration of the drug and cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental, or toxic factors, or other modes of therapy administered to the subject.
Related (Related = flag 'yes' on the AEM Report Form)	The AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to the study drug 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 AE/SAE the Investigator must document in the medical notes that he/she has reviewed the AE 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, the Investigator should 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.

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10.7.9.2. Eliciting, Recording, and Reporting Adverse Events

10.7.9.2.1. Eliciting Adverse Events

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

10.7.9.2.2. Recording Adverse Events

The AE 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 drug administration. If an AE is not resolved or stabilized by this time, the sponsor in consultation with the Investigator will decide whether to continue to monitor the AE or closeout the event in the database if no further follow-up is necessary.

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

Investigator and study personnel will record all AEs 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 SAE Report Form, as appropriate. The following information should be recorded on the AE eCRF:

- Description including onset and resolution dates
- Whether it met SAE criteria
- Severity
- Relationship to study drug 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

10.7.9.2.3. 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 AE.

10.7.9.3. Reporting Serious Adverse Events

All SAEs are subject to reporting requirements.

10.7.9.3.1. Serious Adverse Events

All SAEs, whether or not considered related to study drug, must be immediately reported to Pfizer Safety on the CT SAE Report Form upon awareness **and under no circumstances should the time to report exceed 24 hours of becoming aware of the event.**

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

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

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

10.7.9.3.2. Serious, Unexpected Adverse Drug Reactions

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

The following documents or circumstances will be used to determine whether an AE/ADR is expected:

3. For a medicinal product not yet approved for marketing in a country, the RSI section of a company's IB will serve as the source document in that country
4. Reports that add significant information on specificity or severity of a known, already documented serious ADR constitute unexpected events. For example, an event more specific or more severe than described in the RSI in the IB would be considered "unexpected"

10.7.10. Exposure During Pregnancy and Breastfeeding

10.7.10.1. Exposure During Pregnancy and Breastfeeding

If at any point any pregnancy test is positive, the subject will be withdrawn from the study drug.

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

Pregnancy (during maternal or paternal exposure to study drug) does not meet the definition of an AE; however, to fulfill regulatory requirements, any pregnancy and/or pregnancy outcome should be reported to Pfizer Safety via the CT SAE Report Form and the EDP Supplemental Form **within 24 hours of awareness.**

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.

10.7.10.2. Exposure During Breastfeeding

An exposure during breastfeeding (EDB) occurs if:

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

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form and the EDP supplemental form

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

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

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

10.7.11.1. Exposure During Pregnancy

An environmental exposure during pregnancy (EDP) occurs if:

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

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

10.7.11.2. Exposure During Breastfeeding

An environmental EDB occurs if:

- A female nonparticipant is found to be breastfeeding while being exposed or having been exposed to study intervention.

When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

10.7.11.3. Occupational Exposure

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

10.7.12. Lack of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Refer to Section 8.1 for circumstances which may lead to discontinuation from study treatment. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE**.

10.7.13. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength. Medication errors not associated with an AE/SAE should be recorded as a protocol deviation.

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

10.8. Procedures for Overdose

The current edition of the Investigator's Brochure 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:

5. Closely monitor the subject for any AE/SAE and laboratory abnormalities and follow AE reporting process, including contacting the Medical Monitor
6. Obtain a plasma sample for PK analysis within 7 days from the date of the last dose of study drug, if possible, and if requested by the Medical Monitor
7. 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 drug. 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.

10.9. Health-Related Patient-Reported Outcomes

Patient-reported quality of life instruments will be completed electronically and checked for completeness as indicated in the Schedules of Assessments for each substudy ([Appendix 1](#)) and will be used in support of the efficacy outcomes. In order to gain the most objective results possible, all health-related PRO questionnaires should be completed by the subject prior to performing any other study-related procedure for the visit and prior to any study-specific discussion of how they are feeling. The study site staff should check for completion of all PRO questionnaires, while the subject is still present for the study visit. PROs should be completed in the following order: CD-PRO/SS, IBDQ, PGIC, AP NRS, FACIT-F, EQ-5D-5L, WPAI-CD, SF-36v2, CD related hospitalizations and surgeries.

10.9.1. Inflammatory Bowel Disease Questionnaire

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

10.9.2. Crohn's Disease Patient-Reported Outcomes

The Crohn's Disease Patient-Reported Outcomes Signs and Symptoms (CD-PRO/SS) is a validated instrument designed to assess the signs, symptoms, and impact of CD through 6 modules: Module 1 (Bowel Signs and Symptoms), Module 2 (Abdominal Symptoms), Module 3 (Systemic Symptoms), Module 4 (Coping Strategies), Module 5 (Daily Life Impact), and Module 6 (Emotional Impact) ([Higgins 2018](#)). CD-PRO/SS will not be assessed in SSA-P2.

10.9.3. Abdominal Pain Numerical Rating Scale

The AP numerical rating scale (NRS) is a single item that measures the "worst abdominal pain in the past 24 hours" using an 11-point NRS ranging from zero (no pain) to 10 (pain as bad as can imagine). AP NRS will not be assessed in SSA-P2.

10.9.4. Medical Outcomes Study 36-Item Short Form Health Survey

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

10.9.5. EuroQoL-5 Dimensions 5-Level Version

The EuroQoL-5 Dimensions 5-level version (EQ-5D-5L) is a widely used quality of life instrument developed in Europe. The EQ-5D-5L includes 1 question for each of the 5 quality of life dimensions: mobility, self-care, usual activities, pain/discomfort, and

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anxiety/depression. The EQ-5D-5L questionnaire also includes a visual analog scale, by which respondents can report their perceived health status with a grade ranging from 0 (the worst possible health status) to 100 (the best possible health status).

10.9.6. Work Productivity and Activity Impairment Questionnaire

The Work Productivity and Activity Impairment Questionnaire Crohn's Disease (WPAI CD) consists of 6 questions asking about the effect of CD on the subject's ability to work and perform regular activities.

10.9.7. Patient Global Impression of Change

The Patient Global Impression of Change (PGIC) is a 2 item scale designed to assess a patient impression of the overall change in CD symptoms and whether the change in CD symptoms is meaningful. This questionnaire includes a 7 point Likert scale and is based on a patient's current CD symptoms. PGIC will not be assessed in SSA-P2.

10.9.8. Crohn's Disease-Related Hospitalization and Surgery

Subjects will be queried about CD related hospitalizations and surgery at every study visit. This information will be entered into the eCRF.

10.9.9. Functional Assessment of Chronic Illness Therapy-Fatigue

The Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) scale is a 13-item instrument designed to assess fatigue/tiredness and its impact on daily activities and functioning in a number of chronic diseases. The instrument includes items such as tiredness, weakness, listlessness, lack of energy, and the impact of these feelings on daily functioning (eg, sleeping, and social activities). The FACIT-F scale will not be assessed in SSA-P2.

10.10. Genetic Testing (Substudy A – Phase 2, Substudy 1 – Phase 2b, and Substudy 2 – Induction)

Genetics may be evaluated in this study to assess genetic variation that may impact response to treatment, metabolism, and mechanism of action of etrasimod and for consideration of risks of the disease state.

A blood sample for DNA isolation will be collected from subjects who have consented to participate in the genetic analysis component of SSA-P2, SS1-P2b, or SS2-I, as specified in the Schedules of Assessments ([Appendix 1](#)). Participation is optional. Subjects who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the subject. An additional informed consent form will be provided to subjects for genetic analyses. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

Details on processes for collection and shipment and destruction of these samples are provided in the Laboratory Manual.

10.11. Exploratory Biomarkers

Blood and stool samples and endoscopic tissue samples for exploratory biomarker analysis described in this section are required and will be collected where permitted, as specified in

the Schedules of Assessments ([Appendix 1](#)). Details for collection, processing, and storage will be provided in the Laboratory Manual.

Exploratory analyses may be performed to evaluate biomarker variants thought to play a role in CD and the efficacy and mechanism of action of etrasimod including, but not limited to, exploratory proteomics, transcriptomics, and microbiome analysis to evaluate the association of various biomarkers with the observed clinical responses to etrasimod. Other samples may be used for research to develop methods, assays, prognostics, and/or companion diagnostics related to CD, S1P-mediated cell signaling, and/or the mechanism of action of etrasimod.

10.11.1. Whole Blood Immunophenotyping

Blood will be collected to evaluate immunophenotyping (eg, T cell subsets, B cells, dendritic cell subsets, natural killer cells) in this study to assess disease state and efficacy and mechanism of action of etrasimod. Immunophenotyping will be performed by Epiontis ID. Epiontis ID uses methylation markers specific for different types of immune cells to determine copy number.

10.11.2. Serum Biomarkers/Proteomics

Blood will be collected for exploratory serum biomarkers and proteomic analysis to assess disease state and efficacy and mechanism of action of etrasimod. Proteins will be measured by enzyme-linked immunosorbent assay, proximity extension assay, and/or comparable technology.

10.11.3. Transcriptomics

Blood will be collected for exploratory transcriptomics to be performed by RNAseq or comparable technology to assess disease state and efficacy and mechanism of action of etrasimod.

Intestinal biopsies will be collected during endoscopy for transcriptomics to be performed by RNAseq or comparable technology to assess disease state and efficacy and mechanism of action of etrasimod.

10.11.4. Microbiome

Stool samples will be collected for exploratory microbiome analysis to be performed by 16S ribosomal RNA (rRNA) sequencing or comparable technology to assess the changes in the microbiome associated with disease course and response to etrasimod.

10.11.5. Histopathology of Endoscopic Tissue

In addition to biopsies obtained for the assessment of study eligibility and histopathology endpoints (refer to Section [10.2.10](#)), biopsies, where permitted, may also be collected for immunophenotyping (eg, T cell subsets, B cells, dendritic cell subsets, and natural killer cells) and assessment of other exploratory biomarkers. Such studies will be performed by immunofluorescent histology, in situ hybridization, or Epiontis ID. These analyses will be conducted to further assess disease state and efficacy and the mechanism of action of etrasimod.

11. PLANNED STATISTICAL METHODS

11.1. General Considerations for Overall Study

For this Phase 2/3 study, all 5 substudies will be considered as separate studies. Efficacy data for each substudy will be analyzed separately according to a substudy-specific SAP using its own database. Therefore, statistical considerations related to sample size, type I error rate, and testing procedure are substudy specific and will be described in substudy sections. Further details not described below will be provided in each substudy-specific SAP that will be finalized prior to database lock and unblinding. Safety analyses will be similar across all substudies (Section 11.7). Data analyses that will be performed for the overall study (eg, demographics and baseline characteristics) will be described in the SAP.

For each Phase 3 substudy, the corresponding substudy-specific SAP will describe an overall plan to address the alignment between the target of efficacy estimation (ie, trial objective, or estimand of interest), the analysis set, the method of estimation, and primary method to handle intercurrent events; along with a plan of sensitivity analysis to evaluate the robustness of findings that can sustains to limitations in missing data and intercurrent events of non-adherence to protocol.

Continuous variables will be summarized using the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

11.1.1. Endpoint Definitions

The following definitions will be used to assess efficacy outcomes for all substudies:

- Endoscopic response: endoscopic remission or $\geq 50\%$ decrease from baseline in SES-CD
- Endoscopic remission: $\text{SES-CD} \leq 4$ and at least 2-point reduction from baseline with no subscore > 1
- Clinical response CDAI: Clinical remission CDAI or ≥ 100 -point decrease from baseline in CDAI
- Clinical remission CDAI: $\text{CDAI} < 150$
- Clinical response PRO2: Clinical remission PRO2 or ≥ 8 -point decrease from baseline in PRO2
- Clinical response CDAI-70: Clinical remission CDAI or ≥ 70 -point decrease from baseline in CDAI
- Clinical remission PRO2: $\text{PRO2} < 8$
- Corticosteroid-free remission: $\text{CDAI} < 150$ without receiving corticosteroids for ≥ 8 weeks prior to Week 52 (for subjects receiving corticosteroids at baseline)
- Time to remission: Defined as time to onset of clinical remission PRO2 and disease biomarker normalization, such as FCP and/or CRP. Subjects who do not achieve this remission endpoint or discontinue from study, are censored at 7 days after last study drug dose

- Time to response: Defined as time to onset of clinical response PRO2 and disease biomarker normalization, such as FCP and/or CRP. Subjects who do not achieve this response endpoint or discontinue from study, are censored at 7 days after last study drug dose
- Mucosal healing: SES-CD score ≤ 2
- Histologic response: Proportion of subjects with modified global histologic disease activity score ≤ 4 in those subjects with baseline score > 4

Based on the above definitions, for the criterion of entering the Responder Cohort in SS3-M, responders at end of the Induction Period in substudies SS1-P2b and SS2-I will be defined as subjects who have met at least 1 criterion of endoscopic response, endoscopic remission, clinical response CDAI ≥ 100 improvement, or clinical remission CDAI < 150 .

11.2. Substudy A – Phase 2 Planned Statistical Methods

11.2.1. Substudy A – Phase 2 Statistical Considerations

Details regarding the statistical analyses will be provided in the SAP, which will be finalized prior to database lock and unblinding.

The analysis for the Induction Period will start when all randomized subjects have either completed Week 14 or discontinued study drug treatment. The final analysis for the Extension Period will start when all subjects who enter the Extension Period have completed or discontinued from protocol-specified study drug treatment and safety follow-up.

Descriptive statistics will be used for data analysis on efficacy and safety measures. Continuous variables will be summarized using the number of observations, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

11.2.2. Substudy A – Phase 2 Determination of Sample Size

This Phase 2 substudy is to evaluate the safety, tolerability, and efficacy of 2 doses of etrasimod with no inferential comparison between groups. With a 1:1 randomization ratio, a sample size of approximately 50 subjects (25 per treatment group) will be reasonable to provide numerical description of safety, tolerability, and efficacy at Week 14.

11.2.3. Substudy A – Phase 2 Analysis Sets

For purposes of analysis, the following populations are defined for the Induction Period (Table 19). Analysis sets for the Extension Period are described in Section 11.2.8.

Table 19: Populations for Analyses

Population	Description
Full Analysis Set (FAS)	The FAS will include all randomized subjects, irrespective of whether they received any study drug.
Modified Full Analysis Set (mFAS)	The mFAS will include all randomized subjects who receive at least one dose of study drug and have a baseline measurement and have at least 1 post-randomization measurement. The mFAS is endpoint

Table 19: Populations for Analyses

Population	Description
	specific, therefore subjects included in the analysis set for one endpoint may differ from another endpoint, based on the baseline and post-baseline data.
Per Protocol Set (PP)	The PP will include all subjects from the FAS without major protocol violations that might affect the evaluation of the effect of study drug on the primary endpoint. The PP will be used in sensitivity analyses of the primary and secondary endpoints to evaluate the influence of major protocol violators and protocol deviators on the main efficacy results. Subjects may be excluded from this population if they violate the eligibility criteria or significantly deviate from the study plan. Specific reasons for warranting exclusion from this population will be documented prior to database lock and may include, but are not limited to, study drug noncompliance, receiving incorrect study drug, and missing more than a defined number of visits while still on study. The statistical analysis plan, which will be finalized prior to database lock, will be the final documentation for the Per Protocol Set definition.
Pharmacokinetic Set	The Pharmacokinetic Set will include all subjects in the FAS with at least 1 post-dose PK measurement.
Safety Set	The Safety Set will include all randomized subjects who received at least one dose of study drug.

11.2.4. Substudy A – Phase 2 Missing Data

In order to analyze the secondary efficacy endpoints at Week 14 in the FAS, nonresponder imputation (NRI) method will be used. Specifically, subjects who have missing data at Week 14 due to any reason will be included in the analysis and be considered as “nonresponders” or “failure”. The impact of missing data on efficacy outcomes will be assessed in the sensitivity analyses described in Section 11.2.5.4.

11.2.5. Substudy A – Phase 2 Efficacy Analysis

11.2.5.1. Substudy A – Primary Endpoint

- Proportion of subjects with endoscopic response

11.2.5.2. Substudy A – Phase 2 Secondary Endpoints

Efficacy

- Proportion of subjects with clinical remission CDAI
- Change from baseline in SES-CD score
- Change from baseline in CDAI score

Pharmacokinetics

- Etrasimod plasma concentrations at 4 hours postdose and at steady-state trough concentrations ($C_{\text{trough,ss}}$) at selected timepoints

Pharmacodynamics

- Change and percentage change from baseline in ALC
- Change and percent change from baseline in FCP concentration
- Change and percent change from baseline in CRP

11.2.5.3. Substudy A – Phase 2 Exploratory Endpoints

CDAI/PRO2

- Change from baseline in PRO2 score
- Proportion of subjects with clinical remission by PRO2
- Time to loss of clinical remission
- Time to loss of clinical response
- Time to remission by PRO2 and FCP concentrations
- Time to response by PRO2 and FCP concentrations

Other PROs

- Change from baseline in IBDQ, SF-36, WPAI-CD, and EQ-5D-5L
- Change from baseline in IBDQ Bowel Symptom domain score
- Change from baseline in IBDQ fatigue item score

Fistulas, Hospitalizations, and Surgery

- Proportion of subjects with draining fistulas by visit up to the end of treatment, among subject with draining fistulas at the induction study baseline
- Rate of CD-related hospitalizations and surgery

A complete list of efficacy endpoints and definitions as well as analysis methods will be provided in the SAP.

11.2.5.4. Substudy A – Phase 2 Statistical Analysis Methods

Statistical methods for efficacy analyses are described in [Table 23](#).

Table 20: Statistical Methods for Efficacy Analyses

Category	Main Methods
Proportion-based endpoints	Proportion-based efficacy endpoints at will be summarized using frequency counts and percentages and 90% CI. Missing data is handled by NRI in endoscopic response and clinical remission. Other proportion-based endpoints measured by visit will be summarized by visit on observation basis.
Continuous measures	Continuous variables will be summarized using the number of observations, mean, standard deviation, median, minimum, and maximum, and 90% CI of mean by visit on observation basis.

CI, confidence interval; NRI, nonresponder imputation

Sensitivity Group

In addition to the pre-planned analyses in the FAS or mFAS population, the following sensitivity analyses will be performed for efficacy endpoints using alternative analysis populations:

- Completers analyses (also known as complete cases) for subjects who complete 14 weeks of study drug and with no missing data
- Per protocol set analyses in subjects who meet the criteria of PP definitions finalized prior to database lock

Detailed methods will be described in the SAP.

Subgroup Analysis

Subgroup analyses will be performed in primary and secondary endpoints and selected exploratory endpoints for the following baseline demographics and disease characteristics:

- Sex (male, female)
- Race (white, non-white)
- Age ($\leq$ or $>$ median)
- CD duration (≤ 5 years, > 5 and ≤ 15 years, or > 15 years)
- Baseline CDAI score (≤ 300 or > 300)
- Baseline SES-CD score ($\leq$ or $>$ median)
- CRP (≤ 3 mg/L, > 3 mg/L)
- Baseline biologic treatment failure status (yes or no)
- Baseline oral corticosteroid use (yes or no)

11.2.6. Substudy A – Phase 2 Testing Strategy

There is no pre-planned inferential between-group testing for this study.

11.2.7. Substudy A – Phase 2 Interim Analysis

Interim analyses may be performed periodically to monitor safety, PK, and efficacy.

11.2.8. Substudy A – Phase 2 Statistical Considerations for the Extension Period

The objectives of the Extension Period are to evaluate long-term safety, tolerability, and efficacy up to 52 weeks for eligible subjects who complete the 14-week Induction Period. All subjects who complete the Induction Period are eligible to enter the Extension Period. Subjects will receive etrasimod 3 mg or etrasimod 2 mg in the Extension Period based on pre-defined response criteria at Week 14 as described [Table 1](#).

No inferential between-group comparisons will be performed. Descriptive statistics will be provided, and details will be discussed in the SAP.

Analysis Sets

All safety outcomes will be analyzed in the Safety Set which includes all subjects who receive at least one dose of etrasimod. Efficacy outcomes will be summarized in the efficacy evaluable set which includes subjects who receive at least one dose of etrasimod and have at least one efficacy measurement during the Extension Period; therefore, the efficacy evaluable set is endpoint specific.

Baseline for the Extension Period is defined as the last measurement prior to the first etrasimod dose started at Week 15.

Safety Analyses

Safety analyses will follow the general considerations in Section 11.7 with the following exceptions:

- Two treatment groups in the Extension Period and 2 subgroups of treatment in the Induction Period will be analyzed
- The Extension Period visits will follow Table 29 in Appendix 1
- Change from baseline will be analyzed based on change from the Induction Period baseline and change from Extension Period baseline

Efficacy Analysis

Efficacy endpoints listed in Section 11.2.5 will be measured at scheduled visits in the Extension Period. Endoscopic response and clinical remission outcomes will be assessed at the end of the Extension Period. Continuous variables will be summarized by visit using the number of observations, mean, SD, median, minimum, maximum, and 90% CI; and categorical variables will be summarized by visit using frequency counts, percentages, and 90% CI with following considerations:

- Two treatment groups in the Extension Period and 2 subgroups of treatment in the Induction Period will be analyzed
- Change from baseline in continuous variables will be analyzed on change from Induction Period baseline and change from Extension Period baseline

Subgroup Analyses

Subgroup analyses will be performed for efficacy endpoints and safety endpoints. The subgroup categories will include, but are not limited to the following baseline demographics and disease characteristics and induction efficacy status at Week 14:

- Sex (male, female)
- Race (white, nonwhite)
- Age ($\leq$ or $>$ median)
- CD duration (≤ 5 years, > 5 and ≤ 15 years, or > 15 years)
- Baseline CDAI score (≤ 300 or > 300)
- CRP (≤ 3 mg/L, > 3 mg/L)

- Baseline biologic treatment failure status (yes or no)
- Baseline oral corticosteroid use (yes or no)
- Endoscopic response status at the end of 14-week induction period to address sustained endoscopic response
- Study drug treatment during 14-week induction period

Complete subgroup categories and detailed analysis method will be described in SAP.

11.3. Substudy 1 – Phase 2b Planned Statistical Methods

11.3.1. Substudy 1 – Phase 2b Statistical Considerations

The formal analysis for dose response for the Induction Period in SS1 Cohort 1 will start when approximately 150 randomized subjects from Cohort 1 have completed the Week 14 Visit. The objective of dose response analysis is to determine appropriate etrasimod dose(s) for Phase 3 trials. No CSR will be developed for the analysis of the Induction Period only. Summaries from the analysis of the Induction Period may be provided to applicable regulatory authorities as required per national regulatory requirements and commitments. An analysis may be performed for the Induction Period for Cohort 2 when all subjects in Cohort 2 have completed Induction Period or discontinued. The final analysis for the EI Period will start when all subjects who enter the EI Period have completed the EI Week 6 Visit or discontinued treatment and had safety follow-up. The CSR will be developed for the final analysis after all subjects in SS1-P2b have completed protocol specified treatment including EI period or discontinued treatment and the database is unblinded.

11.3.2. Substudy 1 – Phase 2b Determination of Sample Size

Cohort 1 in this substudy is powered to detect a dose-response relationship in the primary endpoint of endoscopic response at Week 14 based on pair-wise comparisons using 2-sample Fisher's exact test CCI

(Selinger 2018). With a 1:1:1 randomization ratio, a total of 150 evaluable subjects (50 per treatment group) in Cohort 1 will be needed CCI

CCI In order to ensure high confidence that etrasimod demonstrates efficacy for both endoscopic response and CDAI remission, approximately 135 eligible subjects will be randomized into Cohort 2 with a 1:1:1 randomization ratio to receive etrasimod 3 mg, etrasimod 2 mg, or matching placebo. With 45 subjects in each group, CCI

CCI

There is no formal hypothesis testing for Cohort 2.

CCI

11.3.3. Substudy 1 – Phase 2b Analysis Sets Induction Period (Cohort 1 and Cohort 2)

For purposes of the final analysis, the following populations are defined for the Induction Period (Table 22).

Table 22: Analysis Sets for Substudy 1 – Phase 2b Induction Period

Analysis Set	Description
Full Analysis Set (FAS)	The FAS will include all randomized subjects who receive at least 1 dose of study drug.
Modified Full Analysis Set (mFAS)	The mFAS will include all randomized subjects who receive at least one dose of study drug and have a baseline measurement and have at least 1 post-randomization measurement. The mFAS is endpoint specific, therefore subjects included in the analysis set for one endpoint may differ from another endpoint, based on the baseline and post-baseline data.

Table 22: Analysis Sets for Substudy 1 – Phase 2b Induction Period (Continued)

Analysis Set	Description
Pharmacokinetic Set	The Pharmacokinetic Set will include all subjects in the FAS with at least 1 postdose PK measurement.
Safety Set	The Safety Set will include all randomized subjects who received at least one dose of study drug.

11.3.4. Substudy 1 – Phase 2b Induction Period Missing Data (Cohort 1 and Cohort 2)

Subjects who took any prohibited medication during the study, as confirmed after blinded review by clinical and medical team members before unblinding, or who discontinued due to disease worsening will be considered to have an outcome of nonresponse in the analysis of all binary efficacy endpoints on the event date and at any subsequent timepoints. The prohibited medications will be identified by the Pfizer clinical team during blinded data review. Disease worsening will be determined based on discontinuation reasons collected in the CRF.

For the primary endpoint endoscopic response, and secondary endpoints CDAI remission and PRO2 remission, subjects with missing response status will be included in the analyses using multiple imputation (MI) for component sub-scores under Missing At Random and then derive the binary response. The impact of missing data on the primary and secondary efficacy outcomes will be assessed in the sensitivity analyses described in Section 11.3.5.4.

NRI method will be used for exploratory dichotomous endpoints. Specifically, subjects who have missing data at Week 14 due to any reason will be included in the analysis and be considered as “nonresponders” or “failure”.

11.3.5. Substudy 1 – Phase 2b Induction Period Efficacy Analyses (Cohort 1 and Cohort 2)

11.3.5.1. Substudy 1 – Phase 2b Primary Endpoint (Cohort 1 and Cohort 2)

- Proportion of subjects with endoscopic response at Week 14

11.3.5.2. Substudy 1 – Phase 2b Secondary Endpoints (Cohort 1 and Cohort 2)

- Proportion of subjects with clinical remission CDAI at Week 14
- Proportion of subjects with clinical remission by PRO2 at Week 14

11.3.5.3. Substudy 1 – Phase 2b Exploratory Endpoints

CDAI/ PRO2

- Proportion of subjects with clinical remission CDAI by visit up to Week 14
- Proportion of subjects with clinical response CDAI by visit up to Week 14
- Proportion of subjects with clinical response CDAI-70 by visit up to Week 14
- Change from baseline in CDAI score by visit up to Week 14
- Proportion of subjects with clinical response by PRO2 at Week 14

- Change from baseline in unweighted AP or SF subscore of PRO2 by visit up to Week 14
- Change from Baseline in APSF score and proportion of subjects who achieve clinical remission APSF analyses
- Time to remission by PRO2 and FCP concentrations
- Time to response by PRO2 and FCP concentrations

Endoscopic/SES-CD

- Change from baseline in SES-CD scores at Week 14
- Proportion of subjects with endoscopic remission at Week 14 (Cohort 1)
- Proportion of subjects with endoscopic response and clinical remission PRO2 at Week 14

Other PROs

- Change from baseline in health-related patient-reported outcomes by visit up to Week 14 (IBDQ, CD-PRO/SS, SF-36, EQ-5D-5L, WPAI-CD, FACIT-F, AP NRS)
- Proportion of subjects by PGIC score category at Week 14
- Change from baseline in the CD-PRO/SS Bowel and Abdominal Function domain scores at Week 14
- Change from baseline in IBDQ Bowel Symptom domain score by visit up to Week 14
- Change from baseline in IBDQ fatigue item score by visit up to Week 14

Biomarkers

- Change and percentage change from baseline in FCP concentration by visit up to Week 14
- Change and percentage change from baseline in CRP concentration by visit up to Week 14
- Change from baseline in the Robarts Histopathology Index Score (RHIS) at Week 14
- Change and percentage change from baseline in ALC by visit up to Week 14

Fistulas, Hospitalizations, and Surgery

- Proportion of subjects with draining fistulas at Week 14, among subjects with draining fistulas at baseline
- Proportion of subjects with at least a 50% reduction in draining fistulas at Week 14, among subjects with draining fistulas at baseline
- Rate of CD-related hospitalizations and surgery

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Other

- Proportion of subjects who are not on concomitant corticosteroids with clinical remission PRO2 and/or endoscopic response at Week 14

A complete list of exploratory endpoints and definitions as well as analysis methods will be provided in the SAP.

11.3.5.4. Substudy 1 – Phase 2b Induction Period Statistical Analysis Methods (Cohort 1 and Cohort 2)

Statistical methods for efficacy analyses are described in Table 23.

Table 23: Statistical Methods for Efficacy Analyses for Substudy 1 – Phase 2b Induction Period

Category	Main Methods	Analysis Set
Primary endpoint	For the primary endpoint of endoscopic response at Week 14, missing data is handled by MI. Each MI dataset will be analyzed using the Mantel-Haenszel weighted method adjusted for randomization stratification factors. The results will be combined using Rubin's rule (Rubin 1987) to report the final response rate for each treatment group, common risk difference between etrasimod vs placebo with 90% CI and p-value. This method will also be applied to proportion-based secondary endpoints.	FAS
Secondary endpoint	Proportion-based endpoint will be analyzed using the Mantel-Haenszel weighted Method. Missing data is handled by MI.	FAS
Exploratory endpoints	Proportion-based endpoint using the Mantel-Haenszel weighted Method. The number and percentage of subjects achieving the response and the common risk difference in proportion between treatment groups achieving the response, along with p-value and the 90% CIs of common risk will be reported. Missing data will be imputed as nonresponders. Continuous variables measured at scheduled visits up to Week 14 will be analyzed using a MMRM model. The MMRM model will include treatment group, visit, and interaction of treatment-by-visit as factors, and baseline measure and randomization stratification factor as covariates. An unstructured covariance matrix will be specified for the MMRM model. LS means at visit and LS mean differences between treatment group with p-values and corresponding 90% CIs will be reported. This method will also be applied to other score based or continuous measures. No missing data will be imputed. Continuous variables only measured at baseline and Week 14 will be analyzed using analysis of covariance (ANCOVA) model. The ANCOVA model will include treatment group as factor, and baseline measure and randomization stratification factor as covariates. LS means and LS mean differences between treatment group with p-values and corresponding 90% CIs will be reported. No missing date will be imputed. Endpoints to assess up to Week 20 longitudinal efficacy measure will be analyzed using descriptive summary by visit or Kaplan-Meier method. No between-group comparison will be performed.	FAS for binary endpoints, mFAS for continuous endpoints.

Table 23: Statistical Methods for Efficacy Analyses for Substudy 1 – Phase 2b Induction Period

Category	Main Methods	Analysis Set
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ANCOVA, analysis of covariance; CI, confidence intervals; FAS, full analysis set; LS, least squares; mFAS, modified full analysis set; MMRM, mixed effects model with repeated measures; NRI, nonresponder imputation; MI, multiple imputation.

Sensitivity Analyses

In additional to pre-planned analyses listed above, the following sensitivity analyses will be performed for primary and secondary endpoints using alternative methods to handle missing data and/or in alternative analysis populations:

- Treat all missing data as nonresponders. The primary and secondary endpoints will be analyzed using the Mantel-Haenszel weighted method adjusted for randomization stratification factors. The number and percentage of subjects achieving the response and the common risk difference in proportion between treatment groups achieving the response, along with p-value and the 90% CIs of common risk will be reported.
- Supplementary analyses: Same analyses as above may be performed for the primary and secondary endpoints for mFAS, using observed data only.

Detailed methods will be described in the SAP.

Subgroup Analyses (Cohort 1 and Cohort 2)

Subgroup analyses will be performed in primary and secondary endpoints and selected exploratory endpoints. The subgroup categories will include, but are not limited to the following baseline demographics and disease characteristics:

- Sex (male, female)
- Race (white, nonwhite)
- Age ($\leq$ or $>$ median)
- CD duration (≤ 5 years, > 5 and ≤ 15 years, or > 15 years)
- Baseline CDAI score (≤ 300 or > 300)
- CRP (≤ 3 mg/L, > 3 mg/L)
- Baseline biologic treatment failure status (yes or no)
- Baseline oral corticosteroid use (yes or no)

Complete subgroup categories and detailed analysis method will be described in SAP.

11.3.5.5. Substudy 1 – Phase 2b Induction Period Testing Strategy

As SS1-P2b Cohort 1 is a Phase 2, dose ranging substudy to support a dose selection for Phase 3, there will be no multiplicity adjustment for the comparison between each dose of

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etrasimod and placebo. All hypothesis testing will be performed at significance level of 0.05 1-sided.

There is no formal hypothesis testing for Cohort 2.

11.3.6. Substudy 1 – Phase 2b Interim Analysis

No interim analysis for efficacy is planned for this study. An analysis for Cohort 2 induction period may be performed when all subjects in Cohort 2 have completed induction period or discontinued.

11.4. Substudy 2 – Induction Planned Statistical Methods

11.4.1. Substudy 2 – Induction Statistical Considerations

The final analysis will start when all randomized subjects have either completed the Week 14 Visit or discontinued study drug treatment.

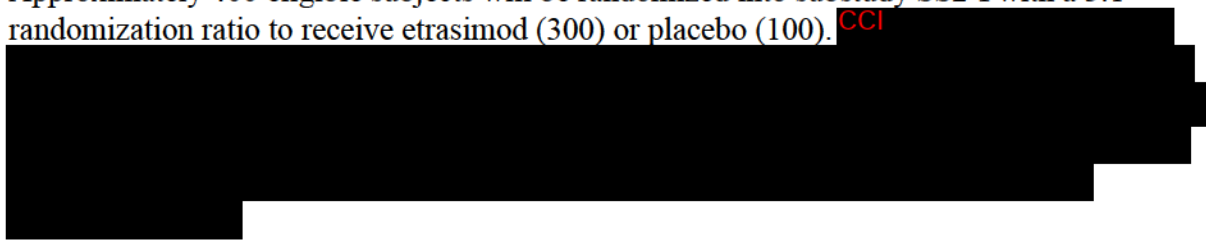
The primary estimand of interest for SS2-I is a composite estimand that accounts for both treatment adherence and response. It will be used for the primary and key secondary binary endpoints. It includes 5 attributes:

- Population: subjects with CD as defined by the inclusion and exclusion criteria.
- Variable: binary endpoints at Week 14.
- Treatment conditions: etrasimod or Placebo.
- Intercurrent Events: discontinuation of the investigational product and prohibited medication use. Subjects with an intercurrent event prior to Week 14 will be considered as “failure” or “nonresponders” and are included in the analysis (ie, NRI).
- Population-level summary: The difference in response proportions between etrasimod and placebo at Week 14.
- A detailed plan for constructing the estimands will be described in the SAP.

11.4.2. Substudy 2 – Induction Determination of Sample Size

This substudy has 2 primary endpoints: 1) endoscopic response ($\geq 50\%$ decrease from baseline in SES-CD) and, 2) clinical remission CDAI < 150 at Week 14. The sample size and power calculations are designed to test the 2 primary endpoints as co-primary endpoints, and these initial assumptions are based on published data from other CD drugs for both endoscopic response rate and clinical remission rate using CDAI < 150 .

Approximately 400 eligible subjects will be randomized into substudy SS2-I with a 3:1 randomization ratio to receive etrasimod (300) or placebo (100). CCI



It is noted that above sample size, along with a similar number of subjects from the Phase 3 induction study ADP334-305 and number of subjects from SS1-P2b is assumed to produce enough eligible subjects CCI to enter the maintenance study (SS3-M) based on projected response rate (defined by clinical response CDAI, clinical remission CDAI, endoscopic response or endoscopic remission) CCI

CCI The response rate and attrition rate for subjects not enrolling in SS3-M CCI will be evaluated at a designated time point by the independent DMC to assess study assumptions and make recommendations on whether the enrollment of additional subjects may be needed to achieve the target sample size for SS3-M. To protect the integrity of SS2-I, the DMC will only communicate the outcome of the projection (ie, the target number of subjects was reached, or additional subjects need to enroll). Further details will be provided in the SS2-I SAP.

The final sample size may be adjusted based on the actual treatment effects observed in SS1-P2b Cohort 1 and Cohort 2 when that data becomes available. As SS2-I will not enroll subjects until the dose selection for phase 3 studies is completed based on the data analyses from SS1-P2b Cohort 1 and Cohort 2, any adjustments to the sample size will be made prior to enrolling subjects in SS2-I.

11.4.3. Substudy 2 – Induction Analysis Sets

For purposes of analysis, the following populations are defined in Table 24.

Table 24: Analysis Sets for Substudy 2 – Induction

Analysis Set	Description
Full Analysis Set (FAS)	The FAS will include all randomized subjects and received at least 1 dose of study drug
Modified Full Analysis Set (mFAS)	The mFAS will include all randomized subjects who receive at least one dose of study drug and have a baseline measurement and have at least 1 post-randomization measurement. The mFAS is endpoint specific, therefore subjects included in the analysis set for one endpoint may differ from another endpoint, based on the baseline and post-baseline data.
Pharmacokinetic Set	The Pharmacokinetic Set will include all subjects in the FAS with at least 1 postdose PK measurement.
Safety Set	The Safety Set will include all randomized subjects who received at least one dose of study drug.

11.4.4. Substudy 2 – Induction Missing Data

In order to analyze the primary and key secondary binary efficacy endpoints at Week 14 in the FAS, NRI method will be used. Specifically, subjects who have missing data at Week 14 due to any reason will be included in the analysis and be considered as “nonresponders” or “failure”. The impact of missing data on efficacy outcomes will be assessed in the sensitivity analyses described in Section 11.5.6.

11.4.5. Substudy 2 – Induction Efficacy Analyses

The efficacy endpoint definitions for SS2-I are described in Section 11.1.1.

11.4.5.1. Substudy 2 – Induction Primary Endpoints

- Proportion of subjects with endoscopic response at Week 14
- Proportion of subjects with clinical remission CDAI at Week 14

11.4.5.2. Substudy 2 – Induction Key Secondary Endpoints

- Proportion of subjects with clinical remission PRO2 at Week 14
- Proportion of subjects with clinical response CDAI at Week 14
- Proportion of subjects with endoscopic response and clinical remission CDAI at Week 14
- Proportion of subjects with endoscopic remission at Week 14
- Change from baseline in CD-PRO/SS at Week 14

11.4.5.3. Substudy 2 – Induction Secondary Endpoints

CDAI /PRO2

- Proportion of subjects with clinical remission CDAI by visit up to Week 14
- Proportion of subjects with clinical response CDAI by visit up to Week 14
- Proportion of subjects with clinical response CDAI-70 by visit up to Week 14
- Change from baseline in CDAI score by visit up to Week 14
- Proportion of subjects with clinical response PRO2 at Week 14
- Change from baseline in PRO2, AP, and SF scores by visit up to Week 14

Endoscopic/SES-CD

- Change from baseline in SES-CD at Week 14
- Proportion of subjects with endoscopic response and clinical remission PRO2 at Week 14

Other PROs

- Change from baseline in the CD-PRO/SS Bowel and Abdominal Function domain scores at Week 14
- Change from baseline in health-related patient-reported outcomes by visit up to Week 14 (CD-PRO/SS, IBDQ, SF-36, FACIT-F)
- Change from baseline in IBDQ Bowel Symptom domain score by visit up to Week 14
- Change from baseline in IBDQ fatigue item score by visit up to Week 14

11.4.5.4. Substudy 2 – Induction Exploratory Endpoints

Other PROs

- Proportion of subjects by PGIC score category at Week 14

- Change from baseline in health-related patient-reported outcomes by visit up to Week 14 (EQ5D5L, WPAICD, AP NRS)

Biomarkers

- Change and percentage change from baseline in ALC by visit up to Week 14
- Change and percent change from baseline in FCP concentration by visit up to Week 14
- Change and percent change from baseline in CRP by visit up to Week 14
- Change from baseline in the Robarts Histopathology Index score at Week 14

Fistulas, Hospitalizations, and Surgery

- Proportion of subjects with draining fistulas at Week 14, among subjects with draining fistulas at baseline
- Rate of CD-related hospitalizations and surgery

Other

- Proportion of subjects who are not on concomitant corticosteroids with clinical remission PRO2 and/or endoscopic remission at Week 14

A complete list of exploratory endpoints and definitions as well as analysis methods will be provided in the SAP.

11.4.5.5. Substudy 2 – Induction Statistical Analysis Methods

Statistical methods for efficacy analyses are described in Table 25.

Table 25: Statistical Methods for Efficacy Analyses for Substudy 2 Induction Period

Category	Main Methods	Analysis Set
Primary endpoint	Proportion-based primary endpoints of endoscopic response and clinical remission at Week 14 will be analyzed using the Mantel-Haenszel weighted method adjusted for randomization stratification factors. The number and percentage of subjects achieving the response and the common risk difference in proportion between treatment groups achieving the response, along with p-value and the 95% confidence intervals (CIs) of the common risk difference will be reported. This method will also be applied to proportion-based secondary and exploratory endpoints. Missing data is handled by NRI.	FAS
Key Secondary endpoint	Proportion-based endpoint will be analyzed using the Mantel-Haenszel Method like that of primary endpoints. Missing data is handled by NRI.	FAS

Table 25: Statistical Methods for Efficacy Analyses for Substudy 2 Induction Period

Category	Main Methods	Analysis Set
Secondary and Exploratory endpoints	Proportion-based endpoint using the Mantel-Haenszel weighted Method. No missing data will be imputed. Continuous variables measured at scheduled visits up to Week 14 will be analyzed using a MMRM model. The MMRM model will include treatment group, visit, and interaction of treatment-by-visit as factors, and baseline measure and randomization stratification factor as covariates. An unstructured covariance matrix will be specified for the MMRM model. LS means at visit and LS mean differences between treatment group with p-values and corresponding 95% CIs will be reported. This method will also be applied to other score based or continuous measures. No missing data will be imputed. Continuous variables only measured at baseline and Week 14 will be analyzed using analysis of covariance (ANCOVA) model. The ANCOVA model will include treatment group as factor, and baseline measure and randomization stratification factor as covariates. LS means and LS mean differences between treatment group with p-values and corresponding 95% CIs will be reported. No missing data will be imputed.	mFAS

ANCOVA, analysis of covariance; CI, confidence intervals; FAS, full analysis set; LS, least squares; mFAS, modified full analysis set; MMRM, mixed effects model with repeated measures; NRI, nonresponder imputation

Sensitivity Analyses

In addition to pre-planned analyses listed above, the following sensitivity analyses will be performed for primary endpoints using alternative methods to handle missing data and/or in alternative analysis populations:

- A sensitivity analysis will be performed for the primary binary endpoints at Week 14 using tipping point approach. The missing data at Week 14 will be imputed using MI procedure from 0 responder to 100% of responders for active treatment and placebo groups. After imputation, each completed dataset will be analyzed using Mantel-Haenszel weighted method. Thirty results of Mantel-Haenszel weighted analysis for each MI dataset will be analyzed and 95% CI and p-value using Rubin's method ([Rubin 1987](#)) will be reported.

Detailed methods will be described in the SAP.

Subgroup Analyses

Subgroup analyses will be performed in primary and secondary endpoints and selected exploratory endpoints. The subgroup categories will include, but are not limited to the following baseline demographics and disease characteristics:

- Sex (male, female)
- Race (white, non-white)
- Age ($\leq$ or $>$ median)
- CD duration (≤ 5 years, > 5 and ≤ 15 years, or > 15 years)

- Baseline CDAI score (≤ 300 or > 300)
- CRP (≤ 3 mg/L, > 3 mg/L)
- Baseline SES-CD score ($\leq$ or $>$ median)
- Baseline biologic treatment failure status (yes or no)
- Baseline oral corticosteroid use (yes or no)
- CD duration (≤ 5 years, > 5 years, ≤ 15 years, > 15 years)
- Involved gastrointestinal areas (ileum only, colon only, ileum, and colon)

Complete subgroup categories and detailed analysis method will be described in SAP.

11.4.6. Substudy 2 – Induction Testing Strategy

There are multiple null hypotheses for the comparison of etrasimod and placebo in the primary and key secondary endpoints. The family-wise Type I error rate will be controlled

[REDACTED]

[REDACTED]

11.4.7. Substudy 2 – Induction Interim Analysis

No interim analysis for efficacy is planned for this study.

11.5. Substudy 3 – Maintenance Planned Statistical Methods

11.5.1. Substudy 3 – Maintenance Phase 3 Statistical Considerations

Only Week 14 etrasimod responders enrolling from induction studies will be included in the formal efficacy analyses. Only the formal efficacy analyses are described here. Efficacy analyses for delayed etrasimod responders, placebo responders, and nonresponders will be defined in the SAP.

The primary estimand of interest for SS3-M is a composite estimand that accounts for both treatment adherence and response. It will be used for the primary and key secondary binary endpoints. It includes 5 attributes:

- Population: subjects with CD as defined by the inclusion and exclusion criteria.
- Variable: binary endpoints at Week 52.
- Treatment conditions: etrasimod or Placebo.
- Intercurrent Events: discontinuation of the investigational product and prohibited medication use. Subjects with an intercurrent event prior to Week 52 will be

considered as “failure” or “nonresponders” and are included in the analysis (ie, NRI).

- Population-level summary: The difference in response proportions between etrasimod and placebo at Week 52.

A detailed plan for constructing the estimands will be described in the SAP.

11.5.2. Substudy 3 – Maintenance Determination of Sample Size

The number of subjects in this substudy will depend on the number enrolling from SS1-P2b, SS2-I, and Study APD334-305. Overall, up to 1125 subjects (both responders and nonresponders) from these 3 studies may be enrolled in SS3-M. Only Week 14 etrasimod responders enrolling from induction studies will be included in the formal efficacy analyses. The study is powered to test hypothesis of 2 primary endpoints in comparison of an etrasimod dose and placebo. For the primary endpoint of clinical remission CDAI < 150 at Week 52, CCI

For the other primary endpoint of endoscopic response at Week 52 CCI

11.5.3. Substudy 3 – Maintenance Analysis Sets

For purposes of analysis, the following populations are defined (Table 26).

Table 26: Analysis Sets for Substudy 3 – Maintenance

Analysis Set	Description
Full Analysis Set (FAS)	The FAS will include all randomized subjects who responded to etrasimod treatment in induction studies who received at least 1 dose of study drug in SS3-M
Modified Full Analysis Set (mFAS)	The mFAS will include subjects who are in the FAS and receive at least 1 dose of study drug and have a baseline measurement and have at least 1 post-randomization measurement. The mFAS is endpoint specific; therefore, subjects included in the analysis set for one endpoint may differ from another endpoint, based on the baseline and postbaseline data.
Pharmacokinetic Set	The Pharmacokinetic Set will include all randomized subjects with at least 1 postdose PK measurement.
Safety Set	The Safety Set will include all enrolled subjects who received at least 1 dose of study drug.

Note: Although both etrasimod and placebo responders from the parent substudy or Study APD334-305 will be eligible to participate in this maintenance study, placebo responders will not be randomized or be part of the formal key efficacy analyses.

11.5.4. Substudy 3 – Maintenance Missing Data

In order to analyze the primary and secondary efficacy endpoints at Week 52 in the FAS, NRI will be used. Specifically, etrasimod responders in the Responder Cohort who have missing data at Week 52 due to any reason (eg, loss of clinical response or study drug discontinuation) will be included in the analysis and be considered as “nonresponders”. The impact of missing data on efficacy outcomes will be assessed in the sensitivity analyses described in Section 11.5.5.5.

11.5.5. Substudy 3 – Maintenance Efficacy Analyses

For the formal efficacy analyses, the efficacy endpoint definitions for SS3-M are described in Section 11.1.1. SS3-M baseline is defined as Week 14 for subjects who enroll directly from an Induction Period and EI Week 6 for subjects who enroll from an EI Period. As described in Section 11.5.1, EI Week 6 responders are not included in the formal efficacy analyses.

11.5.5.1. Substudy 3 – Maintenance Primary Endpoints

- Proportion of subjects with clinical remission CDAI at Week 52
- Proportion of subjects with endoscopic response at Week 52

11.5.5.2. Substudy 3 – Maintenance Key Secondary Endpoints

- Proportion of subjects with clinical remission CDAI at Week 52 among subjects in clinical remission CDAI at SS3-M baseline)
- Proportion of subjects with endoscopic response at Week 52 among subjects in endoscopic response at SS3-M baseline
- Proportion of subjects with corticosteroid-free clinical remission CDAI at Week 52 among subjects receiving corticosteroids at SS3-M baseline
- Proportion of subjects with endoscopic remission at Week 52
- Proportion of subjects with clinical remission PRO2 at Week 52
- Proportion of subjects with clinical response or endoscopic response at Week 52

11.5.5.3. Substudy 3 – Maintenance Secondary Endpoints

CDAI//PRO2

- Change from baseline in CDAI score by scheduled visit up to Week 52
- Proportion of subjects with clinical response CDAI at Week 52 among subjects in clinical response CDAI at SS3-M baseline
- Change from baseline in health-related patient-reported outcomes by visit up to Week 52 (CD-PRO, IBDQ, SF-36, FACIT-F)
- Proportion of subjects with clinical remission PRO2 at Week 52 among subjects with clinical remission PRO2 at study entry
- Change from baseline in AP and SF subscores of PRO2 by scheduled visit up to Week 52

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- Time to remission by PRO2 and FCP concentrations
- Time to response by PRO2 and FCP concentrations

Endoscopic/SES-CD

- Change from baseline in SES-CD score at Week 52
- Proportion of subjects with endoscopic response and clinical remission PRO2 at Week 52
- Proportion of subjects with endoscopic remission and clinical remission PRO2 at Week 52

11.5.5.4. Substudy 3 – Maintenance Exploratory Endpoints

Other PROs

- Change from baseline in health-related patient-reported outcomes by visit up to Week 52 (EQ-5D-5L, WPAI-CD, AP NRS)
- Proportion of subjects with improvement in the CD-PRO/SS Bowel and Abdominal Function domain scores by visit up to Week 52
- Change from baseline in IBDQ Bowel Symptom domain score by visit up to Week 52
- Change from baseline in IBDQ fatigue item score by visit up to Week 52
- Proportion of subjects by PGIC categorical score at Week 28 and Week 52

Biomarkers

- Change and percentage change from baseline in ALC by visit up to Week 52
- Change and percent change from baseline in FCP concentration by visit up to Week 52
- Change and percent change from baseline in CRP by visit up to Week 52
- Change from baseline in the Robarts Histopathology Index Score at Week 52

Fistulas, Hospitalizations, and Surgery

- Proportion of subjects with draining fistulas at Week 52 among subjects with draining fistulas at the induction study baseline (Day 1)
- Rate of CD related hospitalizations and surgery

11.5.5.5. Substudy 3 – Maintenance Statistical Analysis Methods

Statistical methods for efficacy analyses are described in [Table 27](#).

Table 27: Statistical Methods for SS3-M Efficacy Analyses

Category	Main Methods	Analysis Set
Primary endpoint	Two proportion-based primary endpoints of clinical remission and endoscopic response at Week 52 will be analyzed using the Mantel-Haenszel weighted method adjusted for randomization stratification factors. The number and percentage of subjects achieving the response and the common risk difference in proportion between treatment groups achieving the response, along with p-value and the 95% CIs of the common risk difference will be reported. This method will also be applied to proportion-based secondary and exploratory endpoints. Missing data will be handled by NRI.	FAS
Key Secondary endpoint	Proportion-based endpoint will be analyzed using the Mantel-Haenszel weighted method in the same manner as the primary endpoint. Missing data will be handled by NRI.	FAS
Secondary and Exploratory endpoints	Proportion-based endpoint using the Mantel-Haenszel weighted Method. No missing data will be imputed. Continuous variables measured at scheduled visits up to Week 52 will be analyzed using a MMRM model. The MMRM model will include treatment group, visit, and interaction of treatment-by-visit as factors, and baseline measure and randomization stratification factor as covariates. An unstructured covariance matrix will be specified for the MMRM model. LS means at visit and LS mean differences between treatment group with p-values and corresponding 95% CIs will be reported. This method will also be applied to other score based or continuous measures. No missing data will be imputed. Continuous variables only measured at baseline and Week 52 will be analyzed using an ANCOVA model. The ANCOVA model will include treatment group as factor, and baseline measure and randomization stratification factor as covariates. LS means and LS mean differences between treatment group with p-values and corresponding 95% CIs will be reported. No missing data will be imputed.	mFAS

ANCOVA, analysis of covariance; CI, confidence intervals; FAS, full analysis set; LS, least squares; mFAS, modified full analysis set; MMRM, mixed effects model with repeated measures; NRI, nonresponder imputation

Sensitivity Analyses

In addition to pre-planned analyses listed above, the following sensitivity analyses will be performed for primary endpoints using alternative methods to handle missing data and/or in alternative analysis populations:

- Analyses of proportion-based endpoints at Week 52 in FAS with missing data being imputed using MI techniques. The missing values of score measurement (ie, SES-CD), from which the dichotomous endpoint (ie, endoscopic response) would be derived, will be imputed using MI procedure. Thirty results of Mantel-Haenszel weighted analysis for each MI dataset will be analyzed and reported along with 95% CI and p-value using Rubin's method ([Rubin 1987](#))

Detailed methods will be described in the SAP.

Subgroup Analyses

Subgroup analyses will be performed in primary and secondary endpoints and selected exploratory endpoints. The subgroup categories will include, but are not limited to the following baseline demographics and disease characteristics:

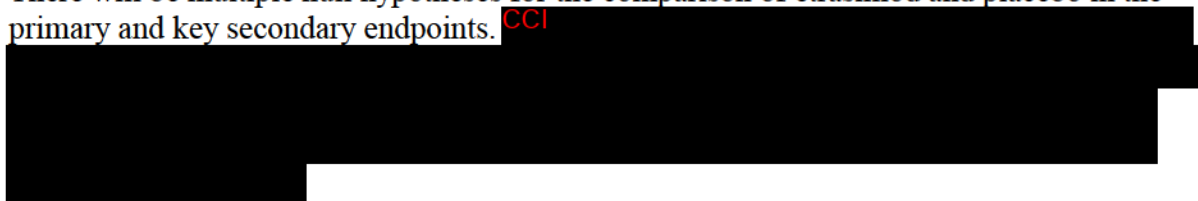
- Sex (male, female)
- Race (white, nonwhite)
- Age ($\leq$ or $>$ median)
- Baseline CDAI score (≤ 300 or > 300)
- Baseline SES-CD score ($\leq$ or $>$ median)
- CRP (≤ 3 mg/L, > 3 mg/L)
- Baseline biologic treatment failure status (yes or no)
- Baseline oral corticosteroid use (yes or no)
- Endoscopic response status at the end of 14-week induction period (yes or no)
- Clinical remission CDAI status at the end of 14-week induction period (yes or no)
- CD duration (≤ 5 years, > 5 years, ≤ 15 years, > 15 years)
- Involved gastrointestinal areas (ileum only, colon only, ileum and colon)

Complete subgroup categories and detailed analysis method will be described in SAP.

11.5.6. Substudy 3 – Maintenance Testing Strategy

Two primary endpoints with dichotomous measures (ie, proportion based) will be analyzed using the Mantel-Haenszel weighted method, stratified by randomization stratification factors. Results will be expressed as the number of subjects in response, response percentages, common risk difference in response percentages, and associated 95% CIs, and p-values.

There will be multiple null hypotheses for the comparison of etrasimod and placebo in the primary and key secondary endpoints. CCI



11.5.7. Substudy 3 – Maintenance Interim Analysis

No interim analysis is currently planned for this study; but if a need for an interim analysis is identified while the study is ongoing, a detailed plan for its conduct will be produced and submitted for review by regulatory agencies prior to its conduct.

11.6. Substudy 4 – Long-Term Extension Planned Statistical Considerations

11.6.1. Substudy 4 – Long-Term Extension Determination of Sample Size

No formal sample size calculations were performed. Since all subjects will enroll from parent studies SSA-P2 and SS3-M, the maximum number of subjects planned for this substudy will not exceed the total number of subjects enrolled into these two studies. Actual enrollment will depend on the number of subjects who meet eligibility criteria for this study and consent to enroll.

11.6.2. Substudy 4 – Long-Term Extension Analysis Sets

For purposes of analysis, the following populations are defined (Table 28).

Table 28: Analysis Sets for Substudy 4 – Long-Term Extension

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

11.6.3. Substudy 4 – Long-Term Extension Missing Data

All data will be evaluated as observed, and no imputation method for missing values will be used other than simple imputation of last observation carried forward, which may be applied to dichotomous endpoints.

11.6.4. Substudy 4 – Long-Term Extension Efficacy Analyses

The efficacy endpoint definitions for SS4-E are described in Section 11.1.1.

11.6.4.1. Secondary Efficacy Endpoints

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

11.6.4.2. Exploratory Efficacy Endpoints

CDAI/ PRO2

- Change from baseline in CDAI score by visit up to the end of treatment

- Change from baseline in PRO2 score by visit up to the end of treatment
- Time to loss of clinical remission
- Time to loss of clinical response
- Time to remission by PRO2 and FCP concentrations
- Time to response by PRO2 and FCP concentrations

Other PROs

- Change from baseline in IBDQ, SF-36, CD-PRO/SS, FACIT-F, WPAI-CD, and EQ-5D-5L by visit up to the end of treatment
- Proportion of subjects with improvement in the CD-PRO/SS Bowel and Abdominal Function domain scores by visit up to the end of treatment
- Change from baseline in IBDQ Bowel Symptom domain score by visit up to the end of treatment
- Change from baseline in IBDQ fatigue item score by visit up to the end of treatment

Biomarkers

- Change and percentage change from baseline in ALC by visit up to the end of treatment
- Change and percent change from baseline in FCP concentration by visit up to the end of treatment
- Change and percent change from baseline in CRP by visit up to the end of treatment

Fistulas, Hospitalizations, and Surgery

- Proportion of subjects with draining fistulas by visit up to the end of treatment, among subject with draining fistulas at the induction study baseline
- Rate of CD related hospitalizations and surgery

11.6.5. Substudy 4 – Long-Term Extension Testing Strategy

No formal between group testing will be performed in this study. All descriptive analysis methods and details will be described in the SAP.

11.6.6. Substudy 4 – Long-Term Extension Interim Analysis

An interim analysis may be conducted to support the product registration application.

11.7. Safety Analyses

The safety analysis will be the same for each of the four substudies. A detailed description of all safety analyses will be provided in the SAP.

11.7.1. Safety Endpoints

- Incidence of TEAEs and SAEs

- Incidence and severity of laboratory abnormalities
- Incidence of clinically significant vital sign, ECG, and Holter abnormalities
- Change from baseline in select laboratory values, ECG, and vital signs

11.7.2. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities.

For each treatment group, the proportion of subjects with TEAEs will be summarized overall, by severity, and by relationship to study drug. SAEs will also be summarized by treatment group. A TEAE is defined as:

- An AE that occurs after initiation of study drug that was not present at the time of treatment start
- An AE that increases in severity after the initiation of medication, if the event was present at the time of treatment start

AEs occurring before the first dose of study drug will be summarized separately.

11.7.3. Extent of Exposure

The duration of time on study and time on study drug will be summarized for each treatment group and substudy using descriptive statistics. The number of subjects on treatment for certain time intervals will also be summarized. The total subject-years and total subject-years on study will also be included in this summary.

11.7.4. Clinical Laboratory Parameters

Laboratory parameters will be summarized by treatment group at each scheduled assessment time point using descriptive statistics. Individual subject values will be listed, and values outside of the standard reference range will be noted. Shift tables and analyses of changes from baseline will be produced.

11.7.5. Electrocardiograms and Holter Monitoring

Individual ECG values will be listed by visit and summarized using descriptive statistics. Intervals to be provided for each ECG are: RR, PR, QRS, QT, QTc, QTcB, and QTcF. Post-baseline ECGs for each subject will be compared with the baseline ECG. Any clinically significant change from baseline may be recorded as an AE if deemed appropriate by the Investigator. Outlier analysis will be performed on all subjects with QTcF values greater than 500 ms or change from baseline > 60 ms in the absence of baseline ECG abnormalities that preclude accurate surface ECG assessment of ventricular repolarization (eg, bundle branch block).

A separate data analysis will be performed by a central ECG laboratory on data from continuous Holter recordings to assess for ectopic ventricular beats (single beats and runs), pauses, supraventricular tachycardia, AV block, and any other important arrhythmias. If any significant abnormalities are detected, event reports will be generated and provided to Investigator and may be recorded as an AE if deemed appropriate. In addition, full individual patient Holter reports may be prepared.

11.7.6. Vital Signs

Descriptive statistics for vital signs (BP, HR, body temperature, and respiratory rate) will be presented by treatment group. Incidence of abnormal vital signs parameters will be tabulated.

11.7.7. Physical Examination

Clinically significant physical examination abnormalities will be included in medical history or recorded and summarized as an AE.

11.8. Pharmacokinetic Analyses

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

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

11.9. Health-Related Patient-Reported Outcomes

The PRO measures based on questionnaires (IBDQ, CD-PRO, SF-36, EQ-5D-5L, WPAI-CD, FACIT-F, AP NRS, and PGIC) may be summarized by treatment and visit using descriptive statistics.

11.10. Data Monitoring Committee

An independent DMC will be utilized to monitor the safety of subjects across all 5 substudies 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 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.

12. ETHICAL CONSIDERATIONS

12.1. Regulatory, Ethical, and Study Oversight Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

12.3. Informed Consent and Assent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study. The participant or their legally authorized representative should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative (if allowed by local regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each participant or their legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant or their legally authorized representative must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant or their legally authorized representative.

The participant or their legally authorized representative must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or their legally authorized representative is fully informed about their right to access and correct their personal data and to withdraw consent for the processing of their personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants or their legally authorized representative must be reconsented to the most current version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

A copy of the ICD(s) must be provided to the participant or their legally authorized representative (if allowed by local regulations).

12.4. 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 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.

12.5. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

12.6. Subject Reimbursement

Subjects will be reimbursed according to the guidelines of the relevant IEC/research ethics committees/IRB in order to compensate them for items such as travel, meals, the inconvenience, and their time as appropriate.

13. DATA QUALITY ASSURANCE

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source records and documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on site monitoring), are provided in the data management plan and clinical monitoring plan maintained and utilized by the sponsor or designee.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

13.1. 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 should 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 should also be documented.

14. DATA HANDLING AND RECORD KEEPING

14.1. Data Management

14.1.1. 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. The Trial Master File 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.

14.1.2. 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, subject e-Diaries 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.

14.2. 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 drug.

Records will 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, but may be retained for a longer period of time if required by the applicable regulatory requirements. 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

14.3. Study and Site Start and Closure

The study start date is the date of the first participant's first visit.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time upon notification to the sponsor or designee/CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory

requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

14.4. Clinical Study Report

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

14.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

Pfizer posts clinical trial results on EudraCT/CTIS for Pfizer sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant level data or full CSRs for the purposes of “bona fide scientific research” that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 18

months after study completion. Participant level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

14.6. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

15. RESPONSIBILITIES

15.1. 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

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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 shall, in accordance with the provisions of 21 CFR Part 50, obtain the informed consent of each human subject to whom the drug is administered.

15.2. Sponsor's Medically Qualified Individual

The sponsor will designate a medically qualified individual (MQI, also known as the medical monitor) to advise the investigator on study-related medical questions. The contact information for the study medical monitor is documented in the Study Team Contact List located in the Investigator Site File.

Participants are provided with a Pfizer study information card at the time of informed consent which includes contact information for their investigator in case of study-related medical questions. The study information card contains, at a minimum, (a) study number, (b) participant's study identification number, and (c) principal investigator contact information.

15.3. 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 and all participating Investigators are promptly informed of significant new adverse effects or risks with respect to the drug.

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Appendix 1. SCHEDULES OF ASSESSMENTS

Table 29: Schedule of Assessments for Substudy A – Phase 2

Evaluations	SP	14-Week Induction Period							52-Week Extension Period								ET ^a	4-Week Follow-Up Period ^b	
	Day – 28 to –1	BL Day 1	W1 (± 1D)	W2 (± 3D)	W4 (± 3D)	W6 (± 3D)	W10 (± 3D)	W14 (± 3D)	W15 (± 3D)	End W15 (± 3D)	W20 (± 3D)	W28 (± 7D)	W36 (± 7D)	W44 (± 7D)	W52 (± 7D)	W66 (± 7D)		FU1 (± 3D)	FU2 (± 3D)
Informed consent	x																		
Eligibility criteria	x	x																	
Demographic and medical history ^c	x	x																	
eDiary training ^d	x																		
eDiary review		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Randomization		x																	
Dose IP in clinic ^e		x	x	x		x		x	x	x		x			x				
PK sampling ^f		x	x	x		x		x				x			x		x	x	x ^g
Dispense IP		x	x	x ^h	x ^h	x	x	x	x	x ^h	x	x	x	x	x	x ⁱ			
Drug accountability			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Prior and concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Blood for genetic analysis (optional) ^j		x																	
CDAI and PRO2 calculation	x	x	x	x	x	x	x	x			x	x	x	x	x	x	x		
Health Related PROs		x ^k			x			x				x				x	x		

Table 29: Schedule of Assessments for Substudy A – Phase 2

Evaluations	SP	14-Week Induction Period							52-Week Extension Period								ET ^a	4-Week Follow-Up Period ^b	
	Day – 28 to –1	BL Day 1	W1 (± 1D)	W2 (± 3D)	W4 (± 3D)	W6 (± 3D)	W10 (± 3D)	W14 (± 3D)	W15 (± 3D)	End W15 (± 3D)	W20 (± 3D)	W28 (± 7D)	W36 (± 7D)	W44 (± 7D)	W52 (± 7D)	W66 (± 7D)		FU1 (± 3D)	FU2 (± 3D)
CD-related hospitalization and surgery	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CRP	x	x	x	x	x	x	x	x			x	x	x	x	x	x	x		
Ileocolonoscopy with biopsy ^l	x							x							x		x		
FCP ^m		x		x	x	x	x	x				x			x	x	x		
Stool microbiome		x						x							x				
Exploratory biomarkers		x						x							x				
Seated vital signs	x	x ⁿ	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Physical examination ^o	x	x	x	x	x	x	x	x			x	x	x	x	x	x	x		x
12-lead ECG	x	x ⁿ						x	x			x			x		x		
Holter monitoring			x	x						x									
CBC with differential and platelets	x	x	x	x	x	x	x	x			x	x	x	x	x	x	x	x	x
TBNK panel cell counts	x	x			x	x	x	x			x	x	x	x	x	x	x		x
Serum Chemistry	x	x			x	x	x	x			x	x	x	x	x	x	x		x
Lipid panel ^p , TSH, uric acid		x						x								x	x		
Coagulation panel	x				x	x	x	x				x		x		x	x		

Table 29: Schedule of Assessments for Substudy A – Phase 2

Evaluations	SP	14-Week Induction Period							52-Week Extension Period								ET ^a	4-Week Follow-Up Period ^b	
	Day – 28 to –1	BL Day 1	W1 (± 1D)	W2 (± 3D)	W4 (± 3D)	W6 (± 3D)	W10 (± 3D)	W14 (± 3D)	W15 (± 3D)	End W15 (± 3D)	W20 (± 3D)	W28 (± 7D)	W36 (± 7D)	W44 (± 7D)	W52 (± 7D)	W66 (± 7D)		FU1 (± 3D)	FU2 (± 3D)
Infectious disease serology ^q	x																		
TB questionnaire ^r	x							x				x		x		x			
TB screening ^s	x														x				
VZV IgG screening ^t	x																		
Pregnancy test ^u	x	x				x	x	x	x		x	x	x	x	x	x	x		x
FSH ^v	x																		
Urinalysis	x							x							x		x		
Urine drug screen	x																		
Stool studies ^w	x																		
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ophthalmoscopy and OCT ^x	x							x				x				x	x		
PFT and DLCO ^y	x							x				x				x	x		x

- If a subject ends substudy participation before the end of the Extension Period, the ET visit should be performed. The ET visit should occur within 7 days of last dose and before initiation of any new treatments.
- The FU1 and FU2 Visits should be performed for all subjects at 14 days and 28 days, respectively, following the last dose of study drug.
- Crohn's disease medical history should include date of diagnosis, disease severity, hospitalizations, EIMs, smoking status, duration, disease localization (ileum/colon/both), disease activity, presence and location of fistula, prior treatment, and complications.
- Subjects will begin eDiary entries on the first day of screening after eDiary training is completed.
- On study visit days where PK blood samples are collected, subjects should be instructed to take their dose after blood draws for PK are collected.
- Blood samples for PK will be collected predose (within 60 minutes prior to dosing) and at 4 hours postdose (after ECG) on Day 1 and pre-dose (trough; within 60 minutes prior to dosing) at all other indicated days during the treatment periods. A PK blood sample will also be collected 2 weeks after the last dose of study drug. If possible, a PK blood sample should be collected at the time of an adverse event leading to study drug discontinuation or when there is a significant adverse event such as a severe or atypical infection (including but not limited to systemic infections like sepsis) and severe drug-induced liver injury that meets Hy's criteria. The time of the last study drug should be documented.

Table 29: Schedule of Assessments for Substudy A – Phase 2

Evaluations	SP	14-Week Induction Period							52-Week Extension Period								ET ^a	4-Week Follow-Up Period ^b	
	Day – 28 to –1	BL Day 1	W1 (± 1D)	W2 (± 3D)	W4 (± 3D)	W6 (± 3D)	W10 (± 3D)	W14 (± 3D)	W15 (± 3D)	End W15 (± 3D)	W20 (± 3D)	W28 (± 7D)	W36 (± 7D)	W44 (± 7D)	W52 (± 7D)	W66 (± 7D)		FU1 (± 3D)	FU2 (± 3D)

- g. Blood samples for PK will be collected at the FU2 Visit only from subjects whose lymphocyte count has not returned to ≥ 800 cells/mm³ (0.8×10^9 cells/L) at the FU1 Visit or from subjects who experienced any AEs during the 4-week Follow-Up Period.
- h. Subjects may be re-dispensed IP.
- i. IP will be dispensed only if the subject elects to continue in SS4-E and if the Extension First Dose Visit of SS4-E is not performed on the same day as the W66 Visit.
- j. An additional ICF will be provided to subjects for whole blood genetic analysis. If samples for genetic analysis are not collected at the BL Visit, they may be obtained at the Week 1 Visit (refer to Section 10.10).
- k. PGIC will not be collected at BL.
- l. Video ileocolonoscopy should be performed at least 5 days before the Day 1 (baseline) visit to obtain central reading for eligibility assessment. Ileocolonoscopy to determine study eligibility should be performed after most other screening assessments are completed. A repeat video ileocolonoscopy is NOT required if the ET Visit occurs within 6 weeks of the Day 1, Week 14, or Week 52 Visit. Refer to Section 10.2.9 for more details on post-baseline ileocolonoscopy assessment.
- m. Stool samples for FCP should be obtained at the indicated study visits and at any time during the study when subjects have new or worsened CD symptoms suggestive of disease relapse or progression.
- n. As a part of first-dose cardiac monitoring, vital signs (HR, BP, body temperature, and respiratory rate) collection and 12-lead ECG will be performed prior to randomization to determine if the subject remains eligible for study enrollment. At the BL/Day 1 Visit, HR and BP will also be obtained at Hours 1, 2, 3, and 4 (± 15 minutes) postdose and 12-lead ECG is performed at the Hour 4 discharge assessment. Refer to Section 10.7.8.4 for details of the first-dose cardiac monitoring procedures.
- o. Full physical examinations will be performed at Screening and at the Week 14, Week 28, and Week 66 Visits or at the ET Visit. Symptom-directed physical examination and a physical examination that assesses the presence of abdominal mass and physical signs consistent with EIMs of IBD as described in Section 10.7.2 should be performed at the other study visits.
- p. Subjects should fast for 9 - 12 hours (drinking water only) before the blood sample collection for the lipid panel.
- q. Infectious disease serology tests to be performed at Screening are described in Table 15.
- r. A TB screening questionnaire will be administered to all subjects at Screening and only to subjects residing in countries with high burden of TB or MDR TB also at subsequent visits as described in Appendix 2.
- s. If TB is suspected at any time during the study, subjects should be screened. The TB screening test (eg, IGRA) should be performed by a central laboratory prior to randomization and should only be repeated at Week 52 to screen for latent TB infection in subjects who previously tested negative for latent TB infection at Screening (refer to Appendix 2).
- t. Only subjects for whom the VZV vaccine is indicated should be screened for VZV IgG, if the vaccine is locally available (refer to Section 10.2.8).
- u. For females of childbearing potential only. A serum pregnancy test for β hCG will be performed at Screening to determine eligibility. Urine pregnancy tests (β hCG) should be performed post screening. A monthly pregnancy test in non-visit months should be performed at home (as permitted by local regulations) or at the study site at an unscheduled visit. Any positive result should be immediately reported to the study site. A positive urine pregnancy test must be confirmed with a follow up serum β hCG pregnancy test.
- v. To be performed only for women with no menses for ≥ 12 months to confirm postmenopausal status.
- w. Stool sample for bacterial culture, ova, and parasite evaluation, and C. difficile assay should also be taken at any point in the study when a subject becomes symptomatic, including worsening or return of disease activity.
- x. Unscheduled assessments may also be performed, as clinically indicated, as part of the study visit assessment due to complaints of decreased vision or identification of worsening visual acuity (refer to Section 10.7.7). If ophthalmoscopy and OCT were performed within 2 weeks of the ET Visit, repeat assessments are not required at the ET Visit.

Table 29: Schedule of Assessments for Substudy A – Phase 2

Evaluations	SP	14-Week Induction Period							52-Week Extension Period								ET ^a	4-Week Follow-Up Period ^b	
	Day – 28 to –1	BL Day 1	W1 (± 1D)	W2 (± 3D)	W4 (± 3D)	W6 (± 3D)	W10 (± 3D)	W14 (± 3D)	W15 (± 3D)	End W15 (± 3D)	W20 (± 3D)	W28 (± 7D)	W36 (± 7D)	W44 (± 7D)	W52 (± 7D)	W66 (± 7D)		FU1 (± 3D)	FU2 (± 3D)

y. Visit windows for performing PFT and DLCO (where locally available) are described in Section 10.7.6. Unscheduled PFT assessments should be performed for subjects reporting any respiratory symptoms (eg, dyspnea, shortness of breath, chest tightness, or wheezing), preferably on the same day (refer to Section 10.7.6). If PFT and DLCO were performed within 2 weeks of the ET Visit, repeat assessments are not required at the ET Visit.

AE, adverse event; β-hCG, beta human chorionic gonadotropin; BL, baseline; BP, blood pressure; CBC, complete blood count; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; D, day; DLCO, diffusing capacity of the lungs for carbon monoxide; ECG, electrocardiogram; eDiary, electronic diary; EIMs, extraintestinal manifestation; ET, Early Termination; FCP, fecal calprotectin; FSH, follicle-stimulating hormone; HR, heart rate; IBD, inflammatory bowel disease; ICF, informed consent form; IgG, immunoglobulin G; IP, investigational product; med, medical; MDR, multi-drug resistance; OCT, optical coherence tomography; PFT, pulmonary function test; PGIC, Patient Global Impression of Change; PK, pharmacokinetic; PRO, patient-reported outcome; SP, Screening Period; SS4-E, Substudy 4 – Extension; TB, tuberculosis; TBNK, T Cell, B Cell, and natural killer (cells); TSH, thyroid stimulating hormone; VZV, varicella zoster virus; W, week; WBC, white blood cells

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Table 30: Schedule of Assessments for Substudy 1 – Phase 2b

Evaluations	Screening Period	14-Week Induction Period						Extended Induction Period ^a			ET ^b	4-Week Follow-Up Period ^c	
	Day –40 to –1	BL Day 1	W1 (± 1D)	W2 (± 3D)	W6 (± 3D)	W10 (± 3D)	W14 (± 3D)	EIFD (± 3D)	EI-W1 (± 3D)	EI-W6 (± 3D)		FU1 (± 3D)	FU2 (± 3D)
Visit Type	Site	Site	Site or Remote	Site	Site	Site	Site	Site or Remote	Site or Remote	Site	Site	Site or Remote	Site or Remote
Informed consent	x												
Inclusion/exclusion criteria	x	x											
Demographic and medical history ^d	x	x											
eDiary training ^e	x												
eDiary review		x	x	x	x	x	x	x	x	x	x		
Randomization		x						x ^f					
Dose IP in clinic ^g		x	x	x	x		x	x	x	x			
PK sampling ^h		x	x	x	x		x			x	x	x	x ⁱ
Dispense IP		x	x		x	x	x ^j	x	x	x ^j			
Drug accountability			x	x ^k	x	x	x	x	x	x	x		
Prior and concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x
Blood for genetic analysis (optional) ^l		x											
CDAI	x	x		x	x	x	x			x	x		
PRO2 calculation	x	x	x	x	x	x	x	x	x	x	x		

Table 30: Schedule of Assessments for Substudy 1 – Phase 2b

Evaluations	Screening Period	14-Week Induction Period						Extended Induction Period ^a			ET ^b	4-Week Follow-Up Period ^c	
	Day –40 to –1	BL Day 1	W1 (± 1D)	W2 (± 3D)	W6 (± 3D)	W10 (± 3D)	W14 (± 3D)	EIFD (± 3D)	EI-W1 (± 3D)	EI-W6 (± 3D)		FU1 (± 3D)	FU2 (± 3D)
Visit Type	Site	Site	Site or Remote	Site	Site	Site	Site	Site or Remote	Site or Remote	Site	Site	Site or Remote	Site or Remote
Health-Related PROs		x ^m					x			x	x		
CD-related hospitalization and surgery	x	x	x	x	x	x	x	x	x	x	x	x	x
CRP	x	x	x	x	x	x	x		x	x	x		
Ileocolonoscopy with biopsy ⁿ	x						x				x		
FCP ^o		x		x	x	x	x			x	x		
Stool microbiome		x					x			x			
Exploratory biomarkers		x					x			x			
Seated vital signs	x	x ^p	x	x	x	x	x	x ^p	x	x	x	x	x
Physical examination ^q	x	x		x	x		x			x	x		x
12-lead ECG	x	x ^p					x	x ^p			x		
Holter monitoring			x	x									
CBC with differential and platelets	x	x	x	x	x	x	x			x	x	x	x

Table 30: Schedule of Assessments for Substudy 1 – Phase 2b

Evaluations	Screening Period	14-Week Induction Period						Extended Induction Period ^a			ET ^b	4-Week Follow-Up Period ^c	
	Day –40 to –1	BL Day 1	W1 (± 1D)	W2 (± 3D)	W6 (± 3D)	W10 (± 3D)	W14 (± 3D)	EIFD (± 3D)	EI-W1 (± 3D)	EI-W6 (± 3D)		FU1 (± 3D)	FU2 (± 3D)
Visit Type	Site	Site	Site or Remote	Site	Site	Site	Site	Site or Remote	Site or Remote	Site	Site	Site or Remote	Site or Remote
TBNK panel cell count	x	x		x	x	x	x			x	x		x
Serum chemistry	x	x			x	x	x			x	x		x
Lipid panel ^f , TSH, uric acid		x					x			x	x		
Coagulation panel	x			x	x	x	x			x	x		
Infectious disease serology ^g	x												
TB questionnaire ^h	x						x						
TB screening ⁱ	x												
VZV IgG screening ^v	x												
Pregnancy test ^w	x	x		x	x	x	x			x	x		x
FSH ^x	x												
Urinalysis	x						x				x		
Urine drug screen	x												
Stool studies ^y	x												
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x

Table 30: Schedule of Assessments for Substudy 1 – Phase 2b

Evaluations	Screening Period	14-Week Induction Period						Extended Induction Period ^a			ET ^b	4-Week Follow-Up Period ^c	
	Day –40 to –1	BL Day 1	W1 (± 1D)	W2 (± 3D)	W6 (± 3D)	W10 (± 3D)	W14 (± 3D)	EIFD (± 3D)	EI-W1 (± 3D)	EI-W6 (± 3D)		FU1 (± 3D)	FU2 (± 3D)
Visit Type	Site	Site	Site or Remote	Site	Site	Site	Site	Site or Remote	Site or Remote	Site	Site	Site or Remote	Site or Remote
Ophthalmoscopy and OCT ^z	x						x				x		
PFT and DLCO ^{aa}	x						x				x		x

- Only subjects who do not meet response criteria (Section 3.1.2) at the W14 Visit will enter the EI Period (refer to Section 9.5.3.2). The EIFD Visit is the first visit of the EI Period and should occur within 1 week (± 3 days) of the W14 Visit but may be performed on the same day as the W14 Visit. No repeat assessments are required if the EIFD Visit is performed on the same day as the W14 Visit.
- If a subject ends study participation before the end of the substudy (ie, the W14 Visit or EI-W6 Visit for subjects who complete the EIFD Visit), the ET Visit should be performed. The ET Visit should occur within 7 days of last dose and before initiation of any new treatments (refer to Section 9.5.5).
- The FU1 and FU2 Visits should be performed for all subjects at 14 days and 28 days, respectively, following the last dose of study drug.
- CD medical history should include date of diagnosis, disease severity, hospitalizations, EIMs, smoking status, duration, disease localization (ileum/colon/both), disease activity, presence and location of fistula, prior treatment, and complications.
- Subjects will begin eDiary entries on the first day of screening after eDiary training is completed.
- Applies only to subjects who received placebo during the Induction Period who will be randomized (1:1) to receive etrasimod 2 mg or 3 mg (refer to Table 2).
- On study visit days where PK blood samples are collected, subjects should be instructed to take their dose after blood draws for PK are collected.
- Blood samples for PK will be collected predose (within 60 minutes prior to dosing) and at 4 hours postdose (after the ECG) on Day 1 and predose (trough; within 60 minutes prior to dosing) at all other indicated days during the treatment period. A PK blood sample will also be collected 2 weeks after the last dose of study drug. If possible, a PK blood sample should be collected at the time of an AE leading to study drug discontinuation or when there is a significant AE such as a severe or atypical infection (including but not limited to systemic infections like sepsis) and severe drug-induced liver injury that meets Hy's criteria; the time of the last study drug dose should be documented (refer to Section 10.6).
- Blood samples for PK will be collected at the FU2 Visit only from subjects whose lymphocyte count has not returned to ≥ 800 cells/mm³ (0.8×10^9 cells/L) at the FU1 Visit or from subjects who experienced any AEs during the 4-week Follow-Up Period.
- IP will be dispensed only to subjects who elect to continue in the subsequent Treatment Period (eg, EI Treatment Period or SS3-M Treatment Period) and if the first visit of the subsequent Treatment Period (eg, EIFD or MFD Visits) is not performed on the same day.
- After performing drug accountability subjects will be re-dispensed their Week 1 IP at the Week 2 Visit, no new IP will be dispensed at Week 2.
- An additional ICF will be provided to subjects for whole blood genetic analysis. If samples for genetic analysis are not collected at the BL Visit, they may be obtained at the Week 1 Visit (refer to Section 10.10).
- PGIC will not be collected at baseline.

Table 30: Schedule of Assessments for Substudy 1 – Phase 2b

Evaluations	Screening Period	14-Week Induction Period						Extended Induction Period ^a			ET ^b	4-Week Follow-Up Period ^c	
	Day –40 to –1	BL Day 1	W1 (± 1D)	W2 (± 3D)	W6 (± 3D)	W10 (± 3D)	W14 (± 3D)	EIFD (± 3D)	EI-W1 (± 3D)	EI-W6 (± 3D)		FU1 (± 3D)	FU2 (± 3D)
Visit Type	Site	Site	Site or Remote	Site	Site	Site	Site	Site or Remote	Site or Remote	Site	Site	Site or Remote	Site or Remote

- n. Video ileocolonoscopy should be performed at least 5 days before the BL/Day 1 Visit to obtain central reading for eligibility assessment. Ileocolonoscopy to determine study eligibility should be performed after most other screening assessments are completed. A repeat video ileocolonoscopy is NOT required if the ET Visit occurs within 6 weeks of the Day 1 or Week 14 Visit. Refer to Section 10.2.9 for more details on post baseline ileocolonoscopy assessment.
- o. Stool samples for FCP should also be obtained at any time during the study when subjects have new or worsened CD symptoms.
- p. As a part of first-dose cardiac monitoring, vital signs (HR, BP, body temperature, and respiratory rate) collection and 12-lead ECG will be performed prior to randomization for BL/Day 1 Visit (to determine if the subject remains eligible for study enrollment) and predose for the EIFD Visit. In addition, HR and BP will be obtained at Hours 1, 2, 3, and 4 (± 15 minutes) postdose and 12-lead ECG is performed at the Hour 4 discharge assessment as part of the first-dose cardiac monitoring procedure for the BL/Day 1 and EIFD Visits. Refer to Section 10.7.8.4 for details of the first-dose cardiac monitoring procedures.
- q. Full physical examinations will be performed at Screening and at W14 or at the ET Visit. Symptom-directed physical examination and a physical examination that assesses the presence of abdominal mass and physical signs consistent with EIMs of IBD as described in Section 10.7.2 should be performed at the other study visits.
- r. Subjects should fast for 9 - 12 hours (drinking water only) before the blood sample collection for the lipid panel.
- s. Infectious disease serology tests to be performed at Screening are described in Table 15.
- t. A TB screening questionnaire will be administered to all subjects at Screening and only to subjects residing in countries with high burden of TB or MDR TB at subsequent visits as described in Appendix 2.
- u. If TB is suspected at any time during the study, subjects should be screened. The TB screening test (eg, IGRA) should be performed by a central laboratory prior to randomization only in subjects who previously tested negative on the TB screening test (refer to Appendix 2).
- v. Only subjects for whom the VZV vaccine is indicated should be screened for VZV IgG, if the vaccine is locally available (refer to Section 10.2.8).
- w. For females of childbearing potential only. A serum pregnancy test for βhCG- will be performed at Screening to determine eligibility. Urine pregnancy tests (βhCG) should be performed -post screening. A positive urine pregnancy test must be confirmed with a -follow up- serum βhCG- pregnancy test (refer to Section 10.2.6).
- x. To be performed only for women with no menses for ≥ 12 months to confirm postmenopausal status.
- y. Stool sample for bacterial culture, ova, and parasite evaluation, and *C. difficile* assay should also be taken at any point in the study when a subject becomes symptomatic, including worsening or return of disease activity.
- z. Unscheduled assessments may also be performed, as clinically indicated, as part of the study visit assessment due to complaints of decreased vision or identification of worsening visual acuity (refer to Section 10.7.7).
- aa. Visit windows for performing PFT and DLCO (where locally available) are described in Section 10.7.6. Unscheduled PFT assessments should be performed for subjects reporting any respiratory symptoms (eg, dyspnea, shortness of breath, chest tightness, or wheezing), preferably on the same day (refer to Section 10.7.6).
- AE, adverse event; β-hCG, beta human chorionic gonadotropin; BL, baseline; BP, blood pressure; CBC, complete blood count; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; D, day; DLCO, diffusing capacity of the lungs for carbon monoxide; ECG, electrocardiogram; eDiary, electronic diary; EI, extended induction; EIFD, extended induction first dose; EIMs, extraintestinal manifestations; ET, Early Termination; FCP, fecal calprotectin; FSH, follicle-stimulating hormone; FU, follow-up; HR, heart rate; IBD, inflammatory bowel disease; ICF, informed consent form; IgG, immunoglobulin G; IGRA, interferon-gamma release assay; IP, investigational product; MFD, maintenance first dose; MDR, multi-drug resistance; OCT, optical coherence tomography; PFT, pulmonary function test; PGIC, Patient Global Impression of

Table 30: Schedule of Assessments for Substudy 1 – Phase 2b

Evaluations	Screening Period	14-Week Induction Period						Extended Induction Period ^a			ET ^b	4-Week Follow-Up Period ^c	
	Day –40 to –1	BL Day 1	W1 (± 1D)	W2 (± 3D)	W6 (± 3D)	W10 (± 3D)	W14 (± 3D)	EIFD (± 3D)	EI-W1 (± 3D)	EI-W6 (± 3D)		FU1 (± 3D)	FU2 (± 3D)
Visit Type	Site	Site	Site or Remote	Site	Site	Site	Site	Site or Remote	Site or Remote	Site	Site	Site or Remote	Site or Remote

Change; PK, pharmacokinetic; PRO, patient-reported outcome; SS3-M, Substudy 3 – Maintenance; TB, tuberculosis; TBNK, T Cell, B Cell, and natural killer (cells); TSH, thyroid-stimulating hormone; VZV, varicella zoster virus; W, week; WBC, white blood cells

Table 31: Schedule of Assessments for Substudy 2 – Induction

Evaluations	Screening Period	14-Week Induction Period						Extended Induction Period ^a			ET ^b	4-Week Follow-Up Period ^c	
	Day-40 to -1	BL Day 1	W1 ^d (± 1D)	W2 (± 3D)	W6 (± 3D)	W10 (± 3D)	W14 (± 3D)	E1FD (± 3D)	E1-W1 (± 3D)	E1-W6 (± 3D)		FU1 (± 3D)	FU2 (± 3D)
Visit Type	Site	Site	Site or Remote	Site	Site	Site	Site	Site or Remote	Site or Remote	Site	Site	Site or Remote	Site or Remote
Informed consent	x												
Inclusion/exclusion criteria	x	x											
Demographic and medical history ^e	x	x											
eDiary training ^f	x												
eDiary review		x	x	x	x	x	x	x	x	x	x		
Randomization		x											
Dose IP in clinic ^g		x	x	x	x		x	x	x	x			
PK sampling ^h		x		x			x			x	x	x	x ⁱ
Dispense IP		x	x	x ^j	x ^j	x	x ^k	x	x	x ^k			
Drug accountability			x	x	x	x	x	x	x	x	x		
Prior and concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x
Blood for genetic analysis (optional) ^l		x											
CDAI	x	x		x	x	x	x			x	x		
PRO2 calculation	x	x	x	x	x	x	x	x	x	x	x		

Table 31: Schedule of Assessments for Substudy 2 – Induction

Evaluations	Screening Period	14-Week Induction Period						Extended Induction Period ^a			ET ^b	4-Week Follow-Up Period ^c	
	Day-40 to -1	BL Day 1	W1 ^d (± 1D)	W2 (± 3D)	W6 (± 3D)	W10 (± 3D)	W14 (± 3D)	E1FD (± 3D)	E1-W1 (± 3D)	E1-W6 (± 3D)		FU1 (± 3D)	FU2 (± 3D)
Visit Type	Site	Site	Site or Remote	Site	Site	Site	Site	Site or Remote	Site or Remote	Site	Site	Site or Remote	Site or Remote
Health-Related PROs		x ^m			x		x			x	x		
CD-related hospitalization and surgery	x	x	x	x	x	x	x	x	x	x	x	x	x
CRP	x	x	x	x	x		x			x	x		
Ileocolonoscopy with biopsy ⁿ	x						x				x		
FCP ^o		x		x	x	x	x			x	x		
Seated vital signs	x	x ^p	x	x	x	x	x	x ^p	x	x	x		x
Physical examination ^q	x	x		x	x		x			x	x		x
12-lead ECG	x	x ^p					x	x ^p			x		
CBC with differential and platelets	x	x	x	x	x	x	x			x	x	x	x
TBNK panel count	x	x		x	x		x			x	x		x
Serum chemistry	x	x			x	x	x			x	x		x
Coagulation panel	x			x	x	x	x			x	x		
Infectious disease serology ^r	x												

Table 31: Schedule of Assessments for Substudy 2 – Induction

Evaluations	Screening Period	14-Week Induction Period						Extended Induction Period ^a			ET ^b	4-Week Follow-Up Period ^c	
	Day-40 to -1	BL Day 1	W1 ^d (± 1D)	W2 (± 3D)	W6 (± 3D)	W10 (± 3D)	W14 (± 3D)	EIFD (± 3D)	EI-W1 (± 3D)	EI-W6 (± 3D)		FU1 (± 3D)	FU2 (± 3D)
Visit Type	Site	Site	Site or Remote	Site	Site	Site	Site	Site or Remote	Site or Remote	Site	Site	Site or Remote	Site or Remote
TB questionnaire ^s	x						x						
TB screening ^t	x												
VZV IgG screening ^u	x												
Pregnancy test ^v	x	x		x	x	x	x			x	x		x
FSH ^w	x												
Urinalysis	x						x				x		
Urine drug screen	x												
Stool studies ^x	x												
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x
Ophthalmoscopy and OCT ^y	x						x				x		
PFT and DLCO ^z	x						x				x		x

- Only subjects who do not meet response criteria (Section 3.1.2) at the W14 Visit will enter the EI Period (refer to Section 9.6.4). The EIFD Visit is the first visit of the EI Period and should occur within 1 week (± 3 days) of the W14 Visit but may be performed on the same day as the W14 Visit. No repeat assessments are required if the EIFD Visit is performed on the same day as the W14 Visit. If etrasimod 3 mg is the selected Phase 3 dose, an EI-W1 Visit (± 3 days) will be required.
- If a subject ends study participation before the end of the substudy (ie, the W14 Visit or EI-W6 Visit for subjects who complete the EIFD Visit), the ET Visit should be performed. The ET Visit should occur within 7 days of last dose of study drug and before initiation of any new treatments (refer to Section 9.6.6).
- The FU1 and FU2 Visits should be performed for all subjects at 14 days and 28 days, respectively, following the last dose of study drug.
- This study visit will only be required if etrasimod 3 mg is the selected Phase 3 etrasimod dose.
- CD medical history should include date of diagnosis, disease severity, hospitalizations, EIMs, smoking status, duration, disease localization (ileum/colon/both), disease activity, presence and location of fistula, prior treatment, and complications.
- Subjects will begin eDiary entries on the first day of screening after eDiary training is completed.
- On study visit days where PK blood samples are collected, subjects should be instructed to take their dose after blood draws for PK are collected.

Table 31: Schedule of Assessments for Substudy 2 – Induction

Evaluations	Screening Period	14-Week Induction Period						Extended Induction Period ^a			ET ^b	4-Week Follow-Up Period ^c	
	Day-40 to -1	BL Day 1	W1 ^d (± 1D)	W2 (± 3D)	W6 (± 3D)	W10 (± 3D)	W14 (± 3D)	EIFD (± 3D)	EI-W1 (± 3D)	EI-W6 (± 3D)		FU1 (± 3D)	FU2 (± 3D)
Visit Type	Site	Site	Site or Remote	Site	Site	Site	Site	Site or Remote	Site or Remote	Site	Site	Site or Remote	Site or Remote

- h. Blood samples for PK will be collected predose (within 60 minutes prior to dosing), 1.5 hours postdose and at 4 hours postdose (after the ECG) on Day 1 and predose (trough; within 60 minutes prior to dosing) at all other indicated days during the treatment period. A PK blood sample will also be collected 2 weeks after the last dose of study drug. If possible, a PK blood sample should be collected at the time of an AE leading to study drug discontinuation or when there is a significant AE such as a severe or atypical infection (including but not limited to systemic infections like sepsis) and severe drug induced liver injury that meets Hy's criteria; the time of the last study drug dose should be documented (refer to Section 10.6).
- i. Blood samples for PK will be collected at the FU2 Visit only from subjects whose lymphocyte count has not returned to ≥ 800 cells/mm³ (0.8×10^9 cells/L) at the FU1 Visit or from subjects who experienced any AEs during the 4-week Follow-Up Period.
- j. Subjects may be re-dispensed IP.
- k. IP will be dispensed only if the subject elects to continue in the subsequent Treatment Period (eg, EI Treatment Period or SS3-M Treatment Period) and if the first visit of the subsequent Treatment Period (eg, EIFD or MFD Visits) is not performed on the same day.
- l. An additional ICF will be provided to subjects for whole blood genetic analysis. If samples for genetic analysis are not collected at the BL Visit, they may be obtained at the Week 1 Visit. If etrasimod 2 mg is selected as the Phase 3 dose and there is no Week 1 Visit, sample collection will be permitted at the Week 2 Visit if samples for genetic analysis are not collected at the BL Visit (refer to Section 10.10).
- m. PGIC will not be collected at BL.
- n. Video ileocolonoscopy should be performed at least 5 days before the BL/Day 1 Visit to obtain central reading for eligibility assessment. Ileocolonoscopy to determine study eligibility should be performed after most other screening assessments are completed. A repeat video ileocolonoscopy is NOT required if the ET Visit occurs within 6 weeks of the Day 1 or Week 14 Visit. Refer to Section 10.2.9 for more details on post-baseline ileocolonoscopy assessment.
- o. Stool samples for FCP should also be obtained at any time during the study when subjects have new or worsened CD symptoms.
- p. As a part of first-dose cardiac monitoring, vital signs (HR, BP, body temperature, and respiratory rate) collection and 12-lead ECG will be performed prior to randomization for BL/Day 1 Visit (to determine if the subject remains eligible for study enrollment) and predose for the EIFD Visit. In addition, HR and BP will be obtained at Hours 1, 2, 3, and 4 (± 15 minutes) postdose and 12-lead ECG is performed at the Hour 4 discharge assessment as part of the first-dose cardiac monitoring procedure for the BL/Day 1 and EIFD Visits. Refer to Section 10.7.8.4 for details of the first-dose cardiac monitoring procedures.
- q. Full physical examinations will be performed at Screening and at Week 14 or at the ET Visit. Symptom directed physical examination and a physical examination that assesses the presence of abdominal mass and physical signs consistent with EIMs of IBD as described in Section 10.7.2 should be performed at the other study visits.
- r. Infectious disease serology tests to be performed at Screening are described in Table 15.
- s. A TB screening questionnaire will be administered to all subjects at Screening and only to subjects residing in countries with high burden of TB or MDR TB at subsequent visits as described in Appendix 2.
- t. If TB is suspected at any time during the study, subjects should be screened. The TB screening test (eg, IGRA) should be performed by a central laboratory prior to randomization only in subjects who previously tested negative on the TB screening test (refer to Appendix 2).
- u. Only subjects for whom the VZV vaccine is indicated should be screened for VZV IgG, if the vaccine is locally available (refer to Section 10.2.8).
- v. For females of childbearing potential only. A serum pregnancy test for β hCG- will be performed at Screening to determine eligibility. Urine pregnancy tests (β hCG) should be performed -post screening. A positive urine pregnancy test must be confirmed with a -follow-up- serum β hCG- pregnancy test (refer to Section 10.2.6).

Table 31: Schedule of Assessments for Substudy 2 – Induction

Evaluations	Screening Period	14-Week Induction Period						Extended Induction Period ^a			ET ^b	4-Week Follow-Up Period ^c	
	Day -40 to -1	BL Day 1	W1 ^d (± 1D)	W2 (± 3D)	W6 (± 3D)	W10 (± 3D)	W14 (± 3D)	E1FD (± 3D)	E1-W1 (± 3D)	E1-W6 (± 3D)		FU1 (± 3D)	FU2 (± 3D)
Visit Type	Site	Site	Site or Remote	Site	Site	Site	Site	Site or Remote	Site or Remote	Site	Site	Site or Remote	Site or Remote

- w. To be performed only for women with no menses for ≥ 12 months to confirm postmenopausal status (refer to Section 10.2.6).
- x. Stool sample for bacterial culture, ova, and parasite evaluation, and *C. difficile* assay should also be taken at any point in the study when a subject becomes symptomatic, including worsening or return of disease activity.
- y. Unscheduled assessments may also be performed, as clinically indicated, as part of the study visit assessment due to complaints of decreased vision or identification of worsening visual acuity (refer to Section 10.7.7).
- z. Visit windows for performing PFT and DLCO (where locally available) are described in Section 10.7.6. Unscheduled PFT assessments should be performed for subjects reporting any respiratory symptoms (eg, dyspnea, shortness of breath, chest tightness, or wheezing), preferably on the same day (refer to Section 10.7.6).
- AE, adverse event; β -hCG, beta human chorionic gonadotropin; BL, baseline; BP, blood pressure; CBC, complete blood count; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; D, day; DLCO, diffusing capacity of the lungs for carbon monoxide; ECG, electrocardiogram; eDiary, electronic diary; EI, extended induction; E1FD, extended induction first dose; EIMs, extraintestinal manifestations; ET, Early Termination; FCP, fecal calprotectin; FSH, follicle-stimulating hormone; FU, follow-up; HR, heart rate; IBD, inflammatory bowel disease; ICF, informed consent form; IgG, immunoglobulin G; IGRA, interferon-gamma release assay; IP, investigational product; MFD, maintenance first dose; MDR, multi-drug resistance; OCT, optical coherence tomography; PFT, pulmonary function test; PGIC, Patient Global Impression of Change; PK, pharmacokinetic; PRO, patient-reported outcome; SS3-M, Substudy 3 – Maintenance; TB, tuberculosis; TBNK, T Cell, B Cell, and natural killer (cells); VZV, varicella zoster virus; W, week; WBC, white blood cells

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Table 32: Schedule of Assessments for Substudy 3 – Maintenance

Evaluations	Maintenance Treatment Period						Loss-of-Response Visits ^a			ET ^b	4-Week Follow-Up Period ^c	
	MFD ^d (+ 3D)	M-6 (± 3D)	M-14 (± 7D)	M-22 (± 7D)	M-30 (± 7D)	M-38/ Week 52 (± 7D)	LOR ^e	LOR FD ^f	LOR DE ^g		FU1 (± 3D)	FU2 (± 3D)
		Week 6	Week 14	Week 22	Week 30	Week 38*						
Visit Type	Site or Remote	Site	Site	Site	Site	Site	Site	Site	Site or Remote	Site	Site or Remote	Site or Remote
Informed consent	x											
eDiary review	x	x	x	x	x	x	x	x	x	x		
Dose IP in clinic ^h	x		x			x		x	x			
PK sampling ⁱ			x			x				x	x	x ^j
Dispense IP	x	x ^k	x	x	x	x ^l		x	x			
Drug accountability	x	x	x	x	x	x	x	x	x	x		
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x
CDAI calculation		x	x	x	x	x	x	x		x		
PRO2 calculation		x	x	x	x	x	x	x		x		
Health-Related PROs			x			x		x		x		
CD-related hospitalization and surgery	x	x	x	x	x	x	x	x	x	x	x	x
CRP		x	x	x	x	x		x		x		
Ileocolonoscopy with biopsy						x ^m		x ⁿ		x ^o		

Table 32: Schedule of Assessments for Substudy 3 – Maintenance

Evaluations	Maintenance Treatment Period						Loss-of-Response Visits ^a			ET ^b	4-Week Follow-Up Period ^c	
	MFD ^d (+ 3D)	M-6 (± 3D)	M-14 (± 7D)	M-22 (± 7D)	M-30 (± 7D)	M-38/ Week 52 (± 7D)	LOR ^e	LOR FD ^f	LOR DE ^g		FU1 (± 3D)	FU2 (± 3D)
		Week 6	Week 14	Week 22	Week 30	Week 38*						
Visit Type	Site or Remote	Site	Site	Site	Site	Site	Site	Site	Site or Remote	Site	Site or Remote	Site or Remote
FCP ^p			X			X		X		X		
Stool studies ^q							X					
Exploratory biomarkers & stool microbiome ^r						X				X		
Seated vital signs	X	X	X	X	X	X	X	X ^s	X	X		X
Physical examination ^t		X	X	X	X	X	X	X		X		X
12-lead ECG			X			X		X ^s		X		
CBC with differential and platelets		X	X	X	X	X	X	X		X	X	X
TBNK panel cell count		X	X	X	X	X				X		X
Serum chemistry		X	X	X	X	X				X		X
Coagulation panel			X		X	X				X		
TB questionnaire ^u			X		X							
TB screening ^v						X						

Table 32: Schedule of Assessments for Substudy 3 – Maintenance

Evaluations	Maintenance Treatment Period						Loss-of-Response Visits ^a			ET ^b	4-Week Follow-Up Period ^c	
	MFD ^d (+ 3D)	M-6 (± 3D)	M-14 (± 7D)	M-22 (± 7D)	M-30 (± 7D)	M-38/ Week 52 (± 7D)	LOR ^e	LOR FD ^f	LOR DE ^g		FU1 (± 3D)	FU2 (± 3D)
		Week 6	Week 14	Week 22	Week 30	Week 38*						
Visit Type	Site or Remote	Site	Site	Site	Site	Site	Site	Site	Site or Remote	Site	Site or Remote	Site or Remote
Pregnancy test ^w	x	x	x	x	x	x				x		x
Urinalysis						x				x		
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x
Ophthalmoscopy and OCT ^x			x			x				x		
PFT and DLCO ^y			x			x				x		x

*Subjects who complete this 38-week substudy will have completed at least 52 weeks of treatment (induction and maintenance treatment). This is also referred to as 'Week 52' for SS3-M in various sections of the protocol.

- Applicable only to subjects in the SS3-M Responder Cohort who experience sustained disease worsening (refer to Section 9.7.3).
- If a subject ends study participation before the M-38 Visit, the ET Visit should be performed. The ET Visit should occur within 7 days of last dose and before initiation of any new treatments. If ophthalmology, OCT, PFT, and DLCO assessments were performed within 2 weeks of ET Visit, these assessments do not need to be repeated.
- The FU1 and FU2 Visits should be performed for all subjects at 14 days and 28 days, respectively, following the last dose of study drug.
- All subjects, regardless of Cohort, will have a MFD Visit, which is the first visit of SS3-M. The MFD Visit must occur within 7 days of the last visit of the parent study or substudy (ie, within 7 days of the Week 14 or EI-Week 6 Visits). No repeat assessments are required if the MFD Visit is performed on the same day as the last visit of the parent study or substudy (refer to Section 9.7.1).
- LOR assessment may not occur prior to the M-6 Visit but may be performed at any time following the M-6 Visit for subjects in the SS3-M Responder Cohort who experience sustained disease worsening. Assessments may be performed at a scheduled visit during the Maintenance Treatment Period or at an unscheduled LOR Visit. Repeat LOR Visits are permitted, but should be at least 1 week apart (refer to Section 9.7.3).
- An unscheduled LOR FD Visit should be performed for subjects who have met the LOR criteria as determined at a LOR Visit (refer to Section 9.7.3). Subjects should continue with the visit schedule as indicated in the Maintenance Treatment Period, but repeat assessments are not required if the LOR Visit occurs on the same day as a scheduled visit in the Maintenance Treatment Period.
- An unscheduled LOR DE Visit should occur approximately 1 week following the LOR FD Visit and will only be required prior to dose selection or if the selected dose in Phase 3 is etrasimod 3 mg. Subjects should continue with the visit schedule as indicated in the Maintenance Treatment Period, but repeat assessments are not required if the LOR DE Visit occurs on the same day as a scheduled visit in the Maintenance Treatment Period.

Table 32: Schedule of Assessments for Substudy 3 – Maintenance

Evaluations	Maintenance Treatment Period						Loss-of-Response Visits ^a			ET ^b	4-Week Follow-Up Period ^c	
	MFD ^d (+ 3D)	M-6 (± 3D)	M-14 (± 7D)	M-22 (± 7D)	M-30 (± 7D)	M-38/ Week 52 (± 7D)	LOR ^e	LOR FD ^f	LOR DE ^g		FU1 (± 3D)	FU2 (± 3D)
		Week 6	Week 14	Week 22	Week 30	Week 38*						
Visit Type	Site or Remote	Site	Site	Site	Site	Site	Site	Site	Site or Remote	Site	Site or Remote	Site or Remote

- h. On study visit days where PK blood samples are collected, subjects should be instructed to take their dose after blood draws for PK are collected.
- i. Blood samples for PK will be collected predose (trough; within 60 minutes prior to dosing) at indicated study visits during the Maintenance Period. A PK blood sample will also be collected 2 weeks after the last dose of study drug. The time of the last study drug dose prior to the study visit should be documented (refer to Section 10.6).
- j. Blood samples for PK will be collected at the FU2 Visit only from subjects whose lymphocyte count has not returned to ≥ 800 cells/mm³ (0.8×10^9 cells/L) at the FU1 Visit or from subjects who experienced any AEs during the 4-week Follow-Up Period.
- k. Subjects may be re-dispensed IP.
- l. IP will be dispensed only if the subject elects to continue in SS4-E and if the EFD Visit is not performed the same day as M-38 Visit.
- m. For subjects in the SS3-M Responder Cohort that experience a loss of response and switch to the Nonresponder Cohort, an ileocolonoscopy if possible, for SES-CD should occur 52 weeks after the LOR FD Visit instead of at the M-38 Visit (refer to Section 10.5.1).
- n. Subjects will have an ileocolonoscopy (where possible) prior to switching to the Nonresponder Cohort if the LOR Visit occurs more than 6 weeks after the W14 Visit of the parent induction study or substudy.
- o. No additional endoscopy is required if a subject's ET Visit occurs after the M-38 Visit.
- p. Stool samples for FCP should also be obtained at any time during the study when subjects have new or worsened CD symptoms.
- q. Stool sample for bacterial culture, ova, and parasite evaluation, and *C. difficile* assay should be collected at LOR Visit and at any point in the study when a subject becomes symptomatic, including worsening or return of disease activity.
- r. Samples for exploratory biomarkers and stool microbiome will only be collected in subjects who enrolled through SS1-P2b.
- s. First dose cardiac monitoring will be performed for subjects who meet the LOR criteria and return for the LOR FD Visit. Vitals and 12-lead ECG will be performed predose at the LOR FD Visit. As part of the first-dose cardiac monitoring procedure, heart rate and blood pressure will be obtained at Hours 1, 2, 3, and 4 (± 15 minutes) postdose and 12-lead ECG will be performed at the Hour 4 discharge assessment (refer to Section 10.7.8.4).
- t. Full physical examinations will be performed at the M-14 and M-38 Visits or at the ET Visit. Symptom directed physical examination and a physical examination that assesses the presence of abdominal mass and physical signs consistent with extraintestinal manifestations of IBD as described in Section 10.7.2 should be performed at the other study visits.
- u. TB screening questionnaire will be administered only to subjects residing in countries with high burden of TB or multi-drug resistant TB as described in Appendix 2.
- v. If TB is suspected at any time during the study, subjects should be screened. The TB screening test (eg, IGRA) should be performed by a central laboratory prior to randomization and annually only in subjects who previously tested negative on the TB screening test (refer to Appendix 2).
- w. For females of childbearing potential only. A urine pregnancy test for β hCG will be performed at substudy- entry to determine eligibility and thereafter. A monthly pregnancy test in non visit- months should be performed at home (as permitted by local regulations) or at the study site at an unscheduled visit. Any positive result should be immediately reported to the study site. A positive urine pregnancy test must be confirmed with a follow up serum β hCG- pregnancy test (refer to Section 10.3.2).

Table 32: Schedule of Assessments for Substudy 3 – Maintenance

Evaluations	Maintenance Treatment Period						Loss-of-Response Visits ^a			ET ^b	4-Week Follow-Up Period ^c	
	MFD ^d (+ 3D)	M-6 (± 3D)	M-14 (± 7D)	M-22 (± 7D)	M-30 (± 7D)	M-38/ Week 52 (± 7D)	LOR ^e	LOR FD ^f	LOR DE ^g		FU1 (± 3D)	FU2 (± 3D)
		Week 6	Week 14	Week 22	Week 30	Week 38*						
Visit Type	Site or Remote	Site	Site	Site	Site	Site	Site	Site	Site or Remote	Site	Site or Remote	Site or Remote

x. Unscheduled assessments may also be performed, as clinically indicated, as part of the study visit assessment due to complaints of decreased vision or identification of worsening visual acuity (refer to Section 10.7.7).

y. Visit windows for performing PFT and DLCO (where locally available) are described in Section 10.7.6. Unscheduled PFT assessments should be performed for subjects reporting any respiratory symptoms (eg, dyspnea, shortness of breath, chest tightness, or wheezing), preferably on the same day (refer to Section 10.7.6).

AE, adverse event; β-hCG, beta-human chorionic gonadotropin; CBC, complete blood count; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; D, day; DLCO, diffusing capacity of the lungs for carbon monoxide; ECG, electrocardiogram; eDiary, electronic diary; EFD, Extension First Dose; ET, Early Termination; FCP, fecal calprotectin; FU, follow-up; IBD, inflammatory bowel disease; IGRA, interferon gamma release assay; IP, investigational product; LOR, loss-of-response; LOR DE, loss-of-response dose escalation; LOR FD, loss-of-response first dose; M, Maintenance; MFD, maintenance first dose; OCT, optical coherence tomography; PFT, pulmonary function test; PK, pharmacokinetic; SES-CD, Simple Endoscopic Score in Crohn's disease; SS1-P2b, Substudy 1 – Phase 2b; SS3-M, Substudy 3 – Maintenance; SS4-E, Substudy 4 – Extension; TB, tuberculosis; TBNK, T Cell, B Cell, and natural killer (cells); W, week; WBC, white blood cells

Table 33: Schedule of Assessments for Substudy 4 – Long-Term Extension

Evaluations	Long-Term Extension Treatment Period				ET ^a	4-Week Follow-Up Period ^b	
	EFD ^c (± 3D)	E-1 ^d (± 3D)	Every 12 Weeks ^e (± 7D)	Every 52 Weeks ^f (± 7D)		Follow-Up 1 (± 3D)	Follow-Up 2 (± 3D)
Visit Type	Site or Remote	Site or Remote	Site	Site	Site	Site or Remote	Site or Remote
Informed consent	x						
eDiary review	x	x	x	x	x		

Table 33: Schedule of Assessments for Substudy 4 – Long-Term Extension

Evaluations	Long-Term Extension Treatment Period				ET ^a	4-Week Follow-Up Period ^b	
	EFD ^c (± 3D)	E-1 ^d (± 3D)	Every 12 Weeks ^e (± 7D)	Every 52 Weeks ^f (± 7D)		Follow-Up 1 (± 3D)	Follow-Up 2 (± 3D)
Visit Type	Site or Remote	Site or Remote	Site	Site	Site	Site or Remote	Site or Remote
Dose IP in clinic	x						
Dispense IP	x	x	x	x ^g			
Drug accountability	x	x	x	x	x		
Concomitant medications	x	x	x	x	x	x	x
CDAI calculation			x	x	x		
PRO2 calculation		x	x	x	x		
Health Related PROs				x	x		
CD-related hospitalization and surgery	x	x	x	x	x	x	x
CRP			x	x	x		
Ileocolonoscopy with biopsy ^h				x ^h			
Stool sample and FCP ⁱ				x	x		
Seated vital signs	x ^j	x	x	x	x		x
Physical examination ^k			x	x	x		x
12-lead ECG	x ^j			x	x		
CBC with differential and platelets			x	x	x	x	x
TBNK panel cell count			x	x	x		x
Serum chemistry			x	x	x		x

Table 33: Schedule of Assessments for Substudy 4 – Long-Term Extension

Evaluations	Long-Term Extension Treatment Period				ET ^a	4-Week Follow-Up Period ^b	
	EFD ^c (± 3D)	E-1 ^d (± 3D)	Every 12 Weeks ^e (± 7D)	Every 52 Weeks ^f (± 7D)		Follow-Up 1 (± 3D)	Follow-Up 2 (± 3D)
Visit Type	Site or Remote	Site or Remote	Site	Site	Site	Site or Remote	Site or Remote
Coagulation panel				X	X		
TB questionnaire ^l			X	X			
TB screening ^m				X			
Pregnancy test ⁿ	X		X	X	X		X
Urinalysis				X	X		
Adverse events	X	X	X	X	X	X	X
Ophthalmoscopy and OCT ^o				X	X		
PFT and DLCO ^p				X	X		X
EIMs			X	X	X		

- If a subject ends study participation before the end of the study, the ET Visit should be performed. The ET Visit should occur within 7 days of last dose and before initiation of any new treatments. If ophthalmology, OCT, PFT, and DLCO assessments were performed within 2 weeks of ET Visit, these assessments do not need to be repeated.
- The FU1 and FU2 Visits should be performed for all subjects at 14 days and 28 days, respectively, following the last dose of study drug. If the ET Visit is ≥ 28 days after the last dose of study drug, the FU1 and FU2 Visits are not required.
- The EFD Visit must occur no later than 14 days after the last visit of the parent substudy. No repeat assessments are required if the EFD Visit is performed on the same day as the last visit of the parent study or substudy (refer to Section 9.8.1).
- Prior to dose selection the E-1 Visit will only be required for subjects from the Responder Cohort of SS3-M. After dose selection, the E-1 Visit will only be required for subjects from the Responder Cohort of SS3-M if etrasimod 3 mg is the selected Phase 3 etrasimod dose and should occur within 1 week (± 3 days) following the EFD Visit.
- Visits will occur every 12 weeks ($\pm 7D$) following the EFD Visit and includes the following scheduled visits at Weeks 12, 24, 36, 64, 76, 88, 116, 128, 140, 168, 180, and 192.
- Visits will occur every 52 weeks ($\pm 7D$) following the EFD Visit and includes the following scheduled visits at Weeks 52, 104, 156, and 208.
- IP will not be dispensed at the last visit of the LTE Treatment Period (ie, the last annual visit of SS4-E/Week 208 of the LTE Treatment Period).
- Subjects will undergo ileocolonoscopy with biopsy at Week 52 and Week 104. Subjects with LOR in SS3-M should have a colonoscopy during SS4-E that occurs 52 weeks and 104 weeks after the LOR FD Visit.

Table 33: Schedule of Assessments for Substudy 4 – Long-Term Extension

Evaluations	Long-Term Extension Treatment Period				ET ^a	4-Week Follow-Up Period ^b	
	EFD ^c (± 3D)	E-1 ^d (± 3D)	Every 12 Weeks ^e (± 7D)	Every 52 Weeks ^f (± 7D)		Follow-Up 1 (± 3D)	Follow-Up 2 (± 3D)
Visit Type	Site or Remote	Site or Remote	Site	Site	Site	Site or Remote	Site or Remote

- i. Stool samples for FCP, bacterial culture, ova, and parasite evaluation, and *C. difficile* assay should be obtained at any time during the study when a subject has new or worsened CD symptoms suggestive of disease relapse or progression.
- j. As a part of first-dose cardiac monitoring, vital signs (HR, BP, body temperature, and respiratory rate) collection and 12-lead ECG will be performed prior to randomization at EFD Visit for subjects enrolling from the Etrasimod and Placebo Responder Cohorts of SS3-M. In addition, HR and BP will also be obtained at Hours 1, 2, 3, and 4 (± 15 minutes) postdose and 12-lead ECG is performed at the Hour 4 discharge assessment as part of the first-dose cardiac monitoring procedure at the EFD Visit for subjects enrolling from the Responder Cohorts of SS3-M. Refer to Section 10.7.8.4 for details regarding first-dose cardiac monitoring.
- k. Full physical examinations will be performed annually and at the FU2 Visit or at the ET Visit. Symptom-directed physical examination and a physical examination that assesses the presence of abdominal mass and physical signs consistent with EIMs of IBD as described in Section 10.7.2 should be performed at the other study visits.
- l. A TB screening questionnaire will be administered only to subjects residing in countries with high burden of TB or MDR TB as described in Appendix 2.
- m. If TB is suspected at any time during the study, subjects should be screened. The TB screening test (eg, IGRA) should be performed by a central laboratory prior to randomization and annually only in subjects who previously tested negative on the TB screening test (refer to Appendix 2).
- n. For females of childbearing potential only. A urine pregnancy test for βhCG will be performed at substudy- entry to determine eligibility and thereafter. A monthly pregnancy test in non-visit months should be performed at home (as permitted by local regulations) or at the study site at an unscheduled visit. Any positive result should be immediately reported to the study site. A positive urine pregnancy test must be confirmed with a follow up- serum βhCG- pregnancy test (refer to Section 10.4.2).
- o. Unscheduled assessments may also be performed, as clinically indicated, as part of the study visit assessment due to complaints of decreased vision or identification of worsening visual acuity (refer to Section 10.7.8.6).
- p. Visit windows for performing PFT and DLCO (where locally available) are described in Section 10.7.6. Unscheduled PFT assessments should be performed for subjects reporting any respiratory symptoms (eg, dyspnea, shortness of breath, chest tightness, or wheezing), preferably on the same day (refer to Section 10.7.6).

AE, adverse event; β-hCG, beta-human chorionic gonadotropin; BP, blood pressure; BL, Baseline; CBC, complete blood count; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; D, day; DLCO, diffusing capacity of the lungs for carbon monoxide; E, Extension Week; ECG, electrocardiogram; eDiary, electronic diary; EFD, Extension First Dose; EIMs, extraintestinal manifestations; ; ET, early termination; FCP, fecal calprotectin; FU, follow-up; HR, heart rate; IBD, inflammatory bowel disease; IGRA, IGRA, interferon gamma release assay; IP, investigational product; LOR, loss-of-response; LTE, Long-Term Extension; MDR, multi-drug resistance; OCT, optical coherence tomography; PFT, pulmonary function test; PK, Pharmacokinetic; SS3-M, Substudy 3 – Maintenance; SS4-E, Substudy 4 – Long-Term Extension; TB, tuberculosis; TBNK, T Cell, B Cell, and natural killer (cells);

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Appendix 2. TUBERCULOSIS SCREENING AND MONITORING

Prior to enrolling in this study, all subjects must undergo screening for a history of tuberculosis (TB) infection and testing for latent/active TB infection. Their medical history review must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. 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.

- b. For subjects residing in countries with high burden of TB or multi-drug resistant (MDR) TB as identified by WHO, a TB screening questionnaire will be verbally administered according to the Schedules of Assessments
- c. The IGRA or TST is NOT required at screening (nor annually for TB screening) in subjects with a history of active/latent TB infection
 - Subjects with past or current history of active TB, regardless of treatment history, are excluded from enrollment
 - **Subjects without a history of latent or active TB who have a negative IGRA or TST result at screening are eligible to enroll in the study.**
 - Subjects with a history of latent TB infection diagnosed prior to screening must have documentation of treatment with a full course of an acceptable TB prophylaxis treatment regimen to qualify for enrollment. It is the responsibility of the investigator to verify the adequacy of previous TB treatment and provide appropriate documentation
- d. 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
- e. Subjects with a newly identified positive IGRA or TST result at screening must undergo an evaluation to rule out active TB (eg, chest X-ray to rule out pulmonary TB) and initiate an acceptable TB prophylaxis treatment regimen for at least 4 weeks prior to randomization (with a plan to complete the TB treatment course during study participation) before they can be considered for enrollment. For subjects diagnosed with latent TB infection who reside in countries with high burden of TB or MDR TB
 - The chest computed tomography scan should be performed to rule out current/past pulmonary TB in the event that the chest X-ray reading is equivocal
 - An assessment of the adequacy of the TB prophylaxis treatment regimen and duration of treatment must be performed by an infectious disease consultant or physician TB expert
 - A TB screening questionnaire will be administered at every study visit to monitor for any emergent symptoms of active TB and compliance with TB

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prophylaxis treatment until the subject successfully complete the TB treatment course

f. IGRA and TST interpretation

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

g. Resources

- For the WHO guidelines for the treatment of latent TB visit:
- http://apps.who.int/iris/bitstream/handle/10665/44165/9789241547833_eng.pdf;jsessionid=115F807C3008D688F75118AF16EA53F0?sequence=1
- For a complete list of TB high burden and MDR TB high burden countries during the period 2016 to 2020, visit:
https://worldhealthorg.shinyapps.io/tb_profiles/?_inputs_&entity_type='country'&lan='EN'&iso2='AF'

Tuberculosis Screening Questionnaire

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

1. Have you experienced any of the following symptoms* in the past year?	
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
2. Have you had contact with anyone with active tuberculosis (TB) disease* in the past year?	Yes / No
3. If you have started TB medications to treat a latent TB infection, have you missed taking any doses of the medication(s) as prescribed?	Yes / No
a) Start date of treatment: __ Expected stop date of treatment: __	

Please provide details to any question answered "Yes."

To be completed by the investigator

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

If yes, specify the medication (name, dosage): _____

TB QuantiFERON or Tuberculin Skin Test result: _____ Date: ____

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. SIMPLE ENDOSCOPIC SCORE IN CROHN’S DISEASE

The SES-CD variables and scoring are presented in Table 34. The SES-CD is the sum of all variables for the 5 bowel segments. Values are given to each variable for every examined bowel segment (Daperno 2004).

Table 34: Simple Endoscopic Score in Crohn's Disease Variables and Scoring

Variable	Simple Endoscopic Score in Crohn's Disease Scoring			
	0	1	2	3
Size of ulcers (diameter)	None	Aphthous ulcers (0.1 to 0.5 cm)	Large ulcers (0.5 to 2 cm)	Very large ulcers (> 2 cm)
Ulcerated surface	None	< 10%	10%-30%	> 30%
Affected surface	Unaffected segment	< 50%	50%-75%	> 75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

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Appendix 4. CROHN'S DISEASE ACTIVITY INDEX

The Crohn's Disease Activity Index variables and weighting factors for each variable are listed in Table 35.

Table 35: Crohn's Disease Activity Index Variables and Weighting Factors

CDAI Clinical or Laboratory Variable	Weighting Factor (× variable score)
SF: Number of liquid or soft stools (BSFS type 6 or 7) each day for 7 days	2
AP: Abdominal pain rating graded from 0 (none) to 3 (severe) each day for 7 days	5
General well-being rating assessed from 0 (generally well) to 4 (terrible) each day for 7 days	7
Presence of complications	20
Taking diphenoxylate/atropine, loperamide or opiates for diarrhea	30
Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite)	10
Hematocrit 47-HCT in men and 42-HCT in women	6
Percentage deviation from standard weight	1
Total CDAI score	Sum of variable scores × weighting factor

AP, abdominal pain; BSFS, Bristol Stool Form Scale; CDAI, Crohn's Disease Activity Index; HCT, hematocrit; SF, stool frequency

Appendix 5. BRISTOL STOOL FORM SCALE

Figure 7: Bristol Stool Form Scale



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Appendix 6. GRADING OF CLINICAL AND LABORATORY ADVERSE EVENTS

All clinical and clinically significant laboratory abnormalities will be graded according to the CTCAE Scale for Severity of Adverse Events and Laboratory Abnormalities.

Examples of CTCAE terms and grading are provided for clinical adverse events in Table 36 and for laboratory abnormalities in Table 37.

Table 36: Example of CTCAE Terms and Grading for Clinical Adverse Events

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Cough	Mild symptoms; nonprescription intervention indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	–	–
Definition: A disorder characterized by sudden, often repetitive, spasmodic contraction of the thoracic cavity, resulting in violent release of air from the lungs and usually accompanied by a distinctive sound.					
Dyspnea	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an uncomfortable sensation of difficulty breathing.					
Wheezing	Detectable airway noise with minimal symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe respiratory symptoms limiting self-care ADL; oxygen therapy or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a high-pitched, whistling sound during breathing. It results from the narrowing or obstruction of the respiratory airways.					
Dizziness	Mild unsteadiness or sensation of movement	Moderate unsteadiness or sensation of movement; limiting instrumental ADL	Severe unsteadiness or sensation of movement; limiting self-care ADL	–	–
Definition: A disorder characterized by a disturbing sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking.					
Blurred vision	Intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self-care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	–

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Table 36: Example of CTCAE Terms and Grading for Clinical Adverse Events

Definition: A disorder characterized by visual perception of unclear or fuzzy images.					
Blood and lymphatic system disorders					
Anemia	Hgb < LLN– 10.0 g/dL; < LLN- 6.2 mmol/L; < LLN-100 g/L	Hgb < 10.0- 8.0 g/dL; < 6.2-4.9 mmol/L; < 100-80 g/L	Hgb < 8.0 g/dL ,< 4.9 mmol/L; < 80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	
Definition: A disorder characterized by a reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.					

ADL, activities of daily life; CTCAE, Common Terminology Criteria for Adverse Events; Hgb, hemoglobin.

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Table 37: Example of CTCAE Terms and Grading for Laboratory Abnormalities and Pulmonary Functions Tests

Investigations					
CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Alanine aminotransferase increased	> ULN-3.0 × ULN if baseline was normal; 1.5-3.0 × baseline if baseline was abnormal	> 3.0-5.0 × ULN if baseline was normal; > 3.0-5.0 × baseline if baseline was abnormal	> 5.0-20.0 × ULN if baseline was normal; > 5.0-20.0 × baseline if baseline was abnormal	> 20.0 × ULN if baseline was normal; > 20.0 × baseline if baseline was abnormal	–
Definition: A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen. Navigational Note: Also consider Hepatobiliary disorders: Hepatic failure					
Aspartate aminotransferase increased	> ULN-3.0 × ULN if baseline was normal; 1.5-3.0 × baseline if baseline was abnormal	> 3.0-5.0 × ULN if baseline was normal; > 3.0-5.0 × baseline if baseline was abnormal	> 5.0-20.0 × ULN if baseline was normal; > 5.0-20.0 × baseline if baseline was abnormal	> 20.0 × ULN if baseline was normal; > 20.0 × baseline if baseline was abnormal	–
Definition: A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen. Navigational Note: Also consider Hepatobiliary disorders: Hepatic failure					
Platelet count decreased	< LLN-75,000/mm ³ ; < LLN-75.0 × 10 ⁹ /L	< 75,000 – 50,000/mm ³ ; < 75.0-50.0 × 10 ⁹ /L	< 50,000-25,000/mm ³ ; < 50.0-25.0 × 10 ⁹ /L	< 25,000/mm ³ ; < 25.0 × 10 ⁹ /L	–
Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.					
Forced expiratory volume decreased	FEV ₁ % (percentages of observed FEV ₁ and FVC related to their respective predicted values) 99-70% predicted	FEV ₁ 60%-69%	50%-59%	≤ 49%	–
Definition: A finding based on test results that indicate a relative decrease in the fraction of the forced vital capacity that is exhaled in a specific number of seconds. Navigational Note: Also consider Respiratory, thoracic and mediastinal disorders: Respiratory failure or Dyspnea					
Vital capacity abnormal	90%-75% of predicted value	< 75%-50% of predicted value; limiting instrumental ADL	< 50% of predicted value; limiting self-care ADL	–	–
Definition: A finding based on pulmonary function test results that indicate an abnormal vital capacity (amount of exhaled after a maximum inhalation) when compared to the predicted value. Navigational Note: Also consider Investigations: Forced Expiratory Volume; Respiratory, thoracic and mediastinal disorders: Respiratory failure or Dyspnea					
Carbon monoxide diffusing capacity decreased	3-5 units below LLN; for follow-up, a decrease of 3-5 units (mL/min/mm Hg) below the baseline value; asymptomatic and intervention not indicated	6-8 units below LLN; for follow-up, an asymptomatic decrease of > 5-8 units (mL/min/mm Hg) below the baseline value; symptomatic and intervention not indicated	Asymptomatic decrease of > 8 units drop; > 5 units drop along with the presence of pulmonary symptoms (eg, > Grade 2 hypoxia or > Grade 2 dyspnea); intervention indicated	–	–

ADL, activities of daily life; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; ULN, upper limit of normal

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Appendix 7. GUIDANCE FOR THE MANAGEMENT OF CLINICAL AND LABORATORY ADVERSE EVENTS

Clinical AEs and abnormal results of laboratory tests and safety assessments considered to be an AE by the Investigator should be graded according to the severity scale of the CTCAE.

Uniform guidance for the management of AEs is provided in Figure 8.

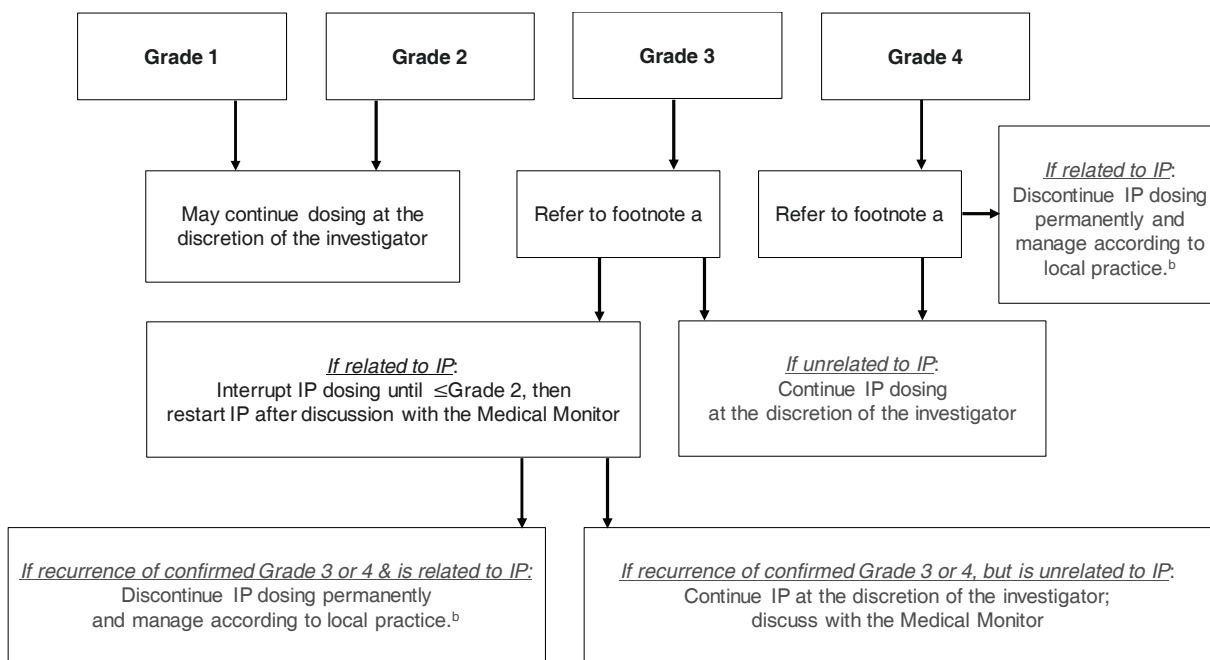
Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within 3 calendar days of receipt of results and before investigational product (IP) discontinuation, unless such a delay is not consistent with Good Medical Practice.

A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new AE grade.

The IP may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (eg, Grade 4 creatinine kinase after strenuous exercise, or triglyceride elevation that is non-fasting or that can be medically managed) or a clinical event considered unrelated to the IP.

Any questions regarding adverse event management should be directed to the Medical Monitor.

Figure 8: Algorithm for the Management of Clinical and Safety Assessment-Related Adverse Events



AE, adverse event; ECG, electrocardiogram; IP, investigational product; PFT, pulmonary function test.

^a Repeat lab tests, ECG, or PFT to confirm AE grade. Clinical adverse event(s) may require additional assessment, therapeutic intervention, and/or consultation with relevant expert.

^b Laboratory and/or clinical AEs should be followed until there is stability, improvement or resolution.

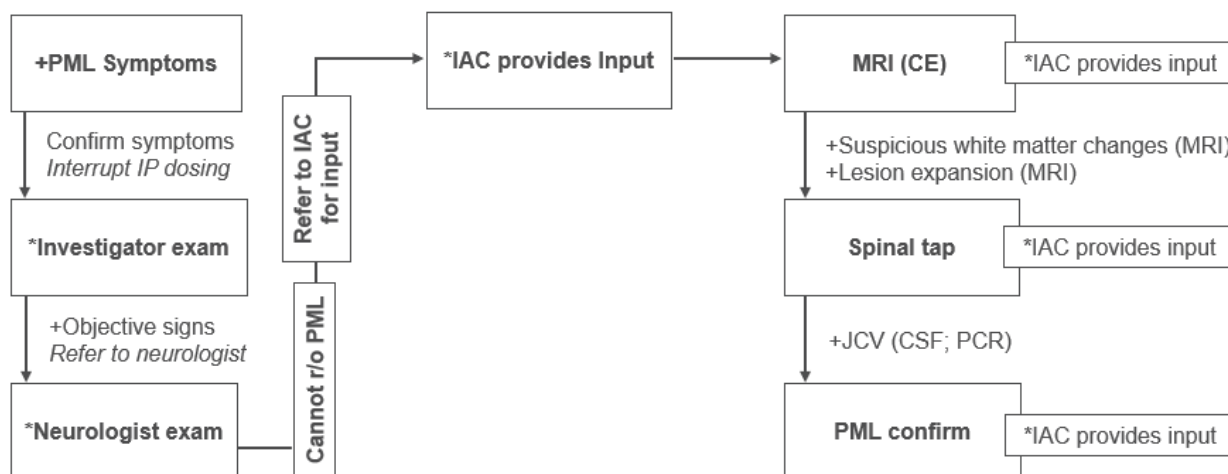
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Appendix 8. GUIDANCE FOR THE ASSESSMENT OF POTENTIAL PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

If a subject exhibits signs and symptoms suspicious for progressive multifocal leukoencephalopathy (PML), the Investigator must interrupt study drug and perform a targeted neurologic examination to assess for signs of PML, which are diverse, progress over days to weeks, and may include progressive weakness on one side of the body or clumsiness of limbs or difficulty with walking or writing or fine motor skills, disturbance of vision, changes in thinking, memory and orientation leading to confusion and personality changes, paresthesia/anesthesia (of any domain: peripheral to central), dysarthria (expressive aphasia), and/or agnosia (receptive aphasia). Consultation with a local neurologist may be warranted, as presented in the PML case evaluation algorithm in Figure 9.

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

Appendix 9. DETERMINATION OF INADEQUATE RESPONSE, LOSS OF RESPONSE, OR INTOLERANCE TO PRIOR TREATMENT FOR CROHN'S DISEASE

The information contained in this appendix should serve as guidance. Local therapeutic standards and Investigator judgment should be used.

Corticosteroids

Inadequate response or loss of response: signs and symptoms of persistently active disease despite a history of at least one 4-week induction regimen that included a dose equivalent to prednisone 30 mg daily orally for 2 weeks or intravenously for 1 week OR 2 failed attempts, on 2 separate occasions, to taper corticosteroids to a dose below a dose equivalent to prednisone 10 mg daily orally.

Intolerance: documented treatment discontinuation for adverse events (AEs) suspected to be related to corticosteroid treatment

As guidance, refer to the adverse reactions listed in United States (US) prescribing information (USPI) for Medrol® ([MEDROL 2019](#)). Investigators should also refer to the latest product label in their respective country.

Immunosuppressants

Azathioprine

Inadequate response or loss of response: signs and symptoms of persistently active disease despite a history of azathioprine (AZA) use for at least 12 weeks at daily dose ≥ 1.5 mg/kg including its use as adjunctive therapy or steroid sparing therapy.

Intolerance: documented treatment discontinuation for AEs suspected to be related to AZA treatment.

As guidance, refer to the adverse reactions listed in the USPI of Imuran® ([IMURAN 2011](#)). Investigators should also refer to the latest label in their respective country.

Mercaptopurine

Inadequate response or loss of response: signs and symptoms of persistently active disease despite a history of mercaptopurine (6-MP) use for at least 12 weeks at daily dose ≥ 0.75 mg/kg, including its use as adjunctive therapy or steroid-sparing therapy.

Intolerance: documented treatment discontinuation for AEs suspected to be related to 6-MP treatment.

As guidance, refer to the adverse reactions listed in the USPI of Purinethol® ([PURINETHOL 2011](#)). Investigators should also refer to the latest label in their respective country.

Methotrexate

Inadequate response or loss of response: Failure to respond to at least one 8-week regimen of or maintain remission at doses of at least 15 mg/week, given by the intramuscular or subcutaneous (SC) route.

Intolerance: documented treatment discontinuation for AEs suspected to be related to methotrexate (MTX) treatment.

As guidance, refer to the adverse reactions listed in the USPI of Methotrexate® ([METHOTREXATE 2016](#)). Investigators should also refer to the latest label in their respective country.

Anti-tumor necrosis factor alpha antagonists

Inadequate response or loss of response: anti-tumor necrosis factor alpha (TNFα) antagonists are rapid in onset of effect, with benefit often noted within 2 weeks of initiating therapy. As a result, assessment of inadequate response may be done sooner than with immunosuppressants. These include signs and symptoms of persistently active disease despite at least one 4-week induction regimen with the following minimum doses of:

infliximab (5 mg/kg intravenous (IV), 2 doses at least 2 weeks apart)

adalimumab (one 80 mg SC dose followed by one 40 mg dose at least 2 weeks apart)

certolizumab pegol (400 mg SC, 2 doses at least 2 weeks apart) or recurrence of symptoms during maintenance therapy

Intolerance: defined as documented treatment discontinuation for adverse events suspected to be related to anti-TNFα agents.

As guidance, refer to the adverse reactions listed in the USPI of Humira® ([HUMIRA 2002](#)). Investigators should also refer to the latest label in their respective country.

Vedolizumab

Inadequate response or loss of response: Persistent signs and symptoms of active disease despite at least 14-week regimen with vedolizumab 300 mg IV (administered at week 0, 2, 6 and every 8 weeks)

Intolerance: defined as documented treatment discontinuation for adverse events suspected to be related to vedolizumab treatment.

As guidance, refer to the adverse reactions listed in the USPI of Entyvio® ([ENTYVIO 2014](#)). Investigators should also refer to the latest label in their respective country.

Ustekinumab

Inadequate response or loss of response: Persistent signs and symptoms of active disease despite induction treatment consisting of single intravenous infusion dose of Stelara® using the weight-based dosage regimen or failure to maintain remission.

Dosage based on body weight of patient at the time of dosing (recommended dosage of 260 mg for subjects weighing 55 kg or less; recommended dosage of 390 mg for subjects weighing more than 55 kg to 85 kg; recommended dosage of 520 mg for subjects weighing more than 85 kg).

Subcutaneous Maintenance Adult Dosage Regimen: The recommended maintenance dosage is a subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.

Intolerance: defined as documented treatment discontinuation for adverse events suspected to be related to ustekinumab treatment.

As guidance, refer to the adverse reactions listed in the USPI of Stelara[®] ([STELARA 2009](#)). Investigators should also refer to the latest label of their respective country.

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Appendix 10. Liver Safety: Suggested Actions and Follow-Up Assessments

Potential Cases of Drug-Induced Liver Injury

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

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

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

- Participants with AST/ALT and T bili baseline values within the normal range who subsequently present with AST OR ALT values $\geq 3 \times \text{ULN}$ AND a T bili value $\geq 2 \times \text{ULN}$ with no evidence of hemolysis and an alkaline phosphatase value $< 2 \times \text{ULN}$ or not available.
- For participants with baseline AST **OR** ALT **OR** T bili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
 - Preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥ 2 times the baseline values AND $\geq 3 \times \text{ULN}$; or $\geq 8 \times \text{ULN}$ (whichever is smaller).
 - Preexisting values of T bili above the normal range: T bili level increased from baseline value by an amount of $\geq 1 \times \text{ULN}$ **or** if the value reaches $\geq 3 \times \text{ULN}$ (whichever is smaller).

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

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

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

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

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

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Appendix 11. Country-Specific Requirements

Canada

1. SSA is not applicable to Canada
2. Inclusion Criterion 7b for SS1 and SS2:
 - a. A female who is of childbearing potential must agree to use 2 forms of acceptable contraception methods during treatment and for 4 weeks following treatment. Acceptable methods of contraception include at least 1 form that is considered highly effective (ie, can achieve a failure rate of less than 1% per year when used consistently and correctly) and 1 form that is considered effective. Note: No 1 method of contraception is 100% effective.
The following are considered highly effective birth control methods:
 - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal, or transdermal
 - Progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injected, or implanted
 - IUD
 - IUS
 - Bilateral tubal occlusion
 - Vasectomized partner, provided that partner is the sole sexual partner of the FOCBP 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 drug). 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 acceptableEffective methods of contraception include barrier methods of contraception (eg, male condom, female condom, cervical cap or diaphragm with spermicide, contraceptive sponge).

Russia

1. SS2 and SS3 are not applicable to Russia until Week 14 data are available from SSA.

Japan

1. BACKGROUND OF STUDY CONDUCT IN JAPAN

1.1. Study Organization

In Japan, the study will be conducted by the organizations described below.

1.1.1. Sponsor

Refer to Study Protocol APD334-202, Amendment 3.0.

1.1.2. Medical Expert

1) Main functions

To consult on issues requiring medical judgment, including clinical study protocol, amendments, clinical study report and other documents.

2) Detailed information

Refer to the document “APD334-202 –Sponsor and Vendor Contact Information”.

1.1.3. Independent Data Monitoring Committee

1) Main functions

To conduct reviews of accumulating safety and efficacy data at specified intervals during the conduct of the study, according to the guidelines detailed in the DMC Charter.

2) Detailed information

Refer to the document “APD334-202 –Sponsor and Vendor Contact Information”.

1.1.4. In-Country Caretaker for Clinical trial (ICCC)*

1) Name, address, representative, supervisor of ICCC

In-Country Caretaker for Clinical trial: IQVIA Services Japan K.K.

Address: 4-10-18 Takanawa, Minato-ku, Tokyo, 108-0074

Representative: PPD

Supervisor: PPD

2) Functions managed by ICCC

Refer to the document “APD334-202 –Sponsor and Vendor Contact Information”.

*This section will be invalid on or after March 1, 2024.

1.1.5. Contract Research Organization

Refer to the documents “APD334-202 – Sponsor and Vendor Contact Information” and “APD334-202 – Monitoring Personnel”.

1.1.6. Coordinating Investigator

No Coordinating Investigator is designated in this clinical trial.

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1.1.7. List of Clinical Study Sites and Principal Investigators

Refer to the document “APD334-202 – Clinical Trial Sites and Principal Investigators.”

1.2. Caution for Use Concerning Vacuum Blood-Collection Tubes

Refer to the document “APD334-202 – Caution for Use of Vacuum Blood-collection Tubes” for the appropriate handling of vacuum blood collection tubes employed in the study.

1.3. Statement of GCP Compliance

The study will be conducted in compliance with the Declaration of Helsinki, the clinical study protocol, standards stipulated in Article 14, Paragraph 3 and Article 80-2 of the “Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices”, and “Ministerial Ordinance on Good Clinical Practice for Drugs” (GCP).

1.4. Planned Number of Subjects and Study Period in Japan

Planned number of subjects in Japan:

72-96 subjects

Planned study period in Japan:

Sep 2021- Aug 2029

1.5. Record Retention

The related section of the study protocol APD334-202: Section 14.2, Study Documentation and Records Retention. Additional adaptations for Japan are as follows:

1.5.1. Clinical Study Site

Materials to be retained:

The head of clinical trial site shall retain records, including documents and data, which relate to clinical trial in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline for Good Clinical Practice (GCP) and Japan-GCP (J-GCP).

Retention period:

The head of clinical trial sites shall retain records for 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.

1.5.2. Principal Investigator

The principal investigator shall retain records, including documents and data, which relate to clinical trial in accordance with instruction from the head of the clinical trial site.

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1.5.3. Institutional Review Board (IRB)

Materials to be retained:

The person who establishes the IRB shall retain records, including documents and data, which relate to clinical trial 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, etc. requests to retain records longer than described, the person who establishes the IRB will discuss retention period and method with the Sponsor.

1.5.4. Sponsor and ICCC*

Materials to be retained:

Sponsor and ICCC shall retain records, including documents and data, which relate to clinical trial in accordance with ICH-GCP and J-GCP.

Retention period:

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

*To reflect the termination of the In-Country Caretaker for Clinical Trial contract with IQVIA Services Japan K.K., "ICCC" in this section will be read as "CRO" from March 1, 2024.

2. Protocol Additions, Changes, and Deletions in Addendum

The following sections show the changes in the addendum applicable to subjects participating in study APD334-202 in Japan. Where applicable, original text in the Protocol is shown with the changes in the addendum for comparison. Underlined text or struck-through text indicate text that will be added or deleted, respectively.

2.1. Substudy A – Phase 2 (SSA-P2)

Substudy A will not be conducted in Japan due to study startup timelines.

2.2. Unapproved Medicines/Treatments

The following medicines mentioned in the study protocol are not approved in Japan.

Medicine	Related Sections of the Study Protocol
Prednisone	Criterion 5 of 4.1.1, Criterion 3 of 4.1.2, 6.8.2.1, 6.8.3.1, 6.8.4, Appendix 2, and Appendix 9
Ozanimod	Criterion 6 of 4.1.2 and 6.8.5
Beclomethasone	6.8.2.1 and 6.8.3.1

2.3. Accountability, Retention and Disposal of Study Drug in Japan

(The related sections of the study protocol: 7.4 Accountability; and 7.5 Retention and Disposal)

The head of the study site or the investigational product manager has overall responsibility for administering and dispensing study drug. 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.

2.4. Reporting Serious Adverse Events in Japan

See Section 10.7.9.3.1.

2.5. Local Requirements for Genetic Testing

(The related section of the study protocol: 10.10 Genetic Testing (Substudy A – Phase 2, Substudy 1 – Phase 2b, and Substudy 2 – Induction))

The collected sample will be stored at the study site or at a location selected by the Sponsor. Subjects' identification numbers will be replaced with new coded numbers to further protect the subjects' identity. The collected sample will be stored for up to 10 years or for as long as the study data are stored. If subjects withdraw their consent, the data obtained from the subjects prior to withdrawing consent may still be used. Any remaining samples not yet analyzed will be destroyed. In order to destroy the sample, the sample will be linked back to the subjects' participant identification number. The DNA samples will only be linked back to subjects' participant identification number.

The results will not be provided to the subjects because the results are not used for diagnostic purposes. In addition, the results are not associated with participant identification numbers.

2.6. Addendum Information for Exploratory Biomarkers

(The related section of the study protocol: 10.11 Exploratory Biomarkers)

Transcriptomics, microbiome and immunophenotyping analyses will be performed on samples from subjects who have consented to participate in the genetic analysis component of the study. Participation is optional. Subjects who do not wish to participate in the genetic research may still participate in the study.

2.7. Other Additions and Local Modifications

The following sections show the additions in addendum applicable to patients participating in study APD334-202 in Japan. Original texts in Protocol shall be shown with the additions in addendum for comparison. Underlined texts and deleted struck-through texts are the texts which will be added, changed, or deleted.

Section 4.1.1 Inclusion Criteria for Substudy A – Phase 2, Substudy 1 – Phase 2b and Substudy 2 – Phase 3

Original text in protocol:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal, or transdermal

- Progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injected, or implanted

Additions in addendum:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal, or transdermal
Note: Only oral contraception is acceptable in Japan
- Progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injected, or implanted
Note: Progestogen-only hormonal contraception is not acceptable in Japan.

Section 4.1.2 Exclusion Criteria for Substudy A – Phase 2, Substudy 1– Phase 2 and Substudy 2 – Phase 3

Original text in protocol:

e) Known to have or test positive for HIV (positive HIV antibody), HBV (positive hepatitis B surface antigen or core IgM antibody), or active HCV (positive hepatitis C antibody with detectable HCV RNA)

Change in addendum:

e) Known to have or test positive for HIV (positive HIV antibody), ~~HBV (positive hepatitis B surface antigen or core IgM antibody), or active HCV (positive hepatitis C antibody with detectable HCV RNA)~~ or acute or chronic hepatitis B infection or test positive for hepatitis B virus (HBV) at screening (positive for hepatitis B surface antigen [HBsAg]), or

- Negative for HBsAg and positive for hepatitis B core antibody (HBcAb) and negative for hepatitis B surface antibody (HBsAb) in conjunction with detectable HBV DNA, or
- Negative for HBsAg and negative for HBcAb and positive for HBsAb in conjunction with detectable HBV DNA, or
- Negative for HBsAg and positive for HBcAb and positive for HBsAb in conjunction with detectable HBV DNA

Switzerland

Section 8.1 Criteria for Discontinuation of Study Drug

Original text in Protocol:

If a subject discontinues due to pregnancy, they are not required to complete the endoscopy.

If the ET Visit is within 6 weeks of the last endoscopy and biopsy, these procedures do not need to be repeated.

New text in addendum:

If a subject discontinues due to pregnancy, they are not required to complete the endoscopy.

If the ET Visit is within 6 weeks of the last endoscopy and biopsy, these procedures do not need to be repeated.

Data and samples that were collected before the subject withdrawal may still be used for analysis. The samples and data will remain coded with the subject ID number.

Section 14 Data Handling and Record Keeping

Original text in Protocol:

None. The following text will be added as an introductory sentence to the main section.

Additions in addendum:

Data and samples of each subject are linked to the corresponding subject ID, which consists of the study number (202), then study site ID, and the subject number assigned sequentially, starting with consent (e.g., 202-XXXXX-001).

Section 14.1 Data Management

Original text in Protocol:

None. The following text will be added as an introductory sentence to the section.

Additions in addendum:

The database that is used in this clinical trial is Medidata RAVE, which complies with the HFG [Swiss Human Research Act (Humanforschungsgesetz)].

Netherlands

1. Background and Rationale

The optional substudy described in this addendum will only be conducted at Amsterdam University Medical Center (UMCs) and Utrecht UMC, The Netherlands, in Substudy A-Phase 2 (SSA-P2) of the APD334-202 protocol.

The mechanism of action of sphingosine 1-phosphate (S1P) receptor modulators is the inhibition of lymphocyte trafficking through retention of lymphocytes within secondary lymphoid organs such as lymph nodes (Brinkmann 2010). Such retention results in a reduction of circulating lymphocytes trafficking to sites of inflammation. The aim of this substudy is to investigate changes in lymphocyte subpopulations in the mucosa, the lymphatic system (lymph nodes), and peripheral blood in response to etrasimod treatment in patients with Crohn's disease (CD). To do so, samples will be collected at baseline and Week 14 of the 14-week double-blind induction treatment period of SSA-P2 in which participants are randomized 1:1 to either etrasimod 2 mg or etrasimod 3 mg. While the effects of etrasimod on immune cells in the blood and mucosa are being studied in APD334-202 SSA-P2, Substudy 1-Phase 2b (SS1-P2b) and Substudy 2-Induction (SS2-I), the effects of etrasimod on cells within the lymph nodes have not been examined. As the primary mechanism of action of S1P receptor modulators is to retain cells within the lymph nodes, this study will provide insight into the fate of the retained cells. Additionally, this study will

examine the activation status of cells associated with CD pathology across the three tissue types to better understand the impact of etrasimod on local and systemic inflammation.

To measure the effects of etrasimod on cells in the lymphatic system, biopsies from inguinal lymph nodes will be taken under ultrasound guidance ([de Hair 2012](#)). This is a specialized and highly technical methodology that is well-established and performed at Amsterdam UMC ([Ramwadhoebe 2019](#)) but not broadly implemented at other institutions. To enable enrollment of subjects at UMC Utrecht and to ensure consistency of the procedure and laboratory analysis, trained staff from Amsterdam UMC will perform the ultrasound-guided biopsy collections at both sites. Immune cell characterization will then be performed by mass cytometry on flash frozen blood and tissue samples at Amsterdam UMC. Due to the technical nature of the sample collection and sample preservation, this substudy is to be performed at only these two sites in The Netherlands. As inguinal lymph node biopsy is an additional invasive procedure, this substudy will only be conducted during the SSA-P2 portion of Study APD334-202 where all participants will be receiving one of the two doses of active drug. As colonoscopy and colonoscopy preparation may impact immune cells in the lymph nodes, inguinal lymph node biopsy collection will be performed prior to colonoscopy and preparation to ensure that changes observed in the lymph nodes are reflective of treatment as opposed to the colonoscopy procedure. During screening, the lymph node biopsies should be performed after most of the inclusion/exclusion criteria for SSA-P2 have been confirmed.

As an optional exploratory study, enrollment will be driven by recruitment into the global parent APD334-202 SSA-P2 study. To develop a robust and informative dataset, the target enrollment is up to 10 subjects with a minimum of 6 subjects.

The procedures in this substudy addendum are to be offered to subjects at Amsterdam UMC and UMC Utrecht, The Netherlands. Participation in this substudy addendum is optional and subjects who do not wish to participate in this substudy addendum may still participate in the main APD334-202 SSA-P2 study. There are no changes to any of the procedures required by the protocol, or any subsequent amendments to that protocol, based on this addendum.

2. Protocol Additions, Changes and Deletions in Addendum

Up to 10 CD patients participating in SSA-P2 will be invited to take part in this substudy. Participants will need to sign an additional informed consent form prior to enrolling in this optional substudy. In addition to the SSA-P2 protocol-defined study procedures and tissue collection, the following additional sample collection will be done:

1. At screening

- 10 cc of peripheral blood
- 4 biopsies of inguinal lymph nodes (under topical anesthesia)

Note: Inguinal lymph node biopsies should be performed prior to colonoscopy and colonoscopy preparation after most of the inclusion/exclusion criteria for SSA-P2 have been confirmed.

- 3 biopsies from the most inflamed area, and 3 biopsies from the least inflamed area will be collected during ileocolonoscopy

2. At Week 14 (end of induction treatment)

- 10 cc of peripheral blood
- 4 biopsies of inguinal lymph nodes (under topical anesthesia)

Note: Inguinal lymph node biopsies should be performed prior to colonoscopy and colonoscopy preparation.

- 3 biopsies from the same area as screening (previously most inflamed area), and 3 biopsies from the same least inflamed area as in screening (previously least inflamed area) will be collected during ileocolonoscopy.

The technique of lymph node biopsy collection has been described previously ([de Hair 2012](#)).

2.1. Analysis Plan

The results of this site-specific substudy will be summarized in a separate report that will be included in the final clinical study report. Data from all subjects will be analyzed, regardless of the number of subjects enrolled.

3. 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.

de Hair MJH, Zijlstra IAJ, Boumans MJH, et al. Hunting for the pathogenesis of rheumatoid arthritis: Core-needle biopsy of inguinal lymph nodes as a new research tool. *Ann Rheum Dis*. 2012;71(11):1911-1912.

Ramwadhoebe TH, van Baarsen LGM, Boumans MJH, et al. Effect of rituximab treatment on T and B cell subsets in lymph node biopsies of patients with rheumatoid arthritis. *Rheumatology*. 2019;58(6):1075-1085.

Israel

Israel specific change to Inclusion criteria #5 (SSA, SS1 and SS2) shown below in bold font:

Demonstrated inadequate response, loss of response to, or intolerance to ≥ 1 of the (a) conventional therapy and **any biologic treatment, such as a** (b) TNF α antagonist, for the treatment of CD:

a) Conventional therapy

- i. Oral corticosteroids (eg, prednisone or its equivalent, budesonide)
- ii. Immunosuppressants (eg, azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX])

b) Any biologic treatment, such as tumor necrosis factor alpha (TNF α) antagonist (eg, infliximab, adalimumab, certolizumab pegol, or biosimilars).