Official Title of Study:

A Phase 2/3, Multicenter, Randomized, Double-blind Study to Evaluate the Efficacy, Safety, Pharmacokinetics and Pharmacodynamics of Oral Ozanimod (RPC1063) in Pediatric Participants with Moderately to Severely Active Crohn's Disease with an Inadequate Response to Conventional Therapy

NCT Number: NCT05470985

Document Date (Date in which document was last revised): 14 Aug 2023

CLINICAL PROTOCOL IM047023

A Phase 2/3, Multicenter, Randomized, Double-blind Study to Evaluate the Efficacy, Safety, Pharmacokinetics and Pharmacodynamics of Oral Ozanimod (RPC1063) in Pediatric Participants with Moderately to Severely Active Crohn's Disease with an Inadequate Response to Conventional Therapy

Brief Title:

Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Oral Ozanimod in Pediatric Participants with Moderately to Severely Active Crohn's Disease with an Inadequate Response to Conventional Therapy

Protocol Amendment 02

[redacted]
Clinical Development Lead
Bristol-Myers Squibb Company
86 Morris Avenue
Summit, NJ 07901
email: [redacted]

[redacted]
Clinical Scientist
Bristol-Myers Squibb Company
3033 Science Park Road, Suite 300
San Diego, CA 92121
email: [redacted]

24-hr Emergency Telephone Number
USA: [redacted]
International: [redacted]

Celgene International II Sàrl
Route de Perreux 1
2017 Boudry, Switzerland
Tel: [redacted]

REGULATORY AGENCY IDENTIFIER NUMBER(S)

IND: 126740
EudraCT: 2021-005019-30

DOCUMENT HISTORY

Document	Date of Issue	Summary of Changes
Protocol Amendment 02	14-Aug-2023	The main purpose of this amendment is to update the participant assessment schedule, which includes removal of [redacted] requirements at all sites, revising prohibited medications, and clarifying rescreening language, for alignment with other protocols within the Inflammatory Bowel Disease programs.
Protocol Amendment 01	22-Dec-2022	The main purpose of this amendment is to update the inclusion criteria to (a) allow for positive varicella zoster virus antibody titers to help fulfill the vaccination requirement and (b) update the drug clearance period for prior biologics from 8 weeks to 4 weeks.
Original Protocol	25-Feb-2022	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 02:

The main purpose of this amendment is to update the participant assessment schedule, which includes removal of [redacted] requirements at all sites, revising prohibited medications, and clarifying rescreening language, for alignment with other protocols within the Inflammatory Bowel Disease programs.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	• Updated Clinical Scientist and Clinical Trial Physician contact information.	• Administrative change.
[redacted]		

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02

Section Number & Title	Description of Change	Brief Rationale
[redacted]		
Section 3.1.2: Summary of Clinical Studies	• Updated summary of clinical study data.	• Updated based on the latest version (v16) of the Investigator's Brochure.
Section 5.1: Overall Design	[redacted]	• Updated for consistency with the rest of the protocol.
Section 6.1: Inclusion Criteria	• Inclusion Criterion #2)e)iii): Corrected timeframe from "...starting 3 weeks prior to Screening..." to "...starting 2 weeks prior to Screening..." • Inclusion Criterion #4: Revised "FOCBP must have a negative highly sensitive serum pregnancy test (...) within 24 hours prior to the start of study intervention" to "FOCBP must have a negative highly sensitive serum pregnancy test (...) prior to randomization."	• Modification of stable dosing to align with ozanimod IBD programs. • Updated, as testing is performed once during the screening window only.
Section 6.2: Exclusion Criteria Section 7.7.2: Prohibited and/or Restricted Treatments	• Added CYP2C8 inducers (eg, rifampicin). • Removed breast cancer resistance protein inhibitors (eg, cyclosporine, eltrombopag).	• Modified to align with ozanimod core company data sheet.
Section 6.4: Screen Failures	• Added the following regarding rescreening of screen failures: "Participants who fail to meet the inclusion/exclusion criteria can be rescreened	• Amended to ensure the process for rescreening and obtaining approval is well-defined.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	once per Investigator discretion. Additional screening attempts beyond the first rescreen must be approved by the Clinical Trial Physician or designee prior to rescreening."	
Section 6.4.1: Retesting During Screening	• Removed the following: "Participant Re-enrollment: This study permits the re-enrollment of a participant who has discontinued the study as a pretreatment failure (ie, participant has not been randomized/has not been treated). If re-enrolled, the participant must be re-consented/re-assented."	• This language pertains to participant reenrollment and not participant retesting; as such, the paragraph is not relevant to the section.
Section 7.7.1: Steroid Taper	• Clarified that steroid tapering should be completed within 6 months after Week 12. • Modified tapering schedule for budesonide from "...taper their dose of 9 mg/day to 9 mg every other day for 2 weeks..." to "taper their dose at a rate of 3 mg every 3 weeks..."	• Added recommendation to ensure tapering is completed within 6 months and avoid long-term corticosteroid use in pediatric participants. • Amended to align with treatment in clinical practice.
Section 7.6: Treatment Compliance	• Clarified that participants will be asked to return any remaining unused IP at the end of the study, as well as at all visits during which IP is dispensed.	• To ensure drug compliance is properly monitored.
Section 9: Study Assessments and Procedures	• Removed the following: o "A screen failure is defined as a participant who has given consent/assent and whose LAR has given informed consent and failed to meet the inclusion and/or exclusion criteria. Participants who fail to meet the inclusion/exclusion criteria can be rescreened per investigator discretion. Additional screening attempts beyond the first should be approved by the Clinical Trial Physician or designee prior to rescreening. Each participant must be re-consented/re-assented, and the participant's LAR must be re-consented prior to each screening attempt." o "Each participant must be re-consented/re-assented prior to each screening attempt."	• To avoid redundancy within the protocol since already included in Section 6.4.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.2.5: Pregnancy	• Removed the following: "In order for the Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form (ICF) for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form."	• Updated toxicological findings have demonstrated there are no significant exposure levels expected in male participants that could potentially affect female partners in the event of pregnancy.
[redacted]		
Section 9.4.11: Visual Acuity Testing	• Added new section.	• Defined Visual Acuity testing associated with the Schedule of Events.
[redacted]		

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Throughout protocol	• Replaced "legally acceptable representative (LAR)" with "parent(s) or guardian(s)." • Added heart rate and blood pressure in the standing position. • Minor editorial and formatting changes, as well as clarifications, that do not affect content.	• For consistency with other BMS protocols. • For assessment of orthostatic hypotension.

TABLE OF CONTENTS

1 PROTOCOL SUMMARY

Protocol Title:

A Phase 2/3, Multicenter, Randomized, Double-blind Study to Evaluate the Efficacy, Safety, Pharmacokinetics and Pharmacodynamics of Oral Ozanimod (RPC1063) in Pediatric Participants with Moderately to Severely Active Crohn's Disease with an Inadequate Response to Conventional Therapy

Brief Title: Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Oral Ozanimod in Pediatric Participants with Moderately to Severely Active Crohn's Disease with an Inadequate Response to Conventional Therapy

Rationale:

Despite recent progress in Crohn's disease (CD) treatment, there remains an unmet need for oral agents that are safe and convenient and that can provide effective induction and long-term maintenance of clinical remission. Ozanimod is a small molecule compound which selectively binds with high affinity to sphingosine 1-phosphate (S1P) receptors 1 and 5. Many cell types express S1P1, including vascular endothelial cells, brain cells, and lymphocytes. Stimulation (agonism) of this receptor results in biological activities that includes lymphocyte retention in peripheral lymphoid organs (eg, lymph nodes and gastrointestinal Peyer's patches), resulting in reversible systemic reduction in circulating lymphocytes. Given the immune-mediated inflammation in CD, prevention of circulation of disease-exacerbating, self-reactive lymphocytes to the gut is likely to have salutary immunomodulatory effects with a consequent dampening of disease processes.

The benefit/risk profile for ozanimod has been evaluated for the indication of CD in adult participants. In an open-label Phase 2 study in adult participants with moderately to severely active CD (RPC01-2201), ozanimod resulted in endoscopic, clinical, and histologic improvement at [redacted] as measured by centrally read Simple Endoscopic Score for Crohn's Disease (SES-CD) scores and histopathology, Crohn's Disease Activity Index (CDAI) and 2-component patient-reported outcome (abdominal pain and stool frequency). [redacted]

Ozanimod is also currently being studied in Phase 3 studies in adult participants with moderate to severe CD as part of a comprehensive inflammatory bowel disease program. [redacted]

In addition, ozanimod has been studied in a completed Phase 2 randomized double-blind controlled trial in adults with ulcerative colitis (UC; RPC01-202) and a completed Phase 3 randomized double-blind controlled trial in adults with UC (RPC01-3101). These studies have

shown high participant retention, consistent efficacy, and no new safety signals emerging in this population.

Given the mechanism of action of ozanimod, the positive results from the Phase 2 CD study (RPC01-2201) and Phase 2 and 3 UC studies (RPC01-202 and RPC01-3101, respectively), as well as an acceptable safety profile observed across indications, ozanimod has the potential to address an unmet need in the pediatric CD population. This study is being conducted to characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of ozanimod once daily and to evaluate the efficacy and safety of ozanimod in pediatric participants at doses equivalent to 0.46 or 0.92 mg/day in adults.

Table 1: Objectives and Endpoints

Objective	Endpoint
Primary – Efficacy	
• To evaluate the efficacy of ozanimod once daily in pediatric participants with moderately to severely active CD: clinical remission by PCDAI at Week 64	• Proportion of participants who achieve PCDAI < 10 at Week 64
• To evaluate endoscopic remission at Week 64 by SES-CD	• Proportion of participants achieving SES-CD ≤ 2 or SES-CD ≤ 4 points with no SES-CD subscore > 1 point at Week 64
Secondary – Efficacy (Key)	
• To evaluate the efficacy of ozanimod once daily in pediatric participants with moderately to severely active CD: clinical remission by PCDAI at Week 12	• Proportion of participants who achieve PCDAI < 10 at Week 12
Secondary – Efficacy (Other)	
• To evaluate endoscopic response by SES-CD	• Proportion of participants who achieve SES-CD decrease from Baseline of≥50% (ER-50) at Week 64; Week 12
• To evaluate clinical response by PCDAI	• Proportion of participants who achieve reduction in PCDAI score ≥ 12.5 and a total PCDAI score of < 30 points at Week 64; Week 12
• To evaluate symptomatic remission (adolescents only)	• Proportion of adolescents who achieve an average daily abdominal pain score ≤ 1 point and an average daily stool frequency ≤ 3 points with abdominal pain and stool frequency no worse than Baseline at Week 64; Week 12
• To evaluate change in CD symptoms over time	• Change from Baseline in stool frequency score over time • Change from Baseline in abdominal pain over time
• To evaluate clinical remission by CDAI (adolescents only)	• Proportion of adolescents who achieve CDAI score < 150 at Week 64; Week 12

Table 1: Objectives and Endpoints

Objective	Endpoint
• To evaluate clinical response by CDAI (adolescents only)	• Proportion of adolescents who achieve CDAI reduction from Baseline of ≥ 100 points or CDAI score < 150 at Week 64; Week 12
• To evaluate corticosteroid-free remission	• Proportion of participants who achieve a PCDAI score < 10 at Week 64 while remaining corticosteroid free in the prior 12 weeks • Proportion of participants who achieve a CDAI score < 150 at Week 64 while remaining corticosteroid free in the prior 12 weeks (adolescents only)
• To evaluate endoscopic remission at Week 12	• Proportion of participants achieving SES-CD ≤ 2 or SES-CD ≤ 4 points with no SES-CD subscore > 1 point at Week 12
Secondary –Pharmacokinetics	
• To characterize the PK of 2 doses of oral ozanimod and its major active metabolites in pediatric participants with moderately to severely active CD	• Steady state systemic exposures of ozanimod and CC112273 at Week 20 and throughout the study
Secondary –Pharmacodynamics	
• To evaluate the PD of 2 dose levels of ozanimod (eg, effects on ALC) in pediatric participants with moderately to severely active CD	• Absolute and percent change from Baseline in ALC at Week 64, Week 12, and throughout the study
Secondary – Safety and Tolerability	
• To evaluate the safety and tolerability of 2 dose levels of oral ozanimod once daily in pediatric participants with moderately to severely active CD	• Number and proportion of participants experiencing AEs, SAEs, AEs leading to discontinuation from treatment, and AESIs throughout the study

Abbreviations: AE, adverse event; AESI, adverse event of special interest; ALC, absolute lymphocyte count; CD, Crohn's disease; CDAI, Crohn's disease activity index; SAE, serious adverse event; SES-CD, simple endoscopic score for Crohn's disease; PCDAI, pediatric Crohn's disese activity index; PD, pharmacodynamics; PK, pharmacokinetics.

Overall Study Design:

This is a Phase 2/3, randomized, double-blind study to evaluate the efficacy, safety, and tolerability of oral ozanimod once daily in pediatric participants aged 2 to 17 years, inclusive, with moderately to severely active CD (defined as a Pediatric Crohn's Disease Activity Index [PCDAI] score of ≥ 30 and an SES-CD score of ≥ 6 [or SES-CD ≥ 4 in participants with isolated ileal disease]) with an inadequate response, intolerance, or loss of response to prior therapy for CD. The study will also evaluate the PK and PD of oral ozanimod administered once daily at 2 dose levels (0.46 or 0.92 mg/day adult equivalent doses) in pediatric participants during a 64-week Induction and Maintenance treatment period.

[redacted].

Participants will be randomized in a 1:1 ratio to receive either 0.46 mg or 0.92 mg/day adult equivalent doses of ozanimod.

The study is composed of a 64-week double-blind treatment period followed by an optional Long-term Extension (LTE) Period of up to approximately 4.5 years. Participants who meet the early discontinuation criteria after at least 7 weeks of treatment in the Induction Period, have confirmed disease worsening during the Maintenance Period, complete Week 12 and are non-responders, or complete Week 64 will have the option to enter the LTE Period.

Number of Participants:

The study is to enroll approximately [redacted] pediatric participants.

Study Population:

Approximately [redacted] pediatric participants aged 2 to 17 years, inclusive, with moderately to severely active CD (defined as a PCDAI ≥ 30 and an SES-CD score of ≥ 6 [or SES-CD ≥ 4 in participants with isolated ileal disease]) with an inadequate response, intolerance, or loss of response to prior therapy for CD will be enrolled in this study.

Intervention Groups and Duration:

[redacted]

Participants will be randomized in a 1:1 ratio to receive either 0.46 or 0.92 mg/day adult equivalent doses of ozanimod. Within the [redacted] of participants aged [redacted], participants will be [redacted] 0.46 and 0.92 mg/day adult equivalent doses [redacted].

Participants may spend up to 81 weeks in this study, excluding the optional LTE Period, including up to 5 weeks in the Screening Period, 12 weeks in the Induction Period, 52 weeks in the Maintenance Period, and up to [redacted] in the Safety Follow-Up Period. Participants that proceed to the optional LTE Period will enter the Safety Follow-Up Period at the completion of their participation in the LTE Period.

The optional LTE Period will allow eligible participants to continue receiving ozanimod for up to approximately 4.5 years or as per national or local requirements.

Study intervention:

All participants [redacted]

- 0.46 mg/day dose: [redacted], then 0.46 mg/day [redacted] and continuing 0.46 mg/day [redacted]
- 0.92 mg/day dose: [redacted] then 0.46 mg/day [redacted], then 0.92 mg/day from [redacted]

Statistical Methods

Efficacy will be evaluated based on the totality of the data and a comprehensive analysis based on descriptive statistics. Hypothesis testing will not be performed.

The primary analyses of the 2 co-primary endpoints, pediatric clinical and endoscopic remission at Week 64, will be based on the intent-to-treat population in which [redacted] will be pooled. The estimated proportions along with their associated 2-sided 95% Wald confidence intervals (CI) using a normal approximation for a single sample proportion will be constructed.

The analyses of the key secondary endpoint (eg, pediatric clinical remission at Week 12) will be conducted in a similar manner as the co-primary endpoint.

Data Monitoring Committee: Yes

A Data Monitoring Committee will be used in the study.

Other Committee: Yes

The Sponsor will select an [redacted]

Access to treatment assignments will be strictly limited to groups directly involved with drug distribution, preparation of unblinded output for [redacted] and personnel involved in the conduct of PD assays.

To assure that all personnel involved in the conduct of the study remain blinded to the results of interim reviews, a blinding plan will be specified in the DMC Charter.

Brief Summary:

The purpose of this study is to evaluate the efficacy and safety of ozanimod in pediatric participants with moderately to severely active CD. This will be evaluated by the proportion of participants who achieve PCDAI < 10 at Week 64 and the proportion of participants in endoscopic remission

(SES-CD ≤ 2 or SES-CD ≤ 4 points with no SES-CD subscore > 1 point) at Week 64. Study details include the following:

- Study duration: 81 weeks (excluding LTE period)
- Study intervention duration: 64 weeks
- Study visit frequency: Up to 3 times during the first 8 days of the Induction Period, then every 4 weeks until Week 12, then every 8 weeks starting at Week 20 in the Maintenance Period.

2 SCHEDULE OF EVENTS

Table 2-1: Schedule of Events for Induction, Maintenance, and Safety Follow-up Periods

	[redacted]
Visit Number	
Week	
Study Entry	
Informed consent/assent[aa]	
Inclusion/exclusion criteria assessment	
Demographics	
Viral serology testing[e]	
Stool culture[f]	
Tuberculosis testing[g]	
TDM[h]	
Safety Assessments	
Medical history[i]	
Prior/concomitant medications	
Prior/concomitant procedures	
Pregnancy test and contraception education	
AEs	
Vital signs	
Height	

Table 2-1: Schedule of Events for Induction, Maintenance, and Safety Follow-up Periods

	[redacted]
Visit Number	
Week	
Weight	
[redacted] collection	
[redacted]	
Complete physical examination[m]	
Interim physical examination[n]	
12-lead ECG	
Visual Acuity test[z]	
Ophthalmological evaluation	
Pulmonary function evaluation	
[redacted]	
Hematology	
Blood chemistry	
Urinalysis	
Efficacy Assessments	
Participant diary for CD activity[r]	
Bristol Stool Scale (adolescents [redacted])	

Table 2-1: Schedule of Events for Induction, Maintenance, and Safety Follow-up Periods

	[redacted]
Visit Number	
Week	
CDAI (adolescents [redacted]	
Colonoscopy/SES-CD/ colonic biopsy[s]	
PCDAI	
ESR for PCDAI	
PK/PD Assessments	
Blood sample for PK[t]	
Blood sample for PD [redacted]	
Serum sample for PD[t]	
Stool sample for [redacted]	
[redacted] blood sample[t]	
IP	
Dispense IP[x]	
Administer IP in clinic	
Review drug compliance	
[redacted]	

Abbreviations: AE, adverse event; AV, atrioventricular; BP, blood pressure; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; d , days; [redacted] DNA, deoxyribonucleic acid, ECG, electrocardiogram, ESR, erythrocyte sedimentation rate; [redacted] F/U, follow-up; [redacted] HR, heart rate; IgG, immunoglobulin G; IgM, immunoglobulin M; IGRA, interferon

gamma release assay; IP, investigational product; [redacted] PD, pharmacodynamic; PK, pharmacokinetic; PCDAI, Pediatric Crohn's Disease Activity Index; [redacted] SES-CD, Simple Endoscopic Score for Crohn's Disease; SFU = Safety Follow-up Visit; TB, tuberculosis; TDM, therapeutic drug monitoring; VZV, varicella zoster virus.

[redacted]

[f] At Screening, the stool sample should be used to rule out serious infection and should include evaluation for *Clostridioides difficile* toxin as well as ova and parasitic examination.

[g] Active TB must be ruled out according to local medical practices. Latent TB must be assessed with a TB skin test, QuantiFERON Gold test, or other IGRA (eg, T-SPOT). Any repeat testing for latent TB should be approved by the Clinical Trial Physician or designee. Participants with latent TB must have documentation of prophylactic treatment by local standard of care. Participants with latent TB who have initiated prophylactic treatment by local standard of care, participants with an indeterminate test result, or participants diagnosed with IGRA tests other than QuantiFERON Gold or T-SPOT must be discussed for eligibility on a case-by-case basis by the Sponsor, Clinical Trial Physician, or designee.

[h] Optional test for participants who are currently being treated with biological agents to be performed via local laboratories. The required drug clearance period will be waived for participants who have undetectable drug levels on TDM testing at Screening or prior to Screening (Section 9).

[i] Medical history will include smoking history and detailed CD medical history. The Day [redacted] medical history can be abbreviated, noting events that occurred between Screening and Visit [redacted].

[redacted]

[redacted]

[redacted]

[m] The complete physical examination will include a full examination of the skin for lesions, a check for visual symptoms (ie, blurred vision or decreased vision), and height and weight. A check for visual symptoms and a full examination of the skin should be repeated every 6 months.

[n] The interim physical examination will include weight, a check for visual symptoms, and an evaluation of body systems with previously noted abnormalities and/or those body systems associated with any new complaints from the participant (see Section 9.4.1).

[redacted]

[redacted]

[redacted]

[r] At Screening, participants [redacted] will be issued a participant diary for CD symptoms and will be trained in the use of the diary. Participant compliance with the completion of the diary data should be assessed at each study visit.

[s] Colonoscopy should be performed upon confirmation of eligibility based on PCDAI and other entry criteria, if possible. A participant's previous colonoscopy may be used if within 35 days of randomization (Day [redacted]).

[redacted]

[t] Blood sample collection for [redacted] PK, and [redacted] will be conducted based on participant weight and blood collection guidelines (see Section 9.4.12. For specific details on laboratory draws by weight, please refer to the Lab Flowchart.

[redacted]

[x] Current IP will be redispensed for participants who are not entering the LTE Period on the same day. Current IP will not be redispensed for participants who are entering the LTE Period on the same day; LTE IP will be dispensed instead.

[redacted]

[z] Visual acuity test results will be recorded based on the age-appropriate tests performed in all participants by an individual with appropriate training.

[aa] Once a participant turns 18 years of age (or local age of majority), he/she may need to sign a consent form, in accordance with regional or local regulations.

[redacted]

Table 2-2: Schedule of Events for Long-term Extension and Safety Follow-up Periods

	[redacted]
Visit Number	
Week	
Safety Assessments	
Prior/concomitant medications	
Prior/concomitant procedures	
Pregnancy test and contraception education[redacted]	
Adverse events	
Vital signs[redacted]	
Height	
Weight	
[redacted] collection[redacted]	
[redacted]	
Complete physical examination[g]	
Interim physical examination[h]	
12-lead ECG[i]	
Visual Acuity Test[t]	

Table 2-2: Schedule of Events for Long-term Extension and Safety Follow-up Periods

	[redacted]
Visit Number	
Week	
Ophthalmologic evaluation[redacted]	
Pulmonary function evaluation[redacted]	
[redacted]	
Hematology	
Blood chemistry	
Urinalysis	
Efficacy Assessments	
Participant diary for CD activity[m]	
Bristol Stool Scale (adolescents[redacted])	
CDAI (adolescents[redacted])	
Reminder phone call for participant diary entry	
Colonoscopy/SES-CD/colonic biopsy[n]	
PCDAI	

Table 2-2: Schedule of Events for Long-term Extension and Safety Follow-up Periods

	[redacted]
Visit Number	
Week	
ESR for PCDAI	
PK/PD Assessments	
Blood sample for PK[o,p]	
Blood sample for PD [redacted][p]	
Serum sample for PD[p]	
Stool sample for [redacted]	
[redacted] blood samples[q]	
IP	
Dispense IP	
Administer IP in clinic	
Review drug compliance	

Abbreviations: CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; d, days; [redacted] ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; [redacted] IP, investigational product; LTE, long-term extension; NA, not applicable; [redacted] PD, pharmacodynamic; PK, pharmacokinetic; PCDAI, Pediatric Crohn's Disease Activity Index; [redacted] SES-CD, Simple Endoscopic Score for Crohn's Disease.

[redacted]

[redacted]

g For all participants, a complete physical examination (which includes height and weight) will be performed at [redacted] The complete physical examination consists of a full examination of the skin for lesions as well as a check for visual symptoms (ie, blurred vision or decreased vision). A check for visual symptoms and a full examination of the skin should be repeated every 6 months.

h At all other visits, other [redacted], an interim physical may be performed. The interim physical examination will include body systems with previously noted abnormalities and/or those body systems associated with any new complaints from the participant.

i If a participant enters the LTE period early prior to completing the Induction Period and did not receive a [redacted] ECG in the Induction Period, a 12-lead ECG should be conducted at the study visit that coincides closest with completion of [redacted] of treatment.

[redacted]

[redacted]

[m] Participants [redacted] who participate in the LTE Period will complete diaries for at least 14 days prior to each scheduled visit, [redacted] Safety Follow-up Visit. Site staff will call participants at least 14 days prior to each study visit to remind them to complete their diaries.

[n] Colonoscopy is not required at any specific time point in the LTE Period; however, if performed, results of colonoscopy evaluation should be documented.

[o] A blood sample for PK should be collected approximately every 48 weeks during treatment with ozanimod, on the same day as a planned hematology collection. One sample should be collected at any time post-dose.

[p] Blood sample collection for [redacted] PK, and [redacted] will be conducted based on participant weight and blood collection guidelines (see Section 9.4.12). For specific details on laboratory draws by weight, please refer to the Lab Flowchart.

[redacted]

[t] Visual acuity test results will be recorded based on the age-appropriate tests performed in all participants by an individual with appropriate training.

[redacted]

Note: Once a participant turns 18 years of age (or local age of majority), he/she may need to sign a consent form, in accordance with regional or local regulations.

It is recommended that study visits are scheduled in the morning (except for [redacted] at which participants are to administer IP at home at least [redacted] prior to arriving for this visit). On study visit days when pre-dose (trough) PK samples are to be drawn, participants should be instructed to withhold the dose until the study visit, and the dose will be administered during the visit.

Whenever possible, the sequence of assessments should remain constant and at approximately the same time of day throughout the study. It is recommended that procedures are performed in the following order (note that not all procedures are performed at every visit):

- Spontaneous or solicited AE reporting
- ECG
- Vital signs
- Clinical laboratory tests, including pre-dose PK sampling

- Physical examination
- Efficacy assessments
- IP administration (on visits when pre-dose PK blood draws are collected; see Section 9.5)

3 INTRODUCTION

Ozanimod hydrochloride (RPC1063; hereafter referred to as ozanimod) is a small molecule compound which selectively binds with high affinity to sphingosine 1-phosphate (S1P) receptors 1 and 5. In vitro, ozanimod has little activity on the other S1P receptors, showing half maximal effective concentration greater than 10,000 nM for S1P2, > 5000 nM for S1P3, and > 2000 nM for S1P4.

Many cell types express S1P1, including vascular endothelial cells, brain cells, and lymphocytes. Stimulation (agonism) of this receptor results in biological activities that include lymphocyte retention in peripheral lymphoid organs (eg, lymph nodes and gastrointestinal [GI] Peyer's patches), resulting in reversible systemic reduction in circulating lymphocytes. Given the immune-mediated inflammation in CD, prevention of circulation of disease-exacerbating, self-reactive lymphocytes to the gut is likely to have salutary immunomodulatory effects with a consequent dampening of disease processes.

Ozanimod is extensively metabolized in humans to form several circulating active metabolites, including 2 major active metabolites (CC112273 [also referred to as RP112273]) and CC1084037 [also referred to as RP100798]). Ozanimod and its active metabolites have similar chemical structures, activity, and selectivity for S1P1 and S1P5 receptors. Following multiple dose administration of ozanimod in healthy adult participants, approximately 94% of circulating total active drug exposure is represented by ozanimod (6%), CC112273 (73%), and CC1084037 (15%). Ozanimod has no unique human metabolites, with all notable human metabolites present in one or more animal species used for safety testing.

Despite recent progress in CD treatment, there remains an unmet need for oral agents that are safe, convenient, and able to provide effective induction and long-term maintenance of clinical remission.

The primary mode of action for ozanimod is thought to be via the S1P1-mediated inhibition of lymphocyte trafficking. More specifically, S1P1 agonism causes internalization of the S1P1 receptors on lymphocytes, resulting in their retention in lymphoid tissues such as lymph nodes, and thus decreased levels of lymphocytes present in the circulation. This may result in fewer immune cells trafficking to inflammatory sites such as the gut and, subsequently, less inflammation.

3.1 Study Rationale

Ozanimod is being studied in a comprehensive inflammatory bowel disease (IBD) program, which includes participants with CD as well as participants with ulcerative colitis (UC). The adult CD program consists of a completed, open-label Phase 2 study demonstrating improvements in endoscopic and clinical outcomes, and an ongoing Phase 3 pivotal program. Results from a [redacted] treated with ozanimod 0.46 and 0.92 mg daily suggested efficacy for induction and maintenance of clinical remission and a dose response relationship. Results from a Phase 3 study confirmed 0.92 mg/day for induction and maintenance of clinical remission for moderate to severe UC. [redacted]

[redacted]

In addition, ozanimod has been studied for the treatment of patients with multiple sclerosis (MS). In MS Phase 3 pivotal trials, treatment with ozanimod 0.92 mg and 0.46 mg/day demonstrated statistically significant, clinically meaningful reductions in annualized relapse rate (ARR) compared with interferon beta-1a (IFN β-1a) at 12 months and 24 months, with a dose-dependent effect favoring the ozanimod 0.92 mg/day dose.

This study is being conducted to evaluate the efficacy and safety of ozanimod in CD in the pediatric population.

3.1.1 Summary of Nonclinical Studies

The nonclinical safety assessment for ozanimod included repeated dose toxicity (rodent and non-rodent), genotoxicity, carcinogenicity, reproductive and developmental toxicity, phototoxicity, and immunotoxicology studies.

The majority of the findings in the chronic toxicology, carcinogenicity, and reproductive toxicology studies are considered target-mediated effects of S1P1 and S1P5 agonists. [redacted]

3.1.2 Summary of Clinical Studies

Multiple Sclerosis

The MS development program comprises the following studies: 1 Phase 2 study (RPC01-201A), 2 Phase 3 studies (RPC01-201B and RPC01-301), and 1 Phase 3 open-label extension (OLE) study (RPC01-3001). In the Phase 2 study RPC01-201A, numerical reductions in ARR of approximately 53% and 31% relative to placebo were observed for ozanimod 0.92 mg/day and ozanimod 0.46 mg/day, respectively. In Phase 3 Studies RPC01-201B and RPC01-301, treatment with ozanimod 0.92 mg/day and 0.46 mg/day resulted in statistically significant, clinically meaningful reductions in ARR compared with IFN β-1a at 12 months and 24 months. A dose-dependent effect

was observed favoring the ozanimod 0.92 mg/day dose over the 0.46 mg/day dose in the pooled analysis and both Phase 3 studies. As of the last data cut-off date for the OLE study RPC01-3001 (01-Feb-2022), participants who had received IFN β-1a or ozanimod in the parent studies had similar cumulative participant-years of exposure to open-label ozanimod, and the majority of participants had received ozanimod 0.92 mg/day in the OLE for a minimum of 36 months. An overall unadjusted ARR of 0.132 was observed in the OLE study with little variability across parent treatment groups.

Across the MS studies, the most frequently reported treatment-emergent adverse events (TEAEs) occurring in ≥ 5% participants in any treatment group included nasopharyngitis, headache, and upper respiratory tract infection. In the active-controlled Phase 3 studies, the incidence of nasopharyngitis was slightly higher in the ozanimod treatment groups than in the IFN β-1a treatment group, but no dose effect was observed. The incidences of headache and upper respiratory tract infection were similar across the 3 treatment groups. In the combined safety pool of all MS studies, the incidence of all TEAEs was slightly higher in the ozanimod 0.92 mg/day treatment group than in the ozanimod 0.46 mg/day treatment group. A greater proportion of participants in the ozanimod 0.92 mg/day treatment group reported increased alanine aminotransferase (ALT) as compared to the ozanimod 0.46 mg/day (all relapsing MS studies) and IFN β-1a treatment groups (Phase 3 studies). Infections more frequently reported with ozanimod primarily involved the upper respiratory tract or urinary tract. Importantly, reductions in absolute lymphocyte count did not appear to be associated with an increased incidence of infections.

Ulcerative Colitis

The development program in adults with moderately to severely active UC includes a completed Phase 2 randomized double-blind controlled trial in adults (RPC01-202) and a completed Phase 3 randomized double-blind controlled trial in adults (RPC01-3101). Participants from both trials were offered the opportunity to roll over into an additional ongoing OLE trial (RPC01-3102). The key efficacy endpoints in both completed studies were the proportion of participants in clinical remission at the end of the induction and maintenance phases.

The Phase 2 UC trial (RPC01-202) demonstrated that, at the conclusion of the 9-week induction phase, the proportion of participants achieving clinical remission (4-component Mayo score ≤ 2 points with no individual subscore > 1 point) with ozanimod 0.92 mg/day was greater than placebo, and the difference was both clinically meaningful and statistically significant. In addition, all secondary endpoints at the conclusion of the induction phase, including clinical response (a reduction of 4-component Mayo score of ≥ 3 points and at least 30% with a reduction from Baseline in the Rectal Bleeding subscore of ≥ 1 point), change in the Mayo score, and mucosal improvement on endoscopy, were positive and nominally significant for the ozanimod 0.92 mg/day dose compared to placebo.[2] Trends were also observed with the 0.46 mg/day dose, consistent with a dose-response relationship.

At the conclusion of the 32-week maintenance phase, the proportion of UC participants achieving clinical remission with either ozanimod 0.46 mg/day or 0.92 mg/day was greater than placebo and the difference was both clinically meaningful and statistically significant. Mucosal improvement

on endoscopy was positive and statistically significant for both doses as well. The secondary endpoints of clinical response and change in Mayo score were also positive and statistically significant for the ozanimod 0.92 mg/day dose. Trends for those endpoints were observed with the 0.46 mg/day dose but statistical significance was not achieved, again consistent with a dose response.

The overall adverse event (AE) profile in the Induction and Maintenance Periods appeared comparable between the ozanimod dose groups and placebo. Worsening of UC was the most common serious AE (SAE), experienced by 3 placebo participants and 2 ozanimod 0.92 mg/day participants. All SAEs were assessed as unrelated or unlikely related to study treatment and all were resolved. The most frequently reported TEAEs leading to treatment discontinuation were Crohn's disease (CD; 5 ozanimod participants) and abdominal abscess (2 ozanimod participants). All other TEAEs leading to treatment discontinuation occurred in 1 participant each. All TEAEs leading to treatment discontinuation also led to study withdrawal.

Adverse events of special interest (AESIs) being monitored included [redacted] macular edema, malignancy, serious or opportunistic infection, pulmonary effects, and hepatic effects. There were no significant cardiac AEs, cardiac AEs reported as AESIs, findings on electrocardiogram (ECG), or findings on 24-hour Holter monitoring in ozanimod-treated participants, which indicates a favorable overall cardiac safety profile and suggests a potential benefit of dose escalation during initiation of ozanimod therapy. Data from the OLE portion of RPC01-202 (> 3 years) has shown high participant retention, consistent efficacy, and no new safety signals emerging in this population.

RPC01-3101, a Phase 3 study in adult participants with moderate to severe UC, met both primary endpoints, demonstrating highly statistically significant results for induction of clinical remission at Week 10 and in maintenance at Week 52. The study also met key secondary endpoints of clinical response and endoscopic improvement compared to placebo in induction at Week 10 and in maintenance at Week 52.[3]

[redacted] Ozanimod was generally well tolerated, with a low rate of discontinuation and low incidence of SAEs. The most frequently reported TEAEs with long-term use of ozanimod 1 mg (≥ 5% of participants) which occurred at a ≥ 1% higher incidence compared with placebo were consistent with the known safety profile of ozanimod and included lymphopenia, nasopharyngitis, anemia, increased ALT, decreased lymphocyte count, headache, arthralgia, and upper respiratory tract infection. [redacted]

No participants experienced a serious infection or opportunistic infection concurrent with an [redacted] Overall, there is [redacted]

Crohn's Disease

The development program in adults with moderately to severely active CD includes a completed Phase 2 open-label trial in adults (RPC01-2201), ongoing double-blind, placebo-controlled Phase 3 induction and maintenance trials in adults (RPC01-3201, RPC01-3202, RPC01-3203), and an OLE trial (RPC01-3204).

RPC01-2201, a Phase 2 study, was conducted in CD to examine endoscopic and clinical outcomes following treatment with ozanimod 0.92 mg daily for 12 weeks in the Induction Period and up to 148 weeks in the Extended Period. Simple Endoscopic Score for Crohn's Disease (SES-CD) reductions of ≥ 50% from Baseline were seen in 28.6% of participants (observed cases), with greater endoscopic response in participants with Baseline SES-CD score ≤ 12 and a shorter disease duration. At Week 52, the proportion of participants achieving reductions of ≥ 50% was maintained at 26.7%. Clinical response was seen in 68.5% and 93.8% of participants (observed cases) at Week 12 and Week 52, respectively. Clinical remission was seen in 46.3% and 65.6% of participants (observed cases) at Week 12 and Week 52, respectively. [redacted]

The safety and tolerability results from the 12-week Induction Period of RPC01-2201 suggest that ozanimod 0.92 mg daily is well tolerated and has an acceptable safety profile in participants with moderately to severely active CD. In the open-label period (OLP), ozanimod 0.92 mg was well tolerated and there were no new safety concerns. The AEs reported in the study were generally consistent with those seen in participants with moderately to severely active UC. No events were designated by the investigators as AESIs for the categories of pulmonary, ophthalmic, or cardiac during the first 12 weeks of the study, and there were no clinically significant episodes of bradycardia or cardiac conduction abnormalities. AESIs for the category of infection were reported in 15.9% of participants in RPC01-2201, with abdominal abscess and herpes zoster each reported in 2.9% of participants.

The Phase 3 adult CD program (RPC01-3201, 3202, 3203, 3204) is being conducted to examine induction and maintenance of clinical remission and endoscopic improvement over 12-week Induction and 52-week Maintenance Periods in participants administered oral ozanimod at 0.92 mg/day. [redacted]

Summary

Given the mechanism of action of ozanimod, data from the preclinical animal model, the positive results from the Phase 2 CD study (RPC01-2201) and Phase 2 and 3 UC studies (RPC01-202 and RPC01-3101, respectively), and an acceptable safety profile observed across indications, ozanimod has the potential to address an unmet need in the pediatric CD population. This study is being conducted to characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of

ozanimod once daily and to evaluate the efficacy and safety of ozanimod doses in pediatric participant equivalent to 0.46 or 0.92 mg/day in adults.

3.2 Background

CD is an immune-mediated inflammatory disease of the GI tract. Annual incidence in adults varies geographically, with estimates ranging from 3.1 to 14.6 per 100,000 people in the United States and from 0.1 to 16 per 100,000 worldwide.[4] Adult and pediatric participants with CD suffer from diarrhea, rectal bleeding, weight loss, abdominal pain, and fever.

CD is characterized by a lifelong chronic course of remissions and exacerbations. The pathology of this disease is characterized by transmural infiltration of lymphocytes and macrophages, granulomas, fissuring ulceration, and submucosal fibrosis. The transmural inflammatory process of CD predisposes participants to the formation of fistulas and it has been estimated that approximately 35% of participants will have at least 1 fistula during the course of their disease.[5] According to a recent study, 50% of adults with CD had undergone bowel surgery within 10 years of diagnosis.[6]

The current standard of medical care for participants with moderately to severely active CD consists of anti-inflammatory approaches, such as corticosteroids, azathioprine (AZA)/6 mercaptopurine (6-MP), methotrexate (MTX), and biologics such as anti-tumor necrosis factor (TNF)α, anti-interleukin (IL)-12/IL-23, or anti-integrins.

Immunomodulators aid in corticosteroid withdrawal and in preventing relapse but are also associated with considerable side effects. Infliximab, an anti-TNFα therapy, can reduce signs and symptoms and induce and maintain remission in most participants for which it is indicated. However, in a large Phase 3 maintenance trial of infliximab for CD in adults (ACCENT I), only 45% of participants were considered in remission at Week 30 in the highest dose group (where remission was defined as the ability to achieve a Crohn's Disease Activity Index [CDAI] of < 150 points).[7] Similarly, the primary response rates in adult trials of adalimumab[8] and certolizumab[9] were approximately 47% and 37%, respectively. Thus, a sizable proportion of the patient population is unresponsive to both conventional therapy and TNF antagonists. Vedolizumab, a gut-specific anti-integrin therapy, is also indicated for achieving clinical response and clinical remission in this population. However, in a large clinical trial of vedolizumab, only 31% of participants had a clinical response at Week 6, and only 39% of participants receiving vedolizumab every 8 weeks that were induction responders were in remission at Week 52.[10] Ustekinumab, a monoclonal antibody to the p40 subunit of IL-12 and IL-23, was studied in adult CD patients who failed, had loss of response, or were intolerant to treatment with immunomodulators, corticosteroids, or 1 or more TNF antagonists. However, in the induction trials of ustekinumab, only 32% of participants were responders at Week 6,[11] and 53% of induction responders were in remission at Week 52 of the maintenance trial.

Crohn's Disease in the Pediatric Population

Approximately 20% to 30% of all cases of IBD are diagnosed in children and adolescents, with 80% of these participants between the ages of 10 and 18.[12] Similar to adults, presentation of CD in this patient population depends on the disease location and the extent of inflammation. Involvement of both small bowel and colon are seen in over half of the population and the most commonly encountered GI symptoms are abdominal pain, diarrhea, and weight loss.[13]

A large proportion of children and adolescents present with complications such as stricturing/penetrating phenotype and extensive small bowel disease involvement. These risk factors present as or progress to developing intestinal complications including fistulae, localized peritonitis, abdominal abscesses and small bowel obstruction.[14,15,16]

Given that presentation in the pre-pubertal or peri-pubertal period is common, pubertal delay and growth restriction are also of significant concern. Approximately 10% to 30% of children and adolescents present with growth failure mediated by several factors including inflammation, malnutrition, and glucocorticoid therapy.[17]

Treatment modalities include corticosteroids, exclusive enteral nutrition (EEN), immunomodulators, and biologics. Corticosteroids are effective for the induction of clinical remission in CD; however, approximately half of the participants become dependent on long-term corticosteroids or require surgery. Less than one-third of participants with CD in clinical remission with corticosteroid treatment achieve mucosal healing. Treatment with EEN can induce remission but is less effective than corticosteroids. EEN is also used less frequently due to concerns with invasiveness and poor compliance.[18]

Approximately 70% to 80% of pediatric participants treated with immunosuppressants such as AZA, 6-MP, and MTX, or biologics such as infliximab and adalimumab, do not experience prolonged clinical remission. Many require dose intensification to maintain remission, and a subset of these participants experience loss of response despite dose intensification due to the development of anti-drug antibodies. One-third of participants discontinue infliximab within 2 to 3 years, either because of primary nonresponse, loss of response, or AEs.[19] Many experience toxicities such as myelosuppression and serious infections. While remission rates for adalimumab are similar to infliximab for infliximab-naïve participants, those who have been previously treated with infliximab have shown significantly lower remission rates (approximately 20%).

In conclusion, although children demonstrate response to treatment with corticosteroids, immunomodulators, and biologic therapies, barriers or reluctance to use these therapies in children include fewer available approved therapies, more impactful long-term effects when administered earlier in life, and interference with children's quality of life including psychosocial needs.[20] Therefore, there is an unmet need for a CD treatment that is safe, effective, and convenient to administer in the pediatric population.

3.3 Benefit/Risk Assessment

Despite recent progress in CD treatment, there remains an unmet need for oral agents that are safe, convenient, and can provide effective induction and long-term maintenance of clinical remission in pediatric participants. The benefit/risk profile for ozanimod has been evaluated in patients with CD. Results from studies in adult participants with moderate to severe disease who failed prior therapy and were treated with ozanimod 0.92 mg daily for at least 12 weeks suggested clinical and endoscopic benefit (RPC01-2201). In addition, safety results suggest that ozanimod is well tolerated in patients with CD and are consistent with those observed in other patient populations treated with ozanimod (UC and MS). Overall, the current data suggest that ozanimod has a potentially favorable benefit/risk profile for pediatric participants with moderate to severe CD who have inadequate response, intolerance, or loss of response to these therapies for the pediatric population: corticosteroids, immunomodulators, or biologics.

3.3.1 Risk Assessment

As of the IB data cut-off date (19-May-2022), [redacted] participants overall have been exposed to at least 1 dose of investigational product (IP) across 31 company-sponsored studies involving healthy participants or participants with MS, UC, or CD. This includes [redacted] participants exposed to at least 1 dose of ozanimod. Important potential risks based on experience with non-selective S1P agonists include symptomatic bradycardia, atrioventricular conduction disorder, liver injury, macular edema, posterior reversible encephalopathy syndrome (PRES), and embryofetal toxicity in exposed pregnant females, malignancies, infections, and pulmonary effects.

Table 3.3.1-1: Risk Assessment

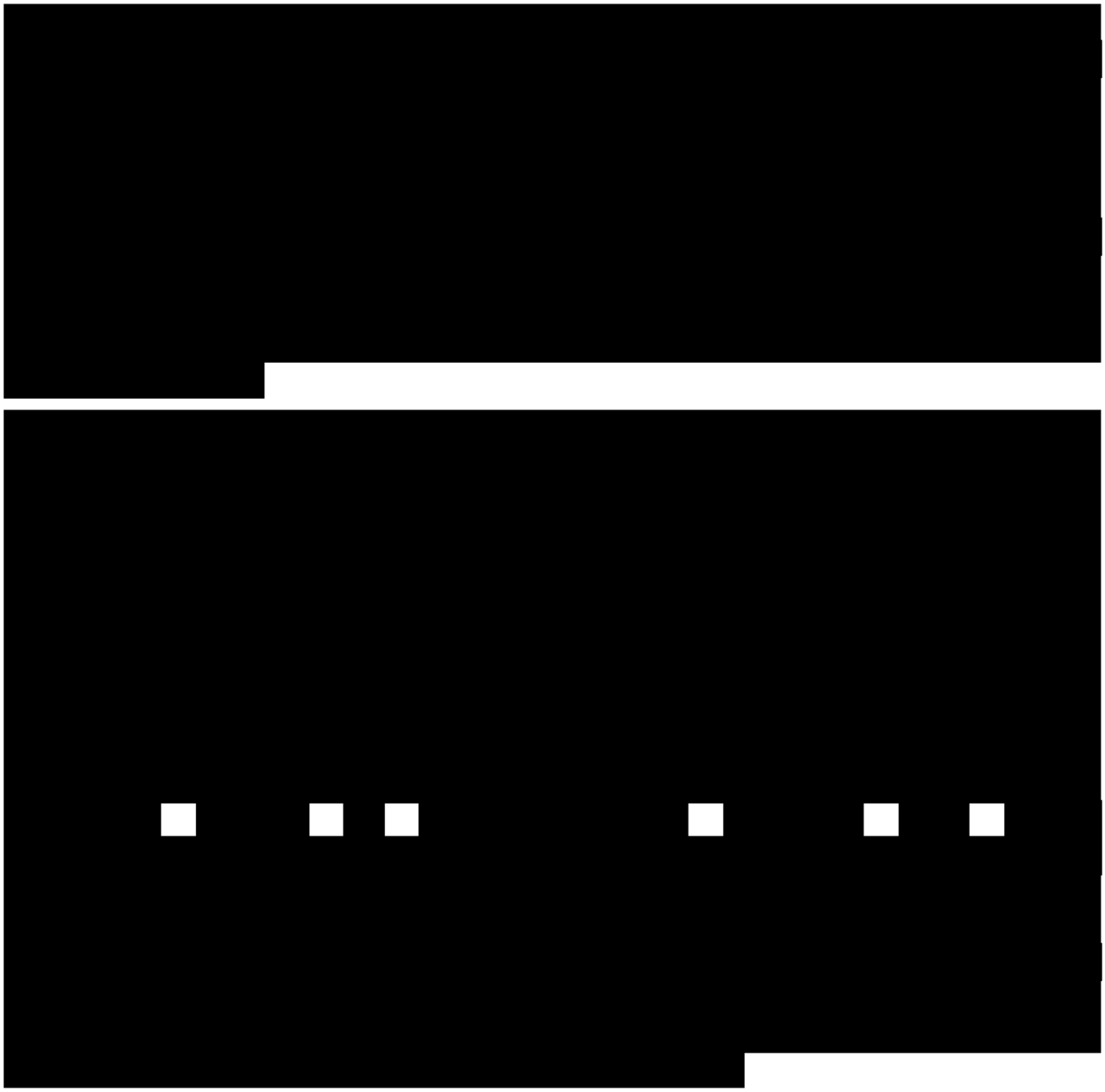
Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s)		
Symptomatic bradycardia	In controlled UC studies, bradycardia was reported in 2 participants during the induction period (1 on Day 1) and no participants during the Maintenance Period on ozanimod and none on placebo. The events were not symptomatic and did not require changes in dosing.	Exclude high-risk participants; require first-dose observation in all participants.
Severe liver injury	In controlled UC studies, elevations of ALT to 5-fold the ULN or greater occurred in 0.9% of participants treated with 0.92 mg during induction and 0.9% during maintenance. Elevations of ALT to 3-fold the ULN or greater occurred in 2.6% of participants during induction and 2.3% during maintenance. In UC studies, the majority (96%) of participants with ALT greater than 3-fold the ULN continued treatment with values	Monitor LFTs. Permanent discontinuation for confirmed severe elevations.

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	returning to less than 3-fold the ULN within approximately 2 to 4 weeks. The discontinuation rate due to elevations in hepatic enzymes was 0.4%. No cases of severe drug-induced liver injury were reported.	
Serious opportunistic infections, including PML	In ozanimod studies, the rate of serious infections was low and similar between ozanimod and control arms. One serious opportunistic infection of PML was reported in an MS OLE study.	Monitor WBC, monitor for PML symptoms, dose interruption for suspected cases of PML, and permanent discontinuation upon confirmation of PML.
Macular edema	In active-controlled MS clinical trials with ozanimod, macular edema was observed in 1 (0.1%) participant with ozanimod 0.92 mg and 3 (0.3%) participants with ozanimod 0.46 mg, all of whom had pre-existing risk factors. In the UC studies, macular edema was reported in up to 0.4% of participants, usually with risk factors, such as diabetes, prior ocular surgery, and history of uveitis.	Monitor visual symptoms (eg, blurred vision, decreased visual acuity).
Malignancy	Malignancies have been reported with ozanimod. The rate of malignancies, including non-melanoma skin cancers, was comparable to that reported in real world data and found to be similar.	Close monitoring for malignancies, including complete dermatologic exam.
Posterior reversible encephalopathy syndrome	One case reported in a patient with MS and autonomic instability.	Monitor symptoms, dose interruption for suspected cases, and permanent discontinuation upon confirmation.
Embryofetal toxicity in exposed pregnant females	Non-clinical data with teratogenicity. Clinical data without suggestion of teratogenicity as of 30-Sep-2020.	Highly effective contraception and regular pregnancy testing in FOCBP. Avoid use during lactation.
Study Procedures		
Colonoscopy	Potential perforation or bleeding.	Standard medical care.

Abbreviations: ALT, alanine aminotransferase; FOCBP, females of childbearing potential; LFT, liver function tests; MS, multiple sclerosis; OLE, open-label extension; PML, progressive multifocal leukoencephalopathy; UC, ulcerative colitis; ULN, upper limit of normal; WBC, white blood cells.

[redacted]



3.3.2 Benefit Assessment

Ozanimod has shown efficacy and tolerability across the 3 indications that have been studied in the clinical setting. In Phase 3 MS Studies RPC01-201B and RPC01-301, treatment with ozanimod 0.92 mg/day and 0.46 mg/day resulted in statistically significant, clinically meaningful reductions in ARR compared with IFN β-1a at 12 months and 24 months. Safety results showed that ozanimod was generally well tolerated (see Section 3.1.2 for AE summary).

The Phase 2 UC trial (RPC01-202) demonstrated that, at the conclusion of the 9-week induction phase and 32-week maintenance phase, the proportion of participants achieving clinical remission with ozanimod 0.92 mg/day was greater than placebo and the difference was both clinically meaningful and statistically significant. In addition, secondary endpoints including clinical response, change in the Mayo score, and mucosal improvement on endoscopy, were positive and

nominally significant for the ozanimod 0.92 mg/day dose compared to placebo.[2] RPC01-3101, a Phase 3 study in adult participants with moderate to severe UC, met both primary endpoints, demonstrating highly statistically significant results for induction of clinical remission at Week 10 and in maintenance at Week 52.[3] The study also met key secondary endpoints of clinical response and endoscopic improvement compared to placebo in induction at Week 10 and in maintenance at Week 52.

The Phase 2 CD trial (RPC01-2201) demonstrated reductions of ≥ 50% from Baseline in SES-CD for 28.6% of participants (observed cases), with greater endoscopic response in participants with Baseline SES-CD score ≤ 12 and a shorter disease duration. The safety and tolerability results from the 12-week Induction Period of RPC01-2201 suggest that ozanimod 0.92 mg daily is well tolerated and has an acceptable safety profile in participants with moderately to severely active CD. In the OLP, ozanimod 0.92 mg was well tolerated and there were no new safety concerns.

Please refer to the IB for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and AE profile of the IP.

3.3.3 Overall Benefit/Risk Conclusion

IM047-023 has been designed to closely monitor study participants' safety throughout the duration of the study. A comprehensive safety monitoring plan utilizes frequent assessments to monitor for disease relapse which allows the participants to proceed to open-label treatment. Additionally, at the investigator's discretion, rescue therapy can be initiated or dosing of study medication can be discontinued at any time during the study. A comprehensive monitoring of safety will be conducted by the investigators, Clinical Trial Physicians, and an independent DMC.

Given the mechanism of action of ozanimod, data from the preclinical animal model, the positive results from the Phase 2 (RPC01-202) and Phase 3 (RPC01-3101) UC studies, the Phase 2 CD study (RPC01-2201), and an acceptable safety profile observed across indications, ozanimod has the potential to address an unmet need in the pediatric CD population. IM047-023 has a potential favorable benefit/risk profile for pediatric patients with moderate to severe CD who have inadequate response or intolerance to corticosteroids, immunomodulators, or biologic therapy.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objective	Endpoint
Primary – Efficacy	
• To evaluate the efficacy of ozanimod once daily in pediatric participants with moderately to severely active CD: clinical remission by PCDAI at Week 64	• Proportion of participants who achieve PCDAI < 10 at Week 64
• To evaluate endoscopic remission at Week 64 by SES-CD	• Proportion of participants achieving SES-CD ≤ 2 or SES-CD ≤ 4 points with no SES-CD subscore > 1 point at Week 64
Secondary – Efficacy (Key)	
• To evaluate the efficacy of ozanimod once daily in pediatric participants with moderately to severely active CD: clinical remission by PCDAI at Week 12	• Proportion of participants who achieve PCDAI < 10 at Week 12
Secondary – Efficacy (Other)	
• To evaluate endoscopic response by SES-CD	• Proportion of participants who achieve SES-CD decrease from Baseline of ≥ 50% (ER-50) at Week 64; Week 12
• To evaluate clinical response by PCDAI	• Proportion of participants who achieve reduction in PCDAI score ≥ 12.5 and a total PCDAI score of < 30 points at Week 64; Week 12
• To evaluate symptomatic remission (adolescents only)	• Proportion of adolescents who achieve an average daily abdominal pain score ≤ 1 point and an average daily stool frequency ≤ 3 points with abdominal pain and stool frequency no worse than Baseline at Week 64; Week 12
• To evaluate change in CD symptoms over time	• Change from Baseline in stool frequency score over time • Change from Baseline in abdominal pain over time
• To evaluate clinical remission by CDAI (adolescents only)	• Proportion of adolescents who achieve CDAI score < 150 at Week 64; Week 12
• To evaluate clinical response by CDAI (adolescents only)	• Proportion of adolescents who achieve CDAI reduction from Baseline of ≥ 100 points or CDAI score < 150 at Week 64; Week 12
• To evaluate corticosteroid-free remission	• Proportion of participants who achieve a PCDAI score < 10 at Week 64 while remaining corticosteroid free in the prior 12 weeks • Proportion of participants who achieve a CDAI score < 150 at Week 64 while remaining corticosteroid free in the prior 12 weeks (adolescents only)

Table 4-1: Objectives and Endpoints

Objective	Endpoint
• To evaluate endoscopic remission at Week 12	• Proportion of participants achieving SES-CD ≤ 2 or SES-CD ≤ 4 points with no SES-CD subscore > 1 point at Week 12
Secondary –Pharmacokinetics	
• To characterize the PK of 2 doses of oral ozanimod and its major active metabolites in pediatric participants with moderately to severely active CD	• Steady state systemic exposures of ozanimod and CC112273 at Week 20 and throughout the study
Secondary –Pharmacodynamics	
• To evaluate the PD effects of 2 dose levels of ozanimod (eg, effects on ALC) in pediatric participants with moderately to severely active CD	• Absolute and percent change from Baseline in ALC at Week 64, Week 12, and throughout the study
Secondary – Safety and Tolerability	
• To evaluate the safety and tolerability of 2 dose levels of oral ozanimod once daily in pediatric participants with moderately to severely active CD	• Number and proportion of participants experiencing AEs, SAEs, AEs leading to discontinuation from treatment, and AESIs throughout the study

[redacted]

Table 4-1: Objectives and Endpoints

Objective	Endpoint
[redacted]	

[redacted]

Endpoint Definitions

Key study definitions are provided below (see Table 4-2).

Table 4-2: Selected Endpoint Definitions

Endpoint	Definition
Clinical remission	CDAI < 150
	PCDAI < 10 points
Clinical response	CDAI reduction from Baseline of ≥ 100 points or CDAI score < 150
	PCDAI reduction from Baseline of ≥ 12.5 and a total PCDAI score of < 30 points
Endoscopic remission	SES-CD ≤ 2 or SES-CD ≤ 4 points and with no SES-CD subscore > 1 point
Endoscopic response	≥ 50% improvement from Baseline in the SES-CD
Corticosteroid-free remission	PCDAI score < 10 at Week 64 while remaining corticosteroid free in the prior 12 weeks CDAI < 150 at Week 64 and receiving no corticosteroids for CD in the prior 12 weeks
Histologic remission	[redacted]
Loss of response	[redacted]
[redacted]	
Symptomatic remission (adolescents only)	Average daily abdominal pain score ≤ 1 point and average daily stool frequency ≤ 3 points with abdominal pain and stool frequency no worse than Baseline

Abbreviations: CDAI, Crohn's Disease Activity Index; [redacted] PCDAI, Pediatric Crohn's Disease Activity Index; [redacted] SES-CD, Simple Endoscopic Score for Crohn's Disease.

5 STUDY DESIGN

5.1 Overall Design

This is a Phase 2/3, randomized, double-blind study designed to evaluate the efficacy, safety, and tolerability of oral ozanimod once daily in pediatric participants aged 2 to 17 years inclusive, with moderately to severely active CD (defined as a Pediatric Crohn's Disease Activity Index [PCDAI] score of ≥ 30 and an SES-CD score of ≥ 6 [or SES-CD ≥ 4 in participants with isolated ileal disease] with an inadequate response, intolerance, or loss of response to prior therapy for CD. The study will also evaluate the PK and PD of oral ozanimod administered once daily at 2 dose levels (0.46 or 0.92 mg/day adult equivalent doses) in pediatric participants during a 64-week Induction and Maintenance treatment period.

The co-primary endpoints of the study are the proportion of participants in clinical remission (PCDAI < 10) at Week 64 and the proportion of participants in endoscopic remission (SES-CD ≤ 2 or SES-CD ≤ 4 points with no SES-CD subscore > 1 point) at Week 64. Key secondary endpoints are provided in Section 4.

The study design schematic is presented in [redacted]

[redacted]

The study is to enroll approximately [redacted] pediatric participants sequentially across [redacted]

[redacted]

[redacted]

The minimum weight requirement [redacted] however, for participants below the 5th percentile in weight for age (per Centers for Disease Control [CDC] growth charts[21]), the investigator should contact the Clinical Trial Physician or designee prior to enrollment.

[redacted] analyses [redacted] will determine the 0.46 and 0.92 mg/day adult equivalent doses [redacted].

[redacted] participants (aged 12 to 17 years, inclusive) will be randomized in a 1:1 ratio to receive either 0.46 or 0.92 mg/day of ozanimod. [redacted]

All participants will undergo [redacted] will initiate treatment [redacted] as it has successfully attenuated the negative cardiac effects of S1P modulation in adults [redacted]

- 0.46 mg dose: [redacted], then 0.46 mg/day [redacted], and continuing 0.46 mg/day [redacted]
- 0.92 mg/day dose: [redacted], then 0.46 mg/day [redacted], then 0.92 mg/day [redacted]

[redacted] and steady state PK data will be evaluated to adjust the escalation regimen as required.

The treatment that each participant will receive will not be disclosed to the investigator, site staff, participant, Sponsor, or the clinical staff at the contract research organization (CRO) involved with study conduct or data collection/analysis. Access to treatment assignments will be strictly limited to groups directly involved with drug distribution, preparation of unblinded output for the [redacted], Clinical Science, safety personnel unblinded to treatment for SAE cases, and personnel involved in the conduct of PK assays.

The blind should be maintained for persons responsible for the ongoing conduct of the study through the completion of the Long-term Extension (LTE) Period. Blinded persons may include but are not limited to the Clinical Trial Physician, Clinical Scientist, Clinical Trial Manager, Study Statistician, Data Manager, Programmers and Clinical Research Associates.

The study will be conducted in compliance with the International Council on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

[redacted]

[redacted] will initiate with randomization (1:1) to either a 0.46 mg/day or 0.92 mg/day dose of oral ozanimod. [redacted]

[redacted] (ie, 0.46 and 0.92 mg/day) [redacted].

[redacted] Participants will be randomized 1:1 to oral ozanimod at the doses that provide comparable exposures as adults administered either 0.46 or 0.92 mg/day ozanimod. [redacted]

Early Discontinuation

After at least 7 weeks of treatment (5 weeks on study and a confirmation visit at least 2 weeks later as described below), participants will have the option to enter the LTE Period [redacted]

[redacted]

Participants with concomitant corticosteroid use from Baseline who have initiated a corticosteroid taper are permitted to increase their dose of corticosteroids back to Baseline dose level (see Section 7.7). Participants who initiate therapy with corticosteroids or increase above Baseline dose level during the double-blind period are considered a treatment failure and must be discontinued from the current period but are eligible to proceed to the LTE Period.

At any time, the decision to discontinue participation in the study is left to the discretion of the participant, the participant's parent or legal guardian, or investigator.

Long-term Extension (LTE) Period

Participants will be entering the LTE Period from the Induction or Maintenance Period of this study. Participants eligible for the LTE Period will have either met early discontinuation criteria (see Section 8), completed Week 12 and are non-responders, or have completed Week 64.

The dose at which a participant enters the LTE will be determined by their clinical response at the time of entry into the LTE Period. Participants who have completed Week 64 and are in clinical remission when entering the LTE will receive ozanimod at the same dose as administered in the Induction and Maintenance Periods. Participants who are not in clinical remission at the time of entering the LTE will receive ozanimod at the of 0.92 mg/day adult equivalent dose. In general, the last visit of the Induction/Maintenance Period or the early termination (ET) visit will serve as the first visit of this LTE Period.

[redacted]

Participants who were not in clinical remission when entering the LTE Period and who meet LTE discontinuation criteria described above after at least 7 weeks of treatment (5 weeks in LTE Period and a confirmation visit at least 2 weeks later) in the LTE Period will be discontinued from the study.

Participants who completed Week 64 and were in clinical remission when entering the LTE Period, and who meet discontinuation criterion described above after 5 weeks of treatment in the LTE Period (with confirmation at least 2 weeks later), will receive ozanimod at the 0.92 mg/day adult equivalent dose appropriate for their age for an additional 5 weeks. If the participant continues to

meet the discontinuation criterion after the 5 additional weeks of treatment (with confirmation at least 2 weeks later [minimum of 14 weeks in LTE Period]), the participant will be discontinued from the study.

Participants can initiate or increase the dose of concomitant medications for the treatment of CD during the LTE Period and concomitant medications are not subject to dose stabilization requirements. The following medications are allowed at a therapeutic dose for CD (dosage regimen can be adjusted to accommodate mg/kg/day dosing as appropriate): oral 5-aminosalicylic acid (5-ASAs) and corticosteroids (prednisone 1.0 mg/kg/day for weights ≤ 40 kg, ≤ 40 mg/day for weights > 40 kg or equivalent, oral budesonide ≤ 9 mg per day, oral beclomethasone ≤ 5 mg per day).

Participants who require initiation of an immunomodulatory agent, including, but not limited to, 6-MP, AZA, or biologic therapy; or who require > 3 days of treatment with higher doses of systemic corticosteroids (e.g. prednisone > 1.0 mg/kg/day for weights ≤ 40 kg or > 40 mg/day for weights > 40 kg or equivalent) will be discontinued from the study.

Study Duration for Participants

Participants may spend up to 69 weeks in this study (excluding the [redacted] in the Safety Follow-up Period) prior to entering the LTE Period. This includes up to 5 weeks in the Screening Period, 12 weeks in the Induction Period, and 52 weeks in the Maintenance Period. For participants not entering LTE, a [redacted] Safety Follow-up Period will be completed for up to a total of 81 weeks in the study.

Participants who meet early discontinuation criteria (after at least 7 weeks of treatment) as described in Section 8, participants who are non-responders at Week 12, and participants who complete the Week 64 visit, will be eligible to enter the optional LTE Period (see Section 8). Participants entering the LTE Period who continue to demonstrate clinical benefit will receive oral ozanimod daily for up to approximately 4.5 years from their first dose (Day 1), or upon ozanimod approval for pediatric CD participants in their country, or as per local or regional requirements. For participants who enter the optional LTE Period, a [redacted] Safety Follow-up Period will be completed and the entire participation period of the study may be up to approximately 6 years from the participant's first dose (Day 1).

Participant Input in Study Design

Parents of, and children living with Crohn's Disease are uniquely positioned to help in the drug development process, and their voices have been incorporated into this protocol.

Parents/guardians/participants believe clinical trials are valuable and advance the science and management of CD. They trust their healthcare providers to discuss and recommend clinical trials available within the IBD community.

[redacted]

[redacted]

5.1.1 Data Monitoring Committee and Other Committees

[redacted]

An external, independent DMC will be charged with monitoring accumulating data from the study, as well as general aspects of study conduct.

The committee will meet periodically during the study to review aggregate analyses by treatment group concerning enrollment, treatment compliance, adherence to follow-up schedule, and safety and efficacy data from the study. The DMC will make dose selection and dose adjustment decisions based on the [redacted] recommendations. The DMC may recommend modifying the study or stopping the study early due to safety concerns based on data reviews.

To assure that all personnel involved in the conduct of the study remain blinded to the results of interim reviews, a blinding plan will be specified in the DMC Charter.

A DMC charter will describe the procedures related to the committee operations in greater detail.

5.2 Number of Participants

Approximately [redacted] pediatric participants aged 2 to 17 years, inclusive, with moderately to severely active CD with an inadequate response, intolerance, or loss of response to prior therapy for CD will be enrolled in this study. [redacted]

5.3 End of Study Definition

The start of the trial is defined as the first participant first visit.

End of trial is defined as the last participant last visit *or* the date of receipt of the last data point from the last participant that is required for primary, secondary, and/or exploratory analysis, as pre-specified in the protocol, whichever is the later date.

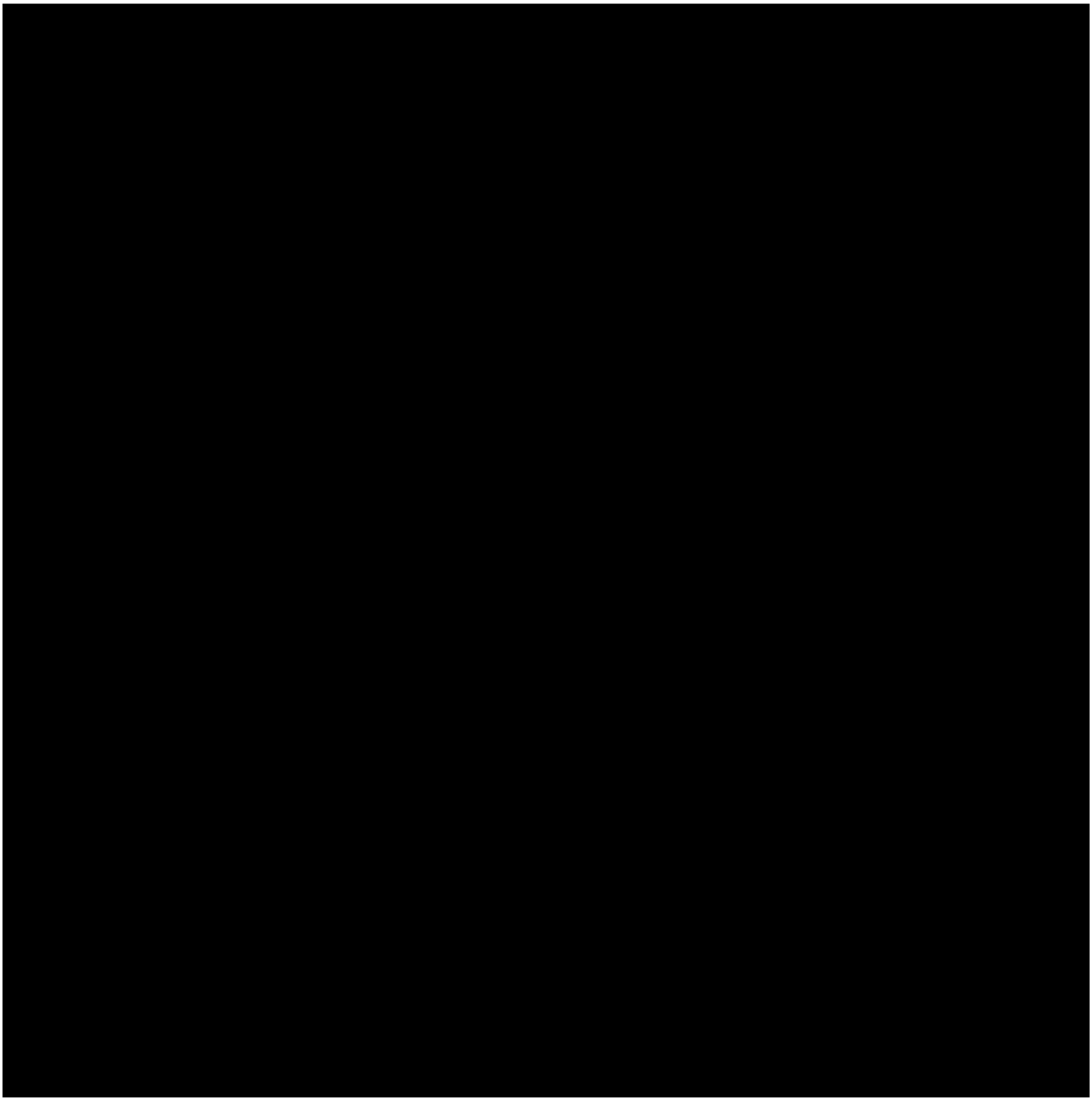
Study completion is defined as the final date on which data for the primary endpoint were or are expected to be collected, if this is not the same.

Participants who continue to demonstrate clinical benefit will be eligible to receive Sponsor-supplied study treatment for a maximum treatment duration as specified per local or regional requirements (see Section 7).

The Sponsor reserves the right to terminate access to Sponsor-supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of ozanimod is terminated for any reason, including but not limited to, lack of efficacy and/or not

meeting study objectives; c) the participant can obtain ozanimod from a government-sponsored or private health program. In all cases, the Sponsor will follow local requirements.

A participant is considered to have completed the study if he/she has completed the last visit or the last procedure shown in Section 2.



[redacted]

[redacted]

6 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1) Signed Written Informed Consent

Participants and their parent or guardian must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written informed consent form (ICF) and assent in accordance with regulatory, local, and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal patient care.

2) Type of Participant and Target Disease Characteristics

a) Participant is willing and able to adhere to the study visit schedule and other protocol requirements including is willing and able to swallow a [redacted] until a [redacted] of ozanimod is available.

b) Participant has been diagnosed with CD ≥ 3 months prior to the Screening Visit. The diagnosis should be confirmed by clinical and endoscopic evidence and corroborated by a histopathology report (Note: Local histopathology sample collection and analysis may also be performed during endoscopy at Screening if no prior report is readily available).

c) Participant has met each of the following 2 criteria:

i) A PCDAI score ≥ 30.

ii) Participant has a SES-CD score ≥ 6 (or SES-CD ≥ 4 in participants with isolated ileal disease).

d) Participant has an inadequate response, intolerance, or loss of response to at least 1 of the following treatments for CD (see Appendix 5).

i) corticosteroids (eg, oral prednisone, oral budesonide MMX, intravenous [IV] corticosteroids).
ii) immunomodulators (eg, AZA, 6-MP, cyclosporine, MTX).
iii) biologic therapy (eg, ustekinumab, abatacept, infliximab, etanercept, adalimumab, anakinra, rituximab, vedolizumab).
iv) other systemic immunomodulatory therapies for CD.

e) If the participant is taking the following background therapies for CD, a stable dose must be maintained as indicated below (dosage regimen can be adjusted to accommodate mg/kg/day dosing as appropriate):

i) Oral aminosalicylates (eg, mesalamine, sulfasalazine, olsalazine, balsalazide), the dose must have been stable starting 3 weeks prior to Screening endoscopy.

ii) Prednisone (≤ 0.5 mg/kg/day up to 20 mg/day), the dose must have been stable starting 2 weeks prior to Screening endoscopy and must remain stable through the first 5 weeks of treatment.

iii) Oral budesonide therapy (doses ≤ 9 mg per day) or oral beclomethasone (doses ≤ 5 mg per day), the dose must have been stable starting 2 weeks prior to Screening endoscopy and must remain stable through the first 5 weeks of treatment.

a) Participant must have documentation of vaccinations per standard immunization schedule including complete varicella vaccination at least 30 days prior to randomization (Day [redacted] or

documentation of positive varicella zoster virus (VZV) immunoglobulin G (IgG) antibody prior to randomization (Day [redacted].[28]

3) Age of Participant

a) Participant must be age 2 to 17 years, inclusive [redacted] at the time of informed consent/assent.

Note: Participants with a weight below the 5th percentile for age (per CDC growth charts)[21] should be discussed with the Clinical Trial Physician or designee prior to enrollment.

4) Reproductive Status

For the purposes of this study, female of childbearing potential (FOCBP) is defined as a female participant ≥ 12 years of age or has reached menarche, and 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been postmenopausal for at least 24 consecutive months (that is, has had menses at any time during the preceding 24 consecutive months).

Investigators shall counsel FOCBP participants on the importance of pregnancy prevention and the implications of an unexpected pregnancy.

- The investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- Local laws and regulations may require the use of alternative and/or additional contraception methods.

a) Female Participants:

i) Females who are not of childbearing potential are exempt from contraceptive requirements.

(1) If at any time during the study the ability to become pregnant changes, they will no longer be exempt from contraceptive requirements. The investigator will educate the participant regarding abstinence or contraception options and the correct and consistent use of effective contraceptive methods in order to successfully prevent pregnancy.

ii) FOCBP must have a negative highly sensitive serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) prior to randomization.

- Additional requirements for pregnancy testing during and after study intervention are located in Section 2.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy. At each visit, the investigator will ask the participant if menarche has occurred since the last visit and this information will be recorded in the electronic case report form (eCRF).

iii) FOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4 and as described below and included in the ICF.

iv) FOCBP are permitted to use hormonal contraception methods (as described in Appendix 4).

v) A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

(1) Is not a FOCBP

OR

(2) Is a FOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), with low user dependency, as described in Appendix 4 during the intervention period and for at least 90 days after and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period

6.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1) Medical Conditions

a) Participant has clinically relevant cardiovascular, hepatic, neurological, pulmonary, ophthalmological, endocrine, psychiatric, or other major systemic disease making implementation of the protocol or interpretation of the study difficult or that would put the participant at risk by participating in the study.

i) Clinically relevant pulmonary conditions include, but are not limited to, history of severe or chronic lung disease, bronchopulmonary dysplasia, cystic fibrosis, or severe asthma (ie, that interferes with normal activities of daily living).

b) Participant is likely to require, in the physician's judgment, bowel resection within 12 weeks of entry into the study.

c) Participant has a diagnosis of UC, indeterminate colitis, radiation colitis, or ischemic colitis, or has strictures with prestenotic dilatation, requiring procedural intervention, or with obstructive symptoms. In addition, participants with colonic or ileal strictures that are not passable with an age-appropriate colonoscope that the endoscopist normally uses in clinical practice, or strictures in the ileum or ileocecal valve that are fibrotic in nature, will be excluded.

d) Participant has current stoma, ileal-anal pouch anastomosis, fistula that is likely to require, in the physician's judgment, surgical or medical intervention within 12 weeks of entry into the study or need for ileostomy or colostomy.

e) Participant has extensive small bowel resection (> 100 cm) or known diagnosis of short bowel syndrome or participant requires total parenteral nutrition.

f) Participant has suspected or diagnosed intra-abdominal or perianal abscess that has not been appropriately treated.

g) Participant has documentation of positive test for toxigenic *Clostridioides difficile* (formerly *Clostridium difficile* [*C difficile*]) by polymerase chain reaction examination of the stool during Screening. If positive, participants may be rescreened after appropriate treatment and negative retest no earlier than 7 days after completion of treatment.

h) Participant has documentation of positive examination for pathogens (ova, parasites, and bacteria). If positive, participants may be treated and rescreened.

i) Participant requires or is expected to undergo apheresis (eg, Adacolumn apheresis) within 2 weeks of randomization (Day [redacted]).

j) Participant is pregnant, lactating, has a positive serum β-subunit human chorionic gonadotropin (β-hCG) measured during Screening or a positive urine pregnancy test on Day [redacted].

k) Participant has a history or presence of the following clinically relevant cardiovascular conditions:

   i) Structural cardiac disease (eg, hypertrophic obstructive cardiomyopathy, unrepaired congenital heart defects). Participants with repaired congenital heart defects should be discussed with the Clinical Trial Physician or designee prior to enrollment.

   ii) Cardiac events (eg, myocardial infarction) or diseases that predispose to cardiac complications.

   iii) History of stroke, heart failure, or symptomatic bradycardia defined as < 5th percentile of normal sinus rhythm HR for age.[29]

   iv) Second degree (Mobitz type II) AV block or higher, sick sinus syndrome, or sino-atrial block.

   v) [redacted]

   vi) During either Screening or Day [redacted]

   vii) Severe untreated sleep apnea.

l) Participant has a history of diabetes mellitus (DM) type 1, or uncontrolled DM type 2 (hemoglobin A1c [HbA1c] > 9%) or is a diabetic participant with significant comorbid conditions such as retinopathy or nephropathy.

m) Participant has a history of uveitis within the last year prior to Screening, or history or evidence of retinal disease (eg, macular edema).

n) Participant has any known active bacterial, viral, fungal (excluding fungal infection of nail beds, minor upper respiratory tract infections, and minor skin infections), mycobacterial infection (including tuberculosis [TB] or atypical mycobacterial disease), or any other infection that required hospitalization or treatment with IV antibiotics within 30 days of Screening or oral antibiotics within 14 days of Screening.

   Note: In the case of prior SARS-CoV-2 infection, symptoms must have completely resolved and based on investigator assessment in consultation with the Clinical Trial Physician or designee, there are no sequelae that would place the participant at a higher risk when receiving IP. SARS-CoV 2 testing may be conducted prior to randomization (Day [redacted]) if required by and in accordance with national, local, or institutional guidelines.

o) Participant has a recurrent or chronic infection (eg, hepatitis A virus, hepatitis B virus, hepatitis C virus, human immunodeficiency virus [HIV]); recurrent urinary tract infections are allowed.

p) Participant has any history of cancer, including solid tumors and hematological malignancies (except basal cell and in situ squamous cell carcinomas of the skin or cervical dysplasia/cancer that have been excised and resolved) or colonic dysplasia that has not been completely removed. Participants at high risk (ie, family history, CD duration) for colonic malignancy has documented evidence of having had a surveillance colonosocpy within the last 2 years or according to local and national medical guidelines to evaluate for polyps, dysplasia, or malignancy (this can be done as part of the colonoscopy performed during screening as needed).

q) Participant has a history of or currently active primary or secondary immunodeficiency, or participants with known genetic disorders as a cause for colitis.

2) Reproductive Status

a) Females who are breastfeeding.

3) Prior/Concomitant Therapy

a) Participant has hypersensitivity to active ingredients or excipients of ozanimod.

b) Participant has prior participation in an ozanimod clinical trial.

c) Participant has been treated with a biologic agent within 4 weeks prior to the first dose of IP. Undetectable drug levels on therapeutic drug monitoring (TDM) assays may be utilized (see Section 6.1).

d) Participant has been treated with an investigational agent, including for SARS-CoV-2 infection, within 5 elimination half-lives of that agent prior to the first dose of IP.

e) Participant has received a live or live attenuated vaccine within 4 weeks prior to the first dose of IP.

Note: Non-live vaccinations can be administered during the study.

f) Participant has received any previous treatment with lymphocyte-depleting therapies (eg, Campath®, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation, alemtuzumab, or daclizumab).

g) Participant has received treatment with D-penicillamine, leflunomide, or thalidomide within 8 weeks of first dose of IP.

h) Participant has received previous treatment with natalizumab, fingolimod, or other S1P receptor modulators.

i) Participant has a history of treatment with IV immune globulin (IVIg), or plasmapheresis within 3 months prior to first dose of IP.

j) Participant has received previous treatment with oral cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil within 16 weeks of initiation of Screening.

k) Participants having delayed growth or delayed pubertal development and unable to maintain a stable dose of corticosteroids through [redacted].

l) Participant has a history of treatment with topical rectal therapy (5-ASA or corticosteroids) within 2 weeks of Screening endoscopy or has planned concurrent use of any per rectum therapy.

m) Participant plans concurrent treatment with immunomodulatory agents (eg, AZA, 6-MP, cyclosporine, or MTX) after randomization (Day [redacted]). Participants receiving AZA, 6-MP, or MTX at Screening must discontinue treatment with these agents prior to first dose of IP.

n) Participant has chronic nonsteroidal anti-inflammatory drug (NSAID) use (Note: Occasional use of NSAIDs and acetaminophen [eg, for treatment of headache, arthritis, myalgias, or menstrual cramps] and aspirin up to 325 mg/day is permitted).

o) Participants receiving treatment with Class Ia or Class III anti-arrhythmic drugs or with 2 or more agents in combination known to prolong PR interval.

p) Exclusion criterion no longer applicable, per Protocol Amendment 02.

q) Participants have received cholestyramine or other drugs interfering with enterohepatic circulation within 3 weeks of Screening.

r) Participants receiving treatment with any of the following drugs or interventions within the corresponding timeframe:

i) Two weeks prior to randomization (Day [redacted])

(1) Monoamine oxidase inhibitors (eg, selegiline, phenelzine)

ii) At randomization (Day [redacted]

(1) CYP2C8 inducers (eg, rifampicin)

4) Physical and Laboratory Test Findings

a) ECG showing any clinically significant abnormality.

b) Participant's serum creatinine is > 1.4 mg/dL for females or > 1.6 mg/dL for males.

c) Participant has liver function impairment or persisting elevations of ALT or aspartate aminotransferase (AST) > 2× upper limit of normal (ULN); or direct bilirubin > 1.5× ULN.

Note: ULN may differ between [redacted] and should be determined by laboratory standards.

d) Participant's platelet count is < 100,000/µL.

e) Participant's hemoglobin is < 8.0 g/dL.

Note: Hemoglobin at the time of each study visit blood draw should be > 7.0 g/dL.

f) Participant's neutrophil count is < 1500/µL.

g) Participant's absolute white blood count < 3500/µL.

h) Participant's ALC is < 800/µL.

i) Participant's stool is positive for pathogens.

[redacted]

Note: Up to 2 repeat tests may be performed for significant variations during Screening Period. Approval from the Clinical Trial Physician or designee must be obtained for additional retesting.

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: Under certain specific circumstances and only in countries where local regulations permit, a person who has been

imprisoned may be included or permitted to continue as a participant. Strict conditions apply, and BMS approval is required.)

Eligibility criteria for this study have been carefully considered to ensure the safety of the study participants and that the results of the study can be used. It is imperative that participants fully meet all eligibility criteria.

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently randomized in the study/included in the analysis population. Participants who fail to meet the inclusion/exclusion criteria can be rescreened once per Investigator discretion. Additional screening attempts beyond the first rescreen must be approved by the Clinical Trial Physician or designee prior to rescreening.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, as applicable, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any SAEs.

6.4.1 Retesting During Screening

Retesting of laboratory parameters and/or other assessments at screening will be permitted (in addition to any parameters that require a confirmatory value). A participant's previous colonoscopy may be used if performed within 35 days of randomization (Day [redacted]) and is not required to be repeated. The permitted frequency of re-testing for exclusion criteria is pre-specified in Section 6.2.

The most current result prior to administration of study intervention is the value by which study inclusion will be assessed, because it represents the participant's most current clinical state.

Laboratory parameters and/or assessments that are included in [redacted] may be repeated in an effort to find all possible well-qualified participants. Consultation with the Clinical Trial Physician or designee may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

Up to 2 retests per procedure may be performed ([redacted] colonoscopy, or any procedures for evaluation of latent TB) for significant variations in protocol-required tests at the discretion of the investigator or at the request of the Sponsor. Retests must be communicated to the Clinical Trial Physician or designee. Approval from the Clinical Trial Physician or designee must be obtained if a test is required to be repeated > 2 times and the permitted frequency is outside the limits pre-specified in the protocol.

SARS-CoV-2-related Retesting

Testing for asymptomatic SARS-CoV-2 infection is not required but may be performed according to national or institutional guidelines. However, some participants may develop suspected or confirmed symptomatic SARS-CoV-2 infection or be found to have asymptomatic SARS-CoV-2 infection during the Screening Period. In such cases, participants may be considered eligible for the study after meeting all inclusion/exclusion criteria related to active infection, and after meeting the following criteria:

- At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result, and
- At least 24 hours have passed since last fever without the use of fever-reducing medications, and
- Symptoms (eg, cough, shortness of breath) have resolved, and
- In the opinion of the investigator, there are no SARS-CoV-2 sequelae that may place the participant at a higher risk of receiving investigational treatment
- A negative follow-up molecular test for SARS-CoV-2 may also be performed if recommended based on institutional, local, or regional guidelines

7 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, procedure(s), or medical device intended to be administered to a study participant according to the study protocol.

Study intervention includes both Investigational [Medicinal] Product (IP/IMP); see Section 7.1) and Non investigational/Auxiliary [Medicinal] Product (Non-IP/Non-IMP/AxMP; see Section 7.7).

An IP, also known as IMP in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as IPs/AxMPs.

7.1 Study Interventions Administered

Ozanimod [redacted], 0.46, and 0.92 mg, developed for adults will be administered in participants [redacted]. The adult [redacted] formulations, with a small [redacted] size [redacted] and [redacted] allow for ease of swallowing. [redacted] excipients include [redacted]

[redacted]

Ozanimod [redacted] will be packaged in [redacted] for treatment medication [redacted] in the dose escalation kits), closed with a [redacted] The cap on the treatment [redacted] will be [redacted], and the [redacted] The labeling will be in accordance with GCP and any other local regulatory requirements.

[redacted]

The label(s) for IP will include Sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable or as dictated by the site's Standard Operating Procedure. Additional information may be included on the label as applicable per local regulations.

[redacted]

Participants should be instructed to take the ozanimod oral dose with or without food. Instructions for administration of the pediatric dosage form (currently in development) will be provided in the Instructions for Use once available.

[redacted] participants will continue to receive the blinded 0.46 or 0.92 mg/day adult equivalent dose [redacted]

[redacted]

[redacted] 0.46 or 0.92 mg/day [redacted]

[redacted]

[redacted] 0.92 mg/day adult equivalent dose [redacted]

Participants should be instructed that if they forget to take a dose, they can take the dose within 4 hours of the normal dosing time. If the participant vomits the dose, he/she should be instructed not to take another dose on the same day, but to take the next dose at the regular time on the following day.

If a single dose is missed during the first 2 weeks of treatment, or for more than 7 consecutive days during Days 15 to 28, treatment must be reinitiated using the 7-day dose escalation regimen [redacted] ozanimod 0.46 mg daily for the 0.92 mg dose. If a participant misses a dose during dose escalation, the Clinical Trial Physician or designee should be contacted to discuss completing the dose escalation schedule. The missed dose and extended days for escalation need to be documented as appropriate in the eCRF.

If a participant misses more than 14 consecutive doses for any reason, the Clinical Trial Physician or designee must be contacted to discuss procedures for resuming therapy, which may include cardiac monitoring and dose escalation procedures on the first day that the participant resumes dosing. [redacted] describes cardiac monitoring procedures to be followed as indicated during dose escalation.

7.2 Method of Study Intervention Assignment

Participants must provide proper informed consent/assent before any trial procedures are performed. [redacted] In addition, a parent or guardian of all participants [redacted] (or local age of majority) must sign an ICF. Once a participant turns 18 years of age (or local age of majority), he/she may need to sign a consent form, in accordance with regional or local regulations. Consented/assented participants meeting all eligibility criteria will be assigned to treatment/randomized using IRT. Further instructions on the use of the system will be provided in a separate IRT manual.

[redacted] participants will be randomized in a double-blind manner to oral ozanimod in a 1:1 ratio. [redacted]

- Ozanimod 0.92 mg/day [redacted] orally starting [redacted] 0.46 mg/day [redacted], [redacted] 0.92 mg/day [redacted]

- Ozanimod 0.46 mg/day [redacted] orally [redacted] 0.46 mg/day [redacted] 0.46 mg/day [redacted]

[redacted], participants will be randomized 1:1 to oral ozanimod 0.46 mg/day or 0.92 mg/day adult equivalent doses [redacted]

[redacted]

7.3 Blinding

This is a double-blind study. Access to treatment codes will be restricted from all participants and site and Sponsor personnel prior to final database lock.

Blinding of study treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual participant in which knowledge of the IP is critical to the participant's management, the blind for that participant may be broken by the investigator. The participant's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual participant's treatment, the investigator should determine that the unblinded information is necessary (ie, that it will alter the participant's immediate management). In many cases, particularly when the emergency is clearly not related to the IP, the problem may be properly managed by assuming that the participant is receiving the highest dose of the IP. It is highly desirable that the decision to unblind treatment assignment be discussed with the Clinical Trial Physician or designee, but the investigator always has ultimate authority for the decision to unblind. The actual task of unblinding can be delegated by the investigator to a designee assigned the task on the Delegation of Authority. The investigator or appointed designee should only call in for emergency unblinding after the decision to unblind the participant has been documented.

For this study, the method of unblinding for emergency purposes is through the IRT by using an emergency unblinding personal identification number, and the investigator should call IRT for unblinded dose information.

In cases of accidental unblinding, contact the Clinical Trial Physician or designee and ensure every attempt is made to minimize additional disclosure and the impact of unblinding.

Any request to unblind a participant for nonemergency purposes should be discussed with the Clinical Trial Physician or designee.

Any results shared by the Nonclinical Disposition and Bioanalysis group with the Sponsor's study team will be blinded to ensure integrity of the study.

Blind break (IRT)	The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

7.4 Dosage Modification

[redacted] There may be a modification to this schedule if there is missed dosing as referenced in Section 7.1.

[redacted] ozanimod 0.46 or 0.92 mg/day adult equivalent dose levels. If this is the case, it will be communicated to the investigator. [redacted] and the dose should not be otherwise modified outside the parameters provided in the protocol.

7.5 Preparation/Handling/Storage/Accountability

The IP must be stored in a secure area according to local regulations. It is the responsibility of the investigator, or designee where permitted, to ensure that IP is only dispensed to study participants. The IP must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the study intervention is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study intervention arise, the study intervention should not be dispensed, and BMS should be contacted immediately.

Study intervention not supplied by BMS will be stored in accordance with the package insert.

IP documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure the drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

7.6 Treatment Compliance

It is the investigator's responsibility to ensure that participants are correctly instructed on how to take their IP and that each participant is fully compliant with their assigned dosage regimen. Records of IP used and intervals between visits will be kept during the study. Drug accountability will be noted by the monitor during site visits and at the completion of the study. Participants will be asked to return any remaining unused IP at all visits during which IP is dispensed (except for Day [redacted]) and at the end of the study. The IP 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 below.

Participants who take less than 80% or more than 120% of IP during the entire treatment period are considered non-compliant.

At each visit, previously dispensed IP will be collected by the investigator and compliance will be assessed on a participant dispensing log. Participants exhibiting poor compliance as assessed by IP counts (2 or more missed IP days in 1 week) should be counseled on the importance of good compliance to the study dosing regimen. Participants who are persistently non-compliant (< 80% or > 120%) should be discussed with the Clinical Trial Physician or designee to determine whether they should be withdrawn from the study.

7.7 Concomitant Therapy

All treatments other than ozanimod being taken by the participants on entry to the study or at any time during the study, including through the [redacted] Safety Follow-up Visit, are regarded as concomitant medications and must be documented on the appropriate section of the eCRF. Complete history of previous treatments for CD must be documented.

NOTE: Prior to randomization (Day [redacted]), all prior medications for the management of CD should be recorded on the prior CD medications eCRF. After randomization (Day [redacted], medications for the management of CD should be recorded on the concomitant medications eCRF (this eCRF also captures ongoing CD medications). All prior medications (including over-the-counter medications) administered 30 days prior to the date of informed consent/assent and any concomitant therapy administered to the participant during the course of the study until [redacted] after the final dose of IP will be recorded. Additionally, all diagnostic, therapeutic, or surgical procedures relating to CD should be recorded. Any medication that is considered necessary for the participant's health (including enteral nutrition) and that is not expected to interfere with the evaluation of or interact with IP may continue during the study.

Participants who are receiving oral corticosteroids at Screening must keep their prescribed dosage steady at least through [redacted] after which the dose should be tapered as described in Section 7.7.1. Oral 5-ASA or oral corticosteroids should not be started in participants who are not receiving them. Participants receiving 5-ASA must keep their prescribed dosage steady at least through [redacted] and should maintain a stable dose through Week 64.

It is also advised, if possible, to keep the prescribed dose of pre- and/or probiotic supplements steady and to avoid initiating treatment with pre- and/or probiotic supplements through Week 64.

Concomitant treatment with medications listed in Section 7.7.2 is not allowed during the study.

The decision to temporarily interrupt dosing for treatment of an intercurrent medical condition, or for major surgery that could present an unreasonable risk to the participant, remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. Prior to interruption of dosing, the investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion. The investigator will report the action taken with IP. The Medical Monitor should be contacted to discuss treatment reinitiation. See Section 8 for permanent discontinuation of IP.

Administration of concomitant medications must be reported in the appropriate section of the eCRF along with dosage information, dates of administration, and reasons for use. For medications with a single active ingredient, generic names for concomitant medication should be used, if possible. For combination products, brand names should be used. The total daily dose should be filled in whenever possible.

In addition, SARS-CoV-2 vaccines administered any time prior to or during the study must be documented, including manufacturer details and dates for each dose. Histories of all other prior medications taken during the 30 days prior to the date of informed consent/assent must also be documented.

If vaccination for SARS-CoV-2 is pursued, ideally randomization (Day [redacted]) should occur after the full dosing schedule has been administered and after resolution of any acute reactions (eg, reactions occurring within 24 hours of vaccine administration). If a participant has received a SARS-CoV-2 vaccination, vaccine details (eg, manufacturer and dose number) should be recorded on the concomitant medication page, if given during the study, or the past history page, if given prior to enrollment.

7.7.1 Steroid Taper

Steroid tapering can start as early as [redacted], and the Investigator must attempt to initiate tapering after Week 12 and have it completed within 6 months after Week 12. Considerations to taper at an earlier time point for adverse events or safety concerns should first be discussed with the Clinical Trial Physician or designee. Below is the recommended tapering schedule. Modification can be made based on body weight following discussion with the Clinical Trial Physician or designee.

Participants receiving prednisone at a dose of > 10 mg/day (or equivalent) are recommended to have their dose reduced at a rate of 5 mg (or equivalent) per week until a ≤ 10 mg/day dose (or equivalent) is achieved. Participants receiving prednisone at doses of 10 mg/day (or equivalent) or have achieved a 10 mg/day dose (or equivalent) by tapering are recommended to have their dose reduced at a rate of 2.5 mg/week until the steroid is discontinued. Participants receiving oral budesonide are recommended to taper their dose at a rate of 3 mg every 3 weeks and then discontinue treatment. Participants receiving oral beclomethasone are recommended to taper their dose over a period of up to 6 weeks.

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

7.7.2 Prohibited and/or Restricted Treatments

The following medications cannot be used during the study through the [redacted] Safety Follow-up Visit, unless otherwise noted to be prohibited through end of treatment only:

- Treatment with Class Ia or Class III anti-arrhythmic drugs (examples of Class Ia or Class III anti-arrhythmic drugs and additional prohibited systemic cardiac medications are provided in Table 7.7.2-1) or treatment with 2 or more agents in combination known to prolong PR interval (eg, combination of a beta blocker and a non-dihydropyridine calcium-channel blocker) are prohibited during the study unless approved by the Sponsor's representative
- Biologic therapies including but not limited to abatacept, infliximab, etanercept, adalimumab, anakinra, rituximab, vedolizumab, ustekinumab, and golimumab
- Systemic immunomodulatory agents (eg, AZA, 6-MP, cyclosporine, MTX, mycophenolate mofetil, tacrolimus, or sirolimus; small molecules [eg, upadacitinib])
- Post-baseline initation, or increase above baseline dose, of systemic corticosteroids during Induction or Maintenance. Increase in systemic corticosteroids, such as oral prednisone > 1.0 mg/kg/day for weights ≤ 40 kg, > 40 mg/day for weights > 40 kg, or equivalent during LTE.
- Any per-rectum therapy including enemas (eg, 5-ASA, corticosteroid), other than that required for endoscopy preparation (prohibited through end of treatment only)
- Any investigational drug other than the IP specified in this study
- Chronic NSAID use (prohibited through end of treatment only. Note: occasional use of NSAIDs and acetaminophen [eg, headache, arthritis, myalgias, or menstrual cramps] and aspirin as needed or up to 325 mg/day if on a stable dose at randomization [Day [redacted]] is permitted.)
- Live vaccines or live attenuated vaccines are not allowed within 4 weeks prior to randomization (Day [redacted])
- IVIg or plasmapheresis is not allowed within 3 months prior to randomization (Day [redacted])
- Treatment with D-penicillamine, leflunomide, or thalidomide
- Treatment with natalizumab, fingolimod, etrasimod, or other S1P modulators
- Immunosuppressive agents that deplete lymphocytes
- Anti-neoplastic medications
- Monoamine oxidase inhibitors (eg, selegiline, phenelzine)
- CYP2C8 inducers (e.g. rifampicin)

For any systemic therapies for CD not mentioned above, please contact the Clinical Trial Physician or designee.

Table 7.7.2-1: Examples of Prohibited Cardiac Medications (Systemic Use)

Pharmaceutical Class	Example Medications
Anti-arrhythmic drugs	amiodarone, bepridil hydrochloride, disopyramide, dofetilide, dronedarone, flecainide, ibutilide, sotalol, lidocaine, procainamide, propafenone, quinidine, tocainide

The following medications should not be used between the [redacted] Safety Follow-up Visit and the [redacted] Safety Follow-up Visit:

- Treatment with Class Ia or Class III anti-arrhythmic drugs (examples of Class Ia or Class III anti-arrhythmic drugs and additional prohibited systemic cardiac medications are provided in Table 7.7.2-1) or treatment with 2 or more agents in combination known to prolong PR interval (eg, combination of a beta blocker and a calcium-channel blocker) are prohibited during the study unless approved by the Sponsor's representative
- Treatment with natalizumab, fingolimod, etrasimod, or other S1P modulators
- Immunosuppressive agents that deplete lymphocytes
- Monoamine oxidase inhibitors (eg, selegiline, phenelzine)
- Live vaccines or live attenuated vaccines

7.7.2.1 Imaging Restriction and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen per imaging study. Imaging contraindications and contrast risks are to be considered in this assessment. Participants with renal insufficiency are to be assessed as to whether or not they should receive contrast and if so, which contrast agent and dose is appropriate. Please see Section 9.1.2 for details on imaging assessments for this study.

7.8 Continued Access to Study Intervention After the End of the Study

At the conclusion of the study, if the study intervention is not available as an approved treatment in the local country, participants who continue to demonstrate clinical benefit will be eligible to receive BMS-supplied study intervention per local or regional requirements. If the study treatment is not available as an approved and available treatment, study intervention will be provided via an extension of the study, a rollover study requiring approval by the responsible Health Authority and ethics committee, or through another mechanism at the discretion of BMS.

BMS reserves the right to terminate access to BMS-supplied study intervention if any of the following occur: a) the study is terminated due to safety concerns; b) the development of ozanimod is terminated for other reasons, including, but not limited to, lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government-sponsored or other health program. In all cases, BMS will follow local regulations.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation From Study Intervention

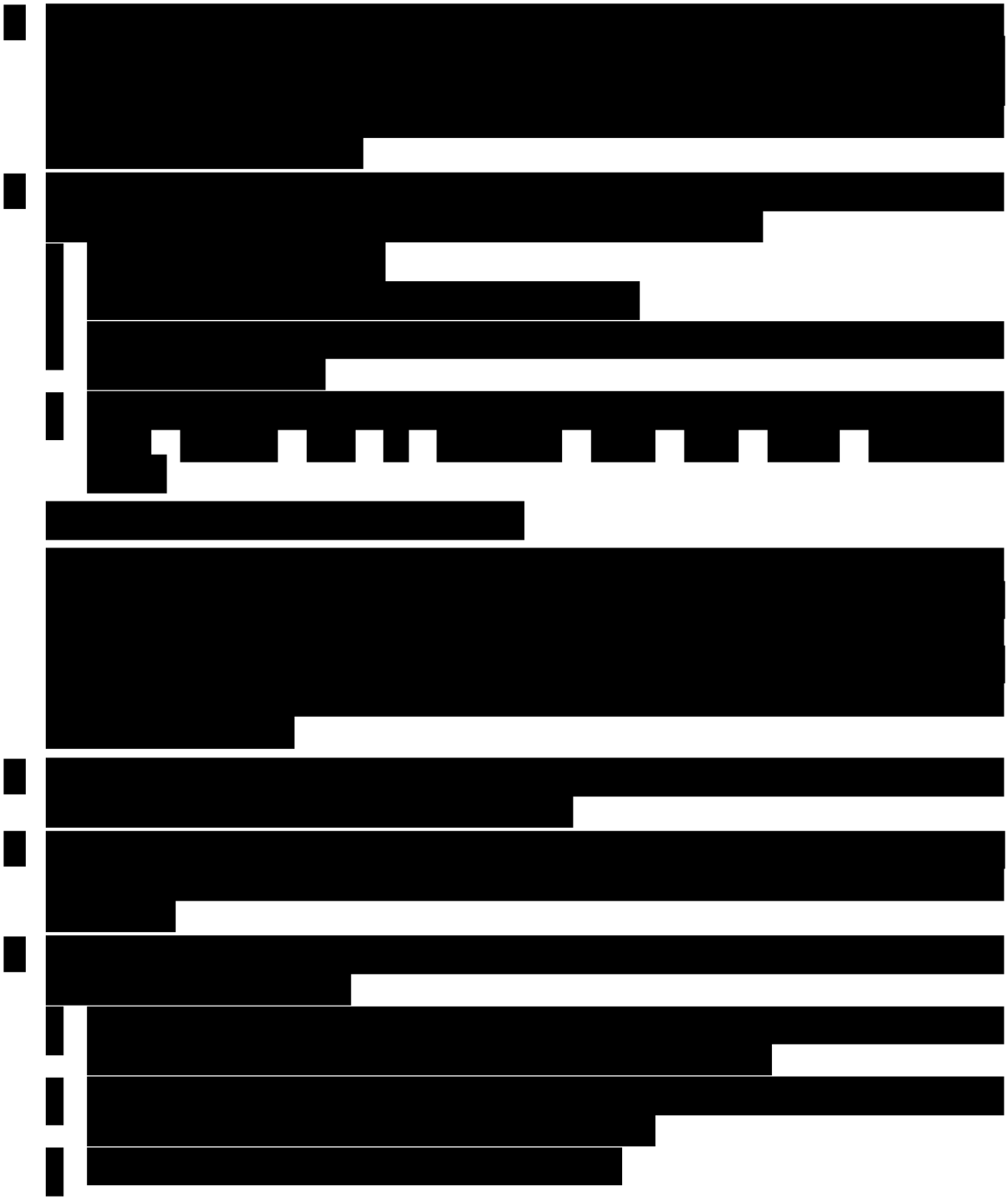
Participants MUST discontinue IP for any of the following reasons:

- Participant's request to stop study intervention. Participants who request to discontinue study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information.
- If a participant who does not meet enrollment criteria is inadvertently enrolled, the Clinical Trial Physician or designee must be contacted, and that participant will be withdrawn from the study if continuation is determined to be a safety risk.
- Any clinical AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Termination of the study by BMS.
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply, and BMS approval is required.)
- Participant meets liver-related laboratory abnormalities (see Section 9.2.9).
- Unblinding of a participant's treatment assignment for any reason (emergency or nonemergency).
- Inability or failure to comply with protocol requirements.
- Pregnancy, positive pregnancy test, or participant no longer wishes to comply with study requirements relating to prevention of pregnancy (see Section 9.2.5).
- Participants who require initiation of an immunomodulatory agent including, but not limited to 6-MP, AZA, or biologic therapy; or who require > 3 days of treatment with higher doses of systemic corticosteroids (e.g. prednisone > 1.0 mg/kg/day for weights ≤ 40 kg or > 40 mg/day for weights > 40 kg or equivalent) will be discontinued from the study.

Reasons for discontinuation include, but are not limited to, the following:

- Physician decision: The investigator must discontinue IP if it is determined that it is not safe or in the participant's best interest to receive further treatment. In participants who obtain a pulmonology or ophthalmology consultation as outlined in Section 9.4.9 and Section 9.4.10, discontinuation may be recommended by the consulting physician. The Clinical Trial Physician or designee should be promptly notified of the decision.
- Noncompliance with IP: After consultation between the investigator, the Clinical Trial Physician or designee, and the Sponsor when appropriate, a participant may be discontinued from the study for failure to comply with dosing regimen as specified by the protocol.

- Noncompliance with protocol/protocol deviation: After consultation between the investigator, the Clinical Trial Physician or designee, and the Sponsor when appropriate, a participant may be discontinued from the study for failure to follow protocol procedures, or other event or decision that stands in contrast to the guidelines set in the protocol.
- Adverse event: A participant must be discontinued from IP if, in the judgment of the investigator or if specified in the protocol, the participant develops an AE such as an intercurrent illness or complication that justifies discontinuation of IP.
  - Particularly, if a participant has developed any of the following AESIs (see Section 9.2.9):



- Lack of efficacy: Decision by the participant and/or the investigator to discontinue IP due to a lack of expected or desired effect related to therapy or if early discontinuation criteria were met (see Section 5.1).
- Withdrawal by participant (or participant's parent or guardian): The participant (or participant's parent or guardian) may choose to discontinue IP at any time. The participant is expected to continue in the study and every effort should be made within the bounds of safety and the participant and their parent or guardian'schoice to have each participant complete the ET Visit and Safety Follow-up Visits. If a participant or participant's parent or guardian withdraws consent/assent, the only additional investigational data to be collected will be the follow-up of SAEs as mandated by the protocol.
- Pregnancy: If a female participant becomes pregnant, IP must be discontinued (see Section 9.2.5).
- Study termination by Sponsor
- Lost to follow-up
- Other
- For participants whose ALC level is confirmed < 200 cells/µL and permanently discontinue IP, an ET Visit should be completed. Central laboratory testing will be conducted every 14 days (± 3 days) after the ET Visit until it is above the lower limit of normal or until the ALC is considered to have stabilized and/or reached a level that is not clinically significant (see Section 9.4.12).

With the exception of participants who withdraw consent/assent or are lost to follow-up, participants who discontinue the study should complete the [redacted] Safety Follow-up Visit after the last dose for the collection of safety data and to assess their disease status. Alternative treatment for CD can be started, if needed, after the ET Visit (see Section 7.7.2 for prohibited concomitant medications within the [redacted]-day Safety Follow-up Period).

Participants who withdraw from the study will not be replaced.

Refer to Section 2 for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

All participants who discontinue study intervention should comply with protocol-specified follow-up procedures as outlined in Section 2. The only exception to this requirement is when a participant withdraws consent for all study procedures, including post-treatment study follow-up, or loses the ability to consent freely (eg, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study intervention is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records per local regulatory requirements in each region/country and entered on the appropriate eCRF page.

8.1.1 Post-study Intervention Study Follow-up

In this study, the proportion of participants who achieve PCDAI < 10 at Week 64 and the proportion of participants who achieve an SES-CD decrease from Baseline of ≥ 50% (ER-50) at Week 64 are key endpoints. Post-study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study intervention must continue to be followed (in this study or a rollover study) for collection of outcomes and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

8.2 Discontinuation From the Study

Participants who request to discontinue study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information.

- Participants should notify the investigator of the decision to withdraw consent from future follow-up.
- The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study intervention only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate eCRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent/assent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.2.1 Individual Discontinuation Criteria

- A participant may withdraw completely from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon. Stopping study intervention is not considered withdrawal from the study.
- At the time of discontinuing from the study, every effort should be made within the bounds of safety and participant and participant's parent or guardian choice to have each participant

complete an ET visit, if possible, as shown in Section 2. See the Section 2 for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent/assent.

8.3 Lost to Follow-up

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three (3)** documented phone calls, faxes, or emails, as well as lack of response by participant to one (1) registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- If the investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining the participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If, after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and timing are summarized in Section 2. Waivers or exemptions from protocol-required evaluations are not allowed.

All immediate safety concerns must be discussed with the Sponsor's Clinical Trial Physician or designee immediately upon occurrence or awareness to determine whether a participant should continue or discontinue treatment.

Adherence to the study design requirements, including those specified in Section 2, is essential and required for study conduct.

All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization (Day [redacted]).

IMPORTANT NOTE: It is recommended that the study visits are scheduled in the morning. On days of study visits when trough (pre-dose) PK samples are to be drawn, participants should be instructed to withhold the dose until the study visit, and the dose will be administered during the visit.

At [redacted], PK evaluations will be [redacted] Therefore, participants should be instructed to take IP at home and note the time taken, allowing for at least [redacted] prior to arriving for this visit.

Whenever possible, the sequence of assessments should remain constant and at approximately the same time of day throughout the study.

It is recommended that procedures are performed in the following order (note that not all procedures are performed at every visit):

- Spontaneous or solicited AE reporting
- ECG
- Vital signs
- Clinical laboratory tests, including pre-dose PK sampling when applicable
- Physical examination
- Efficacy assessments
- IP administration (on visits when trough PK blood draws are collected)

Written, signed, and dated informed consent/assent from the participant or participant's parent or guardian must be obtained by the investigator or designee prior to the performance of any study-related procedures. Assent will be obtained from participants in an age-appropriate manner in conjunction with applicable local regulations. A copy of the signed ICF/assent must be given to the participant's parent or guardian for his/her records.

Screening Period

Screening procedures must be completed within 35 days prior to receiving the first dose of IP. All Screening assessments and procedures as per Section 9 are to be performed by the investigator or a qualified designee.

Active TB must be ruled out according to local medical practices. Latent TB must be assessed for with a TB skin test, QuantiFERON Gold test, or other interferon gamma release assay (IGRA; eg, T-SPOT). Any repeat testing for latent TB should be approved by the Clinical Trial Physician or designee. Participants with latent TB must have documentation of prophylactic treatment by local standard of care. Participants with latent TB who have initiated prophylactic treatment by local standard of care, participants with an indeterminate test result, or participants diagnosed with IGRA tests other than QuantiFERON Gold or T-SPOT, must be discussed for eligibility on a case-by-case basis by the Sponsor Clinical Trial Physician or designee.

TDM assays that measure drug levels of biologic agents can be used as an optional test during the Screening Period. TDM will be performed locally. The biologic washout period may be waived in

participants who have an undetectable drug level on a TDM assay, performed either during a routine clinic visit prior to Screening or during the Screening Period. If a TDM assay is used as an alternative to the washout period for any of the biologics, the result of the TDM assay must be available in source documents, and the participant must not receive another dose of that biologic agent prior to randomization (Day [redacted]).

During Screening, the participant's prior use of medications to treat CD and whether they responded to adequate treatment with each medication will be assessed and documented (see Appendix 5).

Prohibited treatments are listed in Section 7.7.2.

Dose stabilization rules are outlined in Section 7.7. Briefly, 5-ASAs and oral corticosteroids (such as prednisone ≤ 0.5 mg/kg/day for weights ≤ 40 kg, ≤ 20 mg/day for weights > 40 kg, or equivalent; budesonide ≤ 9 mg/day; or beclomethasone ≤ 5 mg/day) are allowed and are subject to dose stabilization rules.

Screening Period schedule and procedures are provided in Section 2. A participant's colonoscopy from a previous Screening in this study may be used if within 35 days of randomization (Day [redacted] To avoid participant's receiving unnecessary endoscopy, this procedure should be performed only after the participant meets all other necessary inclusion/exclusion criteria.

Induction and Maintenance Period

At the Day [redacted] study visit, participants who have completed the Screening procedures and meet the eligibility criteria will be randomized in a 1:1 ratio to receive either 0.46 or 0.92 mg/day equivalent doses for the 12-week induction phase. The randomization process is outlined in Section 7.2. Participants will follow the [redacted]-appropriate dose escalation (minimum of 7 days) until the full daily dose is attained (see Section 7.1), which they will continue to take throughout the Induction and Maintenance treatment periods.

Visits, assessments, and procedures will be performed as specified in Section 2. Prior to each scheduled visit, the participant diary should be reviewed to ensure stool frequency and abdominal pain data are entered daily. Adolescent participants should be educated on the importance of diary completion around the visit at which CDAI scores are to be calculated. If the participant remains non-compliant on diary entries, the participant should be counselled about proper study procedures.

[redacted]

The video recording of each procedure will be reviewed by a central reader, or readers, to determine the SES-CD. For further details regarding endoscopy and endoscopic biopsies, see Section 9.1.5.

Discontinuation criteria are detailed in Section 8. Participants who discontinue study treatment should complete an ET visit and Safety Follow-up Visits as specified in Section 2. For participants

who discontinue study treatment, endoscopy is encouraged but not required at the ET visit. An endoscopy is not required during the LTE Period or at the ET Visit for participants who discontinue the study during the LTE Period. If performed (eg, for discontinuation or clinical evaluation), results of endoscopic evaluation should be documented.

All participants who take at least 1 dose of study treatment will be followed for protocol-specified post-treatment follow-up procedures. The only exception to this is when a participant specifically withdraws consent/assent for any further contact with him/her or with persons previously authorized by the participant to provide this information.

Participants who are likely to derive a clinical benefit from ongoing participation in the study following Week 64, as judged by the investigator, are eligible to enter the LTE Period. Participants who meet the early discontinuation criteria after at least 7 weeks of treatment in the Induction Period, have confirmed disease worsening during the Maintenance Period, complete Week 12 and are non-responders, or complete Week 64 will, have the option to enter the LTE Period.

Early Termination

Evaluations will be performed as specified in Section 2.

LTE Period

Evaluations will be performed as specified in Section 2.

The study will be conducted in compliance with the ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use/GCP and applicable regulatory requirements.

Safety Follow-up Period

For participants who discontinue the study for any reason, every attempt should be made to return to the study site to complete the assessments detailed in the [redacted] Safety Follow-up Visits in Section 2. [redacted] In addition, additional safety assessments may be required for participants who have an ongoing AE or safety issue at the [redacted] Safety Follow-up Visit, at the investigator's discretion. Participants may be followed as necessary for an additional period after the [redacted] Safety Follow-up Visit to review the results of any assessments which were conducted at the [redacted] Safety Follow-up Visit.

9.1 Efficacy Assessments

9.1.1 Pediatric Crohn's Disease Activity Index

The PCDAI is an instrument that was developed and validated for numerical assessment of disease activity in children and adolescents with CD.[30] The PCDAI has a scoring range of 0 to 100. Mild disease corresponds to scores of 11 to 30; moderate to severe disease corresponds to scores > 30. Remission (ie, no disease activity) is defined as a PCDAI score < 10. The PCDAI includes participant historical information, physical examination findings, objective laboratory parameters, data on weight gain/loss, and height velocity. The category of severity for each index item is assigned a score: 0 = normal; 5 = mild abnormality; 10 = severe abnormality. The PCDAI also includes 3 laboratory parameters (ie, hematocrit, erythrocyte sedimentation rate (SR), and albumin level) which are part of the calculation. For hematocrit and erythrocyte SR, the maximum score = 5. For albumin level, the maximum score = 10 (see Appendix 6). Clinical parameters needed for calculation of the PCDAI will be collected from the participant at the scheduled visit (see Section 2). The PCDAI consists of the following 11 variables:

1. Abdominal pain (1 week)
2. Stools per day (1 week)
3. Patient functioning/general wellbeing (1 week)
4. Weight
5. Height velocity (current visit height compared with height measured 6 to 12 months earlier expressed as a standard deviation score)
6. Abdominal tenderness, mass, guarding
7. Peri-rectal disease
8. Extra-intestinal manifestations (fever, arthritis, uveitis, erythema nodosum, pyoderma gangrenosum)
9. Hematocrit (%) for males/females
10. Erythrocyte sedimentation rate (ESR; mm/hour)
11. Albumin (g/dL)

The abdominal pain, stool frequency, and general wellbeing scores from the week prior to each study visit will be used to calculate the PCDAI. If the participant is undergoing a planned colonoscopy, the day(s) of bowel preparation should be excluded from consideration.

9.1.2 Simple Endoscopic Score for Crohn's Disease

The SES-CD assesses the degree of inflammation.[31] The SES-CD assesses the following 4 components: size of ulcers, ulcerated surface, affected surface, and presence of narrowing. Each of these components are scored on a scale of 0 to 3 as outlined in Table 9.1.2-1.

In the SES-CD, each of these 4 components are assessed in the 5 segments of the ileum and colon: ileum, right, transverse, left (descending and sigmoid), and rectum. The SES-CD is the sum of the individual scores of each of the components across the 5 segments.

Endoscopic response is defined in this study as 50% or greater decrease in SES-CD from Baseline. Endoscopic remission is not yet validated and may be defined as SES-CD ≤ 4 points and a SES-CD decrease from Baseline ≥ 2 points, an absence of large ulcers, absence of ulcers, or SES-CD is ≤ 2 points. For the purposes of this study, endoscopic remission is defined as the proportion of participants achieving SES-CD ≤ 2 or SES-CD ≤ 4 points with no SES-CD subscore > 1 point at Weeks 12 and 64.

To ensure quality data and standardization, the same endoscopist and the same diameter colonoscope as used in Screening should be used throughout the study wherever possible. Colonoscopies will be read at a centralized reading facility in a process outlined in the Endoscopy Image Charter. Centralized reading will be the primary assessment for endoscopy; local endoscopy scores will also be collected.

Table 9.1.2-1: Definitions of Simple Endoscopic Score for Crohn's Disease (SES-CD)

	SES-CD Values			
Variable	**0**	**1**	**2**	**3**
Size of ulcers	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

Adapted from: Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc 2004;60(4):505-12.

9.1.3 Crohn's Disease Activity Index

The CDAI is a composite score that is used to measure the clinical activity of CD. CDAI will be collected for adolescent participants (see Section 5). The CDAI uses a questionnaire with responses scored numerically and weighted. Scores range from 0 to approximately 600, with higher scores indicating greater disease activity. The 8 components used to assess the CDAI and their weighting factors are noted in Table 9.1.3-1. The definitions of mild, moderate, and severe CD are provided in Table 9.1.3-2.

Clinical remission based on CDAI score is defined as a CDAI score of < 150. Clinical response is defined as CDAI reduction from Baseline of ≥ 100 points or CDAI score of < 150. Symptomatic remission based on abdominal pain and stool frequency is defined as an average daily stool frequency score ≤ 3 points and an average abdominal pain score ≤ 1 point with a stool frequency no worse than Baseline.

Participant-reported components of the CDAI (stool frequency, abdominal pain components, and general wellbeing) will be collected in an electronic diary. Participants will complete their electronic diary starting at the first Screening visit and will continue throughout the study.

Participants will be instructed on the use and completion of questions on the electronic diary.

The participant's electronic diary entries will be reviewed by site personnel during Screening and throughout the study.

Table 9.1.3-1: Crohn's Disease Activity Index Assessment

Clinical or Laboratory Variable	Weighting Factor, ×
Number of liquid or soft stools each day for 7 days[a]	2
Abdominal pain (graded from 0-3 on severity) each day for 7 days	5
General wellbeing, assessed from 0 (well) to 4 (terrible) daily for 7 days	7
Presence of complications[b]	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 males and 42-HCT in females	6
Percentage deviation from standard weight	1
Total Score	

Abbreviation: HCT = hematocrit.

[a] Liquid or soft stools are characterized by Bristol Stool Scale Types 6 and 7.

[b] One point each is added for each set of complications: arthritis or arthralgia; iritis or uveitis; erythema nodosum, pyoderma gangrenosum, aphthous stomatitis; anal fissure, fistula or perirectal abscess; other bowel-related fistula; febrile (fever) episode over 100 degrees during the past week.

Table 9.1.3-2: Crohn's Disease Severity Definitions

Severity	CDAI Score
Mild	150-219
Moderate	220-450
Severe	> 450

Abbreviation: CDAI = Crohn's Disease Activity Index.

9.1.4 Abdominal Pain and Stool Frequency

The abdominal pain and stool frequency scores are based on 2 components of the PCDAI and CDAI.[30,32] See Sections 9.1.1 and 9.1.3 for more details.

Stool frequency and abdominal pain will be obtained and calculated without a weighting factor for use as part of the inclusion criteria. These unweighted participant-reported assessments will also be used as efficacy endpoints (see Section 4).

The Bristol Stool Scale[33] is an additional tool for the visual evaluation of diarrhea, and will be provided to help with the daily documentation of the number of very soft (loose) or liquid (watery) stools (Bristol Stool Scale Types 6 or 7) recorded in the participant's electronic diary.

9.1.5 Endoscopies and Endoscopic Biopsies

Endoscopies and endoscopic biopsies will be submitted to an imaging core lab.

Endoscopy: Colonoscopy will be performed as indicated in Section 2. An endoscopy is not required during the LTE Period or at the ET Visit for participants who discontinue the study during the LTE Period. However, if performed (eg, for discontinuation or clinical evaluation), results of endoscopic evaluation should be documented.

To ensure quality data and standardization, the same endoscopist should be used throughout the study wherever possible. Endoscopy videos will be obtained during each endoscopy and will be sent for central reading and determination of the SES-CD. A detailed Image Review Charter from the central reading laboratory will describe the approach for utilization of video capture tools and processes for the capture, transmission, and assessment of endoscopy video recordings endoscopic procedures. 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.

[redacted]

9.1.6 Erythrocyte Sedimentation Rate

The ESR will be assessed at visits when the PCDAI is performed at the frequency specified in Section 2. The ESR result is generated at the site from a supply kit provided by the central laboratory, and the site will record the ESR result into the appropriate electronic entry screen for calculating the PCDAI.

[redacted]

[redacted]

9.1.9 Participant Diaries

Participant (or parent/guardian)-reported components of the CDAI (eg, stool frequency, abdominal pain components, and general wellbeing) will be collected in an electronic diary. Adolescent participants will enter their signs and symptoms as prompted by the electronic diary from the first Screening visit until the Week 64 visit or ET visit (see Section 2). Participants who participate in the LTE Period will complete diaries prior to each scheduled visit or ET visit.

Participants (or parent/guardian) will be instructed on the use and completion of questions on the electronic diary.

The diary entries will be reviewed by site personnel during Screening (prior to dosing, if applicable) and during all study visits, except for the Safety Follow-up Visits.

The stool frequency and abdominal pain diary entries will be used to calculate the CDAI. Because colonoscopy preparations can interfere with the assessment of other clinical parameters, diary entries on the days of those assessments cannot be used to calculate CDAI scores.

For additional detail, please refer to Sections 2 and 9.1.3.

9.2 Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, a surrogate, or the participant's parent or guardian).

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue before completing the study.

Refer to Appendix 3 for SAE reporting.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures, and within [redacted] following discontinuation of dosing.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study intervention or protocol-specified procedure (eg, a follow-up skin biopsy).

- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the appropriate section of the eCRF module.

- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of updated information being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

The method of evaluating and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 3.

All participants will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the participant's clinical symptoms; laboratory, pathological, radiological, or surgical findings; physical examination findings; or findings from other tests and/or procedures.

All AEs (SAEs and nonserious AEs), including SARS-CoV-2 infection, must be collected from the time the participant signs informed consent until 90 days after the last dose of IP, as well as those SAEs made known to the investigator at any time thereafter that are suspected of being related to IP.

All AEs (serious/non-serious) must be recorded on the eCRF and in the participant's source documents. All SAEs must have data transmitted electronically to Sponsor Drug Safety (or designee) within 24 hours of the investigator's knowledge of the event. In the event electronic transmission is not available, a paper SAE Report Form will be completed and sent directly to the Sponsor's Drug Safety (or designee), ensuring the event is recorded on the eCRF as well.

Abuse, withdrawal, sensitivity, or toxicity to an IP should be reported as an AE. Overdose, accidental or intentional, if it is associated with an AE, should be reported on the Study Drug Exposure eCRF. Any sequelae of an accidental or intentional overdose of an IP which meets the definition of an AE should be reported as an AE on the eCRF. If the sequela of an overdose meets serious criteria, then it must be marked as serious on the eCRF. The overdose itself should not be reported as an AE.

Participants will be instructed to contact the investigator at any time if they develop an intercurrent illness or signs or symptoms and/or a diagnosis of SARS-CoV-2 infection which will enable close monitoring and additional screening for the infection between study visits.

In participants who are exhibiting symptoms consistent with SARS-CoV-2 infection, the Sponsor advises the investigator to consider holding dosing of IP and consult the Clinical Trial Physician or designee. If a participant has a positive test for SARS-CoV-2, or if no testing is available, the Sponsor advises the investigator to consider holding participant dosing until such time as symptoms resolve. If a positive SAS-CoV-2 test result is reported, please consult with the Clinical Trial Physician or designee on whether resolution of symptoms alone is sufficient to resume dosing

of the IP (Section 3.3.1). Upon a positive test result for SARS-CoV-2 infection, the infection should be reported to the Sponsor within 24 hours.

SARS-CoV-2-related AEs/SAEs will be captured in specific clinical safety program eCRF pages.

9.2.2 Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AEs and/or SAEs. Inquiry about specific AEs should be guided by clinical judgment in the context of known AEs, when appropriate for the program or protocol.

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study intervention and for those present at the end of study intervention as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the eCRF (paper or electronic). Completion of supplemental eCRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and nonserious AESIs (as defined in Section 9.2.9) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

Further information on follow-up procedures is given in Appendix 3.

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

The Sponsor or designee must report AEs to regulatory authorities and ethics committees according to local applicable laws and regulations. A suspected, unexpected serious adverse reaction (SUSAR) is a subset of SAEs and must be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

If, following initiation of the study intervention, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least [redacted] after study product administration, the investigator must immediately notify

the BMS Clinical Trial Physician or designee of this event and complete and forward a Pregnancy Surveillance Form to the BMS designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information, must be reported on the Pregnancy Surveillance Form. Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE eCRF page or SAE eCRF, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the participant to have study intervention discontinued or interrupted
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy

It is expected that, wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia vs low hemoglobin value).

9.2.7 Potential Drug-induced Liver Injury

Specific criteria for identifying a potential drug-induced liver injury (DILI) are outlined in Section 9.2.9 along with instructions on reporting and follow-up of these cases.

9.2.8 Other Safety Considerations

Any significant worsening of conditions noted during interim or final physical examinations, ECG, or any other potential safety assessment required or not required by the protocol should also be recorded as a nonserious AE or SAE, as appropriate, and reported accordingly.

The investigator will report the outcome of the event for each AE.

All SAEs that have not resolved upon discontinuation of the participant's participation in the study must be followed until recovered (returned to Baseline), recovered with sequelae, or death (due to the SAE).

9.2.9 Adverse Events of Special Interest

All AEs and SAEs that arise in the study will be reported and investigated. However, because of the characteristics of the disease under study and ozanimod, in particular, some AEs are considered AESIs. AESIs may be serious or nonserious. Such events may require further investigation to better characterize and understand them. In the ozanimod clinical development program, potential AESIs that may be a consequence of S1P1 modulation will be closely monitored during the study. These AESIs include [redacted]

[redacted] An independent DMC for the study will perform regular safety reviews starting after the first participant is dosed.

[redacted]

[redacted]

[redacted]

9.3 Overdose

For this study, any dose of ozanimod greater than the dose described in the protocol will be considered an overdose. Overdoses that meet the regulatory definition of SAE will be reported as an SAE (see Appendix 3).

Any overdose, with or without associated AEs, must be promptly reported to the Clinical Trial Physician or other designated Drug Safety Center. The overdose should be recorded in the Study Drug Exposure eCRF. AEs associated with an overdose should be reported on relevant AE/SAE sections in the eCRF.

In the event of overdose, the participant should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for ozanimod overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

9.4 Safety

Planned time points for all safety assessments are listed in Section 2.

9.4.1 Physical Examinations

Complete and interim physical examinations will be performed as indicated in Section 2.

Complete physical examinations will include evaluation of heart, lungs, head and neck, abdomen, skin, and extremities, as well as a check for visual or neurologic symptoms. All significant findings that are present at Screening must be reported on the relevant medical history/current medical conditions eCRF. A full examination of the skin and a check for visual symptoms should be repeated every 6 months. Dermatological evaluations should be performed by the treating investigator or designee as part of physical examinations. Participants with any suspicious findings noted during the examination will be referred to an appropriately qualified dermatologist for evaluation and treatment, if warranted.

At all other visits following Screening (except Week 12, Week 64/ET), an interim physical examination will be performed. The interim physical examination will include weight, a check for visual symptoms, and an evaluation of body systems with previously noted abnormalities and/or those body systems associated with any new complaints from the participant.

Significant findings made after randomization (Day [redacted] that meet the definition of an AE must be recorded on the AE eCRF.

9.4.2 Vital Signs

Systolic and diastolic BP and HR will be assessed in a seated and standing position at every visit as indicated in Section 2. An automated validated device may be used, if available. In case the cuff sizes available are not large/small enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. [redacted]

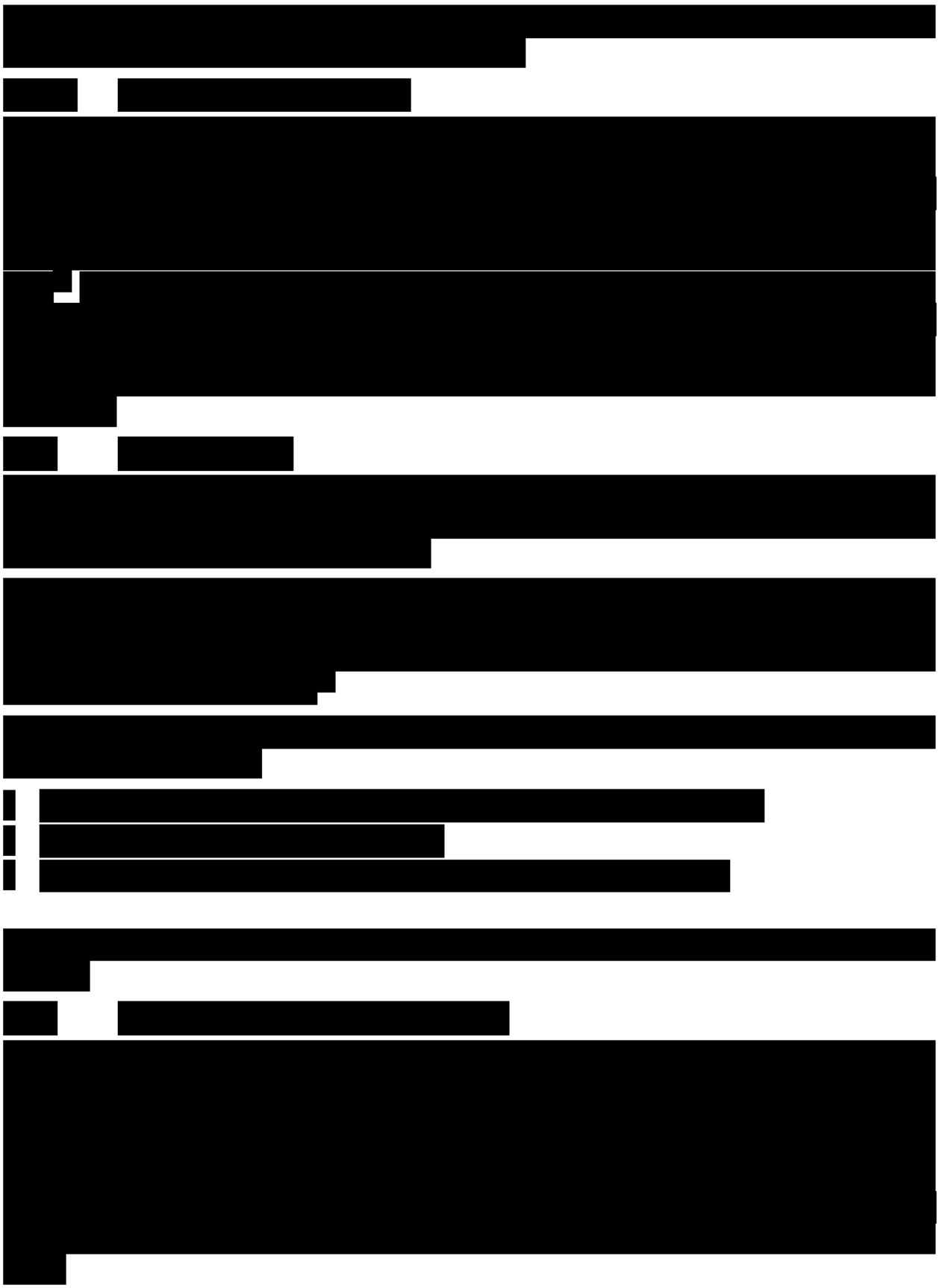
9.4.3 Electrocardiograms

Refer to Schedule of Events (see Section 2).

9.4.4 Height and Weight

Refer to Schedule of Events (see Section 2).

[redacted]



[redacted]

[redacted]

[redacted]

9.4.9 Pulmonary Function Evaluations

At Screening, participants with an underlying history of severe or chronic lung disease, bronchopulmonary dysplasia, cystic fibrosis, severe asthma (ie, that interferes with normal activities of daily living), or other clinically relevant pulmonary conditions must be excluded.

During the study, considering the expected variability of results and the need for age-appropriate procedures for younger participants, pulmonary evaluations should be performed as follows:

- [redacted]
- [redacted]
- [redacted]

As part of the consultations during the treatment period, relevant medical history including infection, respiratory symptoms, exposure to asbestos, and cigarette smoking must be collected and documented.

[redacted]

Participants who experience AEs or symptoms suggestive of decline in pulmonary function may obtain additional pulmonary evaluations at the discretion of the investigator or at the request of the Sponsor.

9.4.10 Ophthalmological Evaluations

At Screening, participants with underlying history or evidence of retinal disorders (eg, macular edema) or other clinically relevant ophthalmological conditions must be excluded.

During the study, considering the expected variability of results and the need for age-appropriate assessments, ophthalmologic evaluations should be performed as follows:

[redacted]

[redacted] are considered source documents that should be made available to the Sponsor upon request.

As part of the ophthalmological evaluations during the treatment period, relevant medical history and visual acuity (see Section 9.4.11) must be collected and documented. Participants who experience symptoms (eg, blurred vision, distorted vision, decreased vision, dimming) at any point during the study may receive additional ocular evaluations at the discretion of the investigator or at the request of the Sponsor. For follow-up examinations for suspected and/or confirmed macular edema, a pediatric retinal specialist is preferred wherever possible.

9.4.11 Visual Acuity Testing

Visual Acuity testing is a measure of the ability of the eye to distinguish shapes and the details of objects at a given distance. Visual acuity test results will be recorded based on age-appropriate tests performed in all participants by an individual with appropriate training at the timepoints indicated in [redacted]

9.4.12 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report. An abnormal laboratory value is considered an AE if the abnormality:

- Results in discontinuation from the study
- Requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention, or
- Is judged to be of significant clinical importance by the investigator (eg, one that indicates a new disease process and/or organ toxicity or is an exacerbation or worsening of an existing condition)

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as an SAE.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded as the AE. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

The central laboratory will analyze routine samples, unless otherwise specified in the protocol. Local laboratories may also be used to conduct safety tests that require quick results (when the central laboratory is unable to provide) only if duplicate test samples are collected at the same time and sent to both the central laboratory and the local laboratory. Prior to utilizing a local laboratory, the Investigator must contact the Clinical Trial Physician or designee for discussion. Limitations of blood volume collection should be considered carefully. The investigator must ensure that the local laboratory certificates and reference ranges are provided to the Sponsor.

Details regarding collection of samples, shipment of samples, reporting of results, laboratory reference ranges, and alerting abnormal values will be supplied to the site before site initiation in a study Lab Flowchart. The results of the analysis will be made available to each site by the central laboratory.

Investigators will be asked to comment on those abnormalities on the respective laboratory result page, including a notation of the clinical significance of each abnormal finding in the participant's source documents. The laboratory sheets will be filed with the participant's source documents.

The decision to temporarily interrupt dosing because of a laboratory abnormality other than ALC < 200 cells/µL remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to interruption, the investigator may contact the Clinical Trial Physician or designee and forward appropriate supporting documents for review and discussion. The investigator will report the action taken with IP. See Section 8.1 for permanent discontinuation of IP.

The amount of blood taken from participants at each visit and cumulatively over the course of the entire study is within the safety limits (1% to 3% of total blood volume, [TBV]) as described in the Regulation (European Union) guidance No 536/2014 and World Health Organization guidance.[40,41] The volume of blood drawn during the study will not exceed 1% of TBV over 24 hours or 3% of TBV over 4 weeks for any participants at any visits. Please reference the Lab Flowchart for study visit blood volumes.

9.4.12.1 Hematology

Red blood cell count, total and differential white blood cell (WBC) count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration, and ESR will be collected (see Section 2). During the treatment period, participants should maintain a hemoglobin level > 7.0 g/dL. For participants with a hemoglobin level

≤ 7.0 g/dL, the Investigator should contact the Clinical Trial Physician or designee for further discussion. Total WBC count and all differential WBC counts will be blinded information for the treating investigator after initiation of IP. Of note, WBC, basophil, eosinophil, lymphocyte, monocyte, and neutrophil counts will not be disclosed to preserve the blind.

[redacted]

The test results will not be disclosed to the Sponsor nor site personnel during the blinded portions of the study and through Week 12 of the LTE Period. Alerts for out-of-range values will be flagged for the site while keeping the numerical results blinded.

[redacted]

9.4.12.2 Chemistry

- Full chemistry panel at Screening: Sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, glucose, HbA1c, albumin, alkaline phosphatase, creatinine, ALT, AST, gamma glutamyl transferase (GGT), total bilirubin, direct bilirubin, total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, and [redacted]
- All other visits: Sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, albumin, alkaline phosphatase, creatinine, ALT, AST, GGT, total bilirubin, direct bilirubin, and [redacted]. Total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein will be included at the [redacted] ET visit.
- [redacted]
  - The investigator should establish causality. Additional testing may be needed, in consultation with the Clinical Trial Physician or designee, which may include coagulation panel, viral hepatitis serology, antinuclear and anti-smooth muscle antibodies, IgG levels, and an abdominal ultrasound.
- Urinalysis: Leukocytes, specific gravity, bilirubin, blood, glucose, ketones, pH, protein, and urobilinogen

9.4.12.3 Serology

Testing will be performed at Screening to determine the participant's immune status with respect to the following viral infections:

- VZV
  - A VZV titer may be performed to determine whether the participant has immunity (positive result for VZV IgG antibody). If VZV antibody titer is negative, the participant may choose to receive VZV vaccination in order to qualify for the study. If the participant receives a VZV vaccination, randomization (Day [redacted]) can occur at a minimum of 30 days after vaccination has been administered.
- HIV
  - A HIV antibody test will be performed. Participants testing positive for HIV (ELISA test result, confirmed by Western blot) will be excluded from the trial.
- HAV
  - An anti-hepatitis A virus (HAV) antibody (anti-HAV IgM) test will be performed. Participants testing positive will be excluded from the trial, unless they are indicative of prior hepatitis A, that is considered cured and accompanied by normal liver transaminase values.
- Hepatitis B Virus (HBV)
  - Hepatitis B surface (HBs) antigen and hepatitis B core (HBc) antibody test will be performed.
  - Participants who test positive for HBs antigen will be excluded from the trial.

  - For participants who test positive only for antibody to HBc antigen, an HBV deoxyribonucleic acid (DNA) test must be performed.
  - If the HBV DNA test is negative (without anti-viral therapy) and the LFTs are normal, the participant will be eligible for this trial. These participants will undergo periodic monitoring for HBV DNA during the trial.
- Hepatitis C Virus (HCV)
  - A HCV antibody (anti-HCV IgG or IgM) test will be performed.
  - Participants testing positive for HCV antibody and a positive confirmatory test will be excluded from the trial.

9.5 Pharmacokinetics

Blood samples will be collected in volumes appropriate for children according to the following schedule [redacted]

[redacted]

Additional samples are to be collected at ET and the [redacted] Safety Follow-up visits. Please reference the Lab Flowchart for study visit blood sample volumes.

In the LTE Period, blood samples for PK should be collected after every approximately 1 year of treatment with ozanimod, on the same day as a planned hematology and stool collection. One sample should be collected at any time post-dose.

Plasma concentrations of ozanimod, CC112273, and CC1084037 will be determined in the blood using a validated bioanalytical method. The concentration-time data of ozanimod and CC112273 will be evaluated using the [redacted]

Treatment assignments will be released to the bioanalytical laboratory in order to minimize unnecessary analysis and/or reanalysis of PK samples.

Concentration analyses for ozanimod will be performed by validated bioanalytical method(s).

Bioanalytical samples designated for assessments [redacted] from the same collection time point may be used interchangeably for analyses, if required [redacted]

[redacted]

[redacted]

9.8 Additional Research

This protocol will include [redacted] for additional research.

For All Sites:

Additional research is required for all study participants, except where prohibited by IRBs/ethics committees, prohibited by local laws or regulations, or academic/institutional requirements.

- If the IRB/ethics committees and site agree to the mandatory additional research retention and/or collection, then the study participant must agree to the mandatory additional research as a requirement for inclusion in the study.
- If optional participation is permitted and approved, then the study participants may opt out of the additional research retention and/or collection.

Additional research is intended to expand the research and development capability at Bristol-Myers Squibb and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment, etc.

Sample Collection and Storage

[redacted]

Samples kept for future research will be stored at the BMS Biorepository in [redacted] or an independent, BMS-approved storage vendor.

The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than fifteen (15) years after the end of the study or the maximum allowed by applicable law.

Transfers of samples by Sponsor to third parties will be participant to the recipient's agreement to establish similar storage procedures.

Samples will be stored in a coded fashion, and no researcher will have access to the key. The key is securely held by the investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual.

Further details of sample collection and processing will be provided to the site in the procedure manual.

[redacted]

9.9 Health Economics OR Medical Resource Utilization and Health Economics

Health economics/medical resource utilization and health economics parameters will not be evaluated in this study.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

No prospective hypotheses are being formally evaluated.

10.2 Sample Size Determination

The PCDAI score is highly correlated with CDAI score[42], therefore given the lack of data on PCDAI clinical remission, CDAI clinical remission is used to determine sample size of the current pediatric study. Clinical remission rates referenced below are based on CDAI.

Assuming the true proportion of clinical remission rate is 21.7% at Week 64 for all the pediatric participants (ages 2 to 17 years) receiving either ozanimod 0.46 mg or 0.92 mg/day, 100 evaluable participants will provide 90% probability to claim the estimated lower 95% CI bound of clinical remission rate is greater than 9.4%. The assumption of 21.7% clinical remission rate at Week 64 is based on the estimated clinical remission rate at Week 52 from an open-label Phase 2 clinical trial (RPC01-2201). The estimated rate of 9.4% clinical remission for placebo is based upon the upper bound of 95% Wald CI of the clinical remission rate from a prior trial using a similar study design and inclusion criteria in adult participants with active CD.[43]

In addition, acceptable conversion factors have been used to convert the CDAI clinical remission (CDAI < 150) rate to PCDAI clinical remission (PCDAI < 10) rate.[44] Based on a conversion factor of 1.38, a sample size of 100 participants will provide a probability of 73% to claim the estimated lower 95% CI bound of ozanimod pediatric clinical remission rate (15.8% as converted from 21.7% CDAI clinical remission rate) is greater than the placebo pediatric clinical remission rate (6.8% as converted from 9.4% CDAI clinical remission rate).

To account for participant drop-out during the study, the study plans to enroll approximately [redacted] participants.

Half width (precision) and the expected lower and upper bound of the 95% Wald CI of the estimated clinical remission rate for overall and [redacted] are provided in Table 10.2-1.

Table 10.2-1: Sample Sizes to Evaluate Week 64 Clinical Remission (CDAI < 150) Rates

[redacted]	Sample Size	Precision (Half-width of 95% CI[a])	Expected Lower Bound of 95% CI[a] of Ozanimod	Expected Upper Bound of 95% CI[a] of Ozanimod
Overall	100	8.1%	13.7%	29.8%
[redacted]				

Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval.

[a] CI obtained assuming an estimated ozanimod Week 64 clinical remission (CDAI < 150) rate of 21.7%. The normal approximation for constructing the 95% CIs may produce an unusually conservative lower bound for sample sizes under 100.

For the co-primary endpoint of endoscopic remission at Week 64, Table 10.2-2 provides half width (precision) and the expected lower and upper bound of 95% Wald CI of the estimated endoscopic remission rate for overall participants and [redacted] The calculation assumes a 5.8% endoscopic remission rate for the ozanimod arms (either dose group), which is the estimated ozanimod endoscopic remission rate in study RPC01-2201.

Table 10.2-2: Sample Sizes to Evaluate Week 64 Endoscopic Remission Rates

[redacted]	Sample Size	Precision (Half-width of 95% CI)[a]	Expected Lower Bound of 95% CI[a] of Ozanimod	Expected Upper Bound of 95% CI[a] of Ozanimod
Overall	100	4.6%	1.22%	10.4%
[redacted]				

Abbreviations: CI, confidence interval.

[a] CI obtained assuming an estimated ozanimod Week 64 endoscopic remission rate of 5.8%. The normal approximation for constructing the 95% CIs may produce an unusually conservative lower bound for sample sizes under 100.

For the endpoint of proportion of participants achieving clinical remission (CDAI < 150) at Week 12, Table 10.2-3 provides half width (precision) and the expected lower and upper bound of 95% Wald CI of the estimated clinical remission rate for overall participants and [redacted] The calculation assumes a 33.3% clinical remission rate for the ozanimod arms (either dose group), which is the estimated ozanimod clinical remission rate in study RPC01-2201.

Table 10.2-3: Sample Sizes to Evaluate Week 12 Clinical Remission (CDAI < 150) Rates

[redacted]	Sample Size	Precision (Half-width of 95% CI[a])	Expected Lower Bound of 95% CI[a] of Ozanimod	Expected Upper Bound of 95% CI[a] of Ozanimod
Overall	100	9.2%	24.1%	42.6%
[redacted]				

Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval.

[a] CI obtained assuming an estimated ozanimod Week 12 clinical remission (CDAI<150) rate of 33.3%. The normal approximation for constructing the 95% CIs may produce an unusually conservative lower bound for sample sizes under 100.

The analyses of the key secondary endpoint (eg, pediatric clinical remission at Week 12) will be conducted in the similar manner as the co-primary endpoint (eg, pediatric clinical remission at Week 64). Details will be described in the Statistical Analysis Plan (SAP).

[redacted] The method of sample size determination for PK evaluation in this study is based on previously published methods.[45]

10.3 Analysis Sets

For the purposes of analysis, the following populations are defined:

Table 10.3-1: Populations for Analysis

Population	Description
Intent-to-Treat	The ITT analysis population will consist of all randomized participants from the screened analysis population that receive at least 1 dose of IP. Participants in the ITT analysis population will be analyzed according to the randomized treatment, regardless of the treatment received.
Safety	The safety analysis population is defined as all participants who are randomized and receive at least 1 dose of IP, analyzed by actual treatment received.
PK	The PK population will consist of ITT participants who have at least 1 post-Screening PK assessment.
Randomized	All participants who were randomized using IRT.

Table 10.3-1: Populations for Analysis

Population	Description
Per-protocol	The PP population will consist of all participants in the ITT population. Those participants who have specific reasons for warranting exclusion from this population will be documented prior to database lock and may include but are not limited to protocol deviations that substantially affect the key efficacy endpoint.

Abbreviations: IP, investigational product; IRT, integrated response technology; ITT, intent-to-treat; PK, pharmacokinetic; PP, per-protocol.

The primary analysis population for all efficacy endpoints will be the intent-to-treat (ITT) analysis population. All safety analyses will be carried out on the Safety population. The PK analyses will be carried out on the PK population. The selected efficacy/safety analysis will be carried out on the PP population as specified.

Participant demographics will be summarized for the ITT population and will include age, sex, race, ethnicity, height, weight, and BMI.

Baseline characteristics will be summarized for the ITT population and will include age at CD symptom onset, age at CD diagnosis, years since CD symptom onset, years since CD diagnosis, prior anti-TNF use, corticosteroid use at Screening, concomitant CD medication use at Baseline, each component of the CDAI score, and PCDAI. Participants should continue to be assessed for PCDAI throughout the trial, regardless of age change.

Compliance with randomized IP will be summarized and will include the number of participants estimated to be < 80% compliant, 80% to 100% compliant, > 100% compliant, and > 120% compliant.

10.4 Statistical Analyses

10.4.1 General Considerations

This is a global, multicenter, randomized, double-blind Phase 2/3 study to evaluate the efficacy, safety, and tolerability of ozanimod in pediatric participants aged 2 to 17 years inclusive with moderately to severely active CD, defined as a PCDAI score of ≥ 30, SES-CD score of ≥ 6 (or SES-CD ≥ 4 in participants with isolated ileal disease), with an inadequate response, intolerance, or loss of response to conventional therapy for CD. The study will also evaluate the PK and PD and evaluate the safety of ozanimod in pediatric participants.

Analysis details not explained in the statistical section of the protocol will be provided in the SAP and PK Analysis Plan.

The detailed definitions of all efficacy endpoints are described in Section 4. Efficacy will be evaluated based on the totality of the data and a comprehensive analysis based on descriptive statistics. Hypothesis testing will not be performed.

The number and percentage of participants in each population will be summarized. Patient disposition, including the number of participants screened, randomized, dosed, completing

Week 64, and not completing Week 64 (overall and by reason for dropout), will be summarized for the ITT population.

10.4.2 Primary Endpoint(s)

The primary analyses of the 2 co-primary endpoints, pediatric clinical and endoscopic remission at Week 64, will be based on the ITT population in which all [redacted] will be pooled. The estimated proportions along with their associated 2-sided 95% Wald CI using a normal approximation for a single sample proportion will be constructed. Summary statistics on the number of events, sample size, and proportions for the overall group and by [redacted] will also be provided.

For participants whose pediatric clinical and endoscopic remission at Week 64 cannot be adequately determined (including missing data, discontinuation, or lost to follow-up), their missing pediatric clinical and endoscopic remission will be imputed using a non-responder imputation.
In addition to the primary overall analysis, a subgroup analysis will be conducted for each of [redacted] A summary will be tabulated and a forest plot showing the proportions with associated 95% CIs will be produced.

Details on the analyses and the evaluations for the co-primary endpoints will be provided in the SAP, which will include comparisons with the external placebo controls as well as data from ozanimod CD adult trials.

10.4.3 Secondary Endpoint(s)

The analyses of the key secondary endpoint (eg, pediatric clinical remission at Week 12) will be conducted in a similar manner as the co-primary endpoint.

[redacted]

10.4.5 Other Safety Analyses

All participants who take at least 1 dose of IP will be included in the safety analyses. AEs will be summarized by worst severity grade. AEs, with particular focus on TEAEs, will be summarized using the Medical Dictionary for Regulatory Activities system organ class and preferred term.

The incidence of TEAEs, IP-related TEAEs, TEAEs leading to discontinuation from treatment, events assessed as Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or Grade 4 (or moderate/severe if other rating scale is used), SAE, and AESIs (see Section 9.2.9) will be summarized for [redacted] The incidence of TEAEs by severity and by relationship to study drug will also be summarized. SAEs will be presented by [redacted] and by relationship to study drug. Summary tables will present incidence estimates and

individual event rates by system organ class as well as within each system organ class. Participants experiencing an event more than once with varying severity will be counted only once with the maximum severity within each system organ class/preferred term. For incidence of relationship to study drug, participants will be counted only once, in the category of the strongest relationship to study drug within each system organ class/preferred term. By-participant listings of death and AEs leading to death will be provided.

Laboratory values, vital signs, and ECG data will be presented in appropriate summary tables.

Cross tabulations will be provided to summarize frequencies of abnormalities.

Descriptive statistics will be provided for vital sign and body weight data.

By-participant listings will be provided for all relevant safety data. Graphical displays and figures will be provided where useful to assist in the interpretation of results.

10.4.6 Other Analyses

[redacted]

10.4.6.2 Scoring Algorithms

Detailed algorithms on how to compute the CDAI scores and subscores are provided in the SAP.

10.4.6.3 Estimand Framework

For each key efficacy endpoint (ie, primary efficacy endpoint and secondary efficacy endpoints), the following primary estimand is specified following the final version of ICH E9 (R1) guidance (Adopted in May 2021). Other details on estimand will be provided in the SAP.

Treatment Condition of Interest

Adult equivalent doses of 0.46 mg and 0.92 mg of ozanimod will be evaluated [redacted] 0.46 mg and 0.92 mg adult equivalent doses will be determined [redacted]

The participants are allowed to take concomitant medications (see Section 7.7) but are prohibited from taking some medications (see Section 7.7.2).

Population of Participants

Pediatric participants aged 2 to 17 years, inclusive, with moderately to severely active CD with an inadequate response, loss of response, or intolerance to prior therapy for CD are enrolled in this study.

Table 10.4.6.3-1: Variables to be Obtained for Each Participant

Measure	Endpoint
Primary – Efficacy	
PCDAI remission	Proportion of participants who achieve PCDAI < 10 at Week 64
SES-CD endoscopic remission	Proportion of participants achieving SES-CD ≤ 2 or SES-CD ≤ 4 points with no SES-CD subscore > 1 point at Week 64
Secondary – Efficacy (Key)	
PCDAI remission	Proportion of participants who achieve PCDAI < 10 at Week 12
Secondary – Efficacy (Other)	
SES-CD endoscopic response	Proportion of participants who achieve a SES-CD decrease from Baseline of ≥ 50% (ER-50) at Week 64
	Proportion of participants who achieve a SES-CD decrease from Baseline of ≥ 50% (ER-50) at Week 12
PCDAI clinical response	Proportion of participants who achieve a decrease from Baseline in PCDAI score ≥ 12.5 and a total PCDAI score of < 30 points at Week 64
	Proportion of participants who achieve a decrease from Baseline in PCDAI score ≥ 12.5 and a total PCDAI score of < 30 points at Week 12
Symptomatic remission (adolescents only)	Proportion of participants who achieve an average daily abdominal pain score ≤ 1 point and average daily stool frequency ≤ 3 points with abdominal pain and stool frequency no worse than Baseline at Week 64
	Proportion of participants who achieve an average daily abdominal pain score ≤ 1 point and average daily stool frequency ≤ 3 points with abdominal pain and stool frequency no worse than Baseline at Week 12
Symptoms over time	Change from Baseline in stool frequency score over time
	Change from Baseline in abdominal pain over time

Table 10.4.6.3-1: Variables to be Obtained for Each Participant

Measure	Endpoint
CDAI clinical remission (adolescents only)	Proportion of participants who achieve CDAI score < 150 at Week 64
	Proportion of participants who achieve CDAI score < 150 at Week 12
CDAI clinical response (adolescents only)	Proportion of participants who achieve CDAI reduction from Baseline of ≥ 100 points or CDAI score < 150 at Week 64
	Proportion of participants who achieve CDAI reduction from Baseline of ≥ 100 points or CDAI score < 150 at Week 12
Corticosteroid-free remission	Proportion of participants who achieve a PCDAI score < 10 at Week 64 while remaining corticosteroid free in the prior 12 weeks
	Proportion of participants who achieve a CDAI score < 150 at Week 64 while remaining corticosteroid free in the prior 12 weeks (adolescents only)
Endoscopic remission	Proportion of participants achieving SES-CD < 2 or SES-CD ≤ 4 points with no SES-CD subscore > 1 point at Week 12

Abbreviations: CDAI, Crohn's Disease Activity Index; ER-50, SES-CD decrease from Baseline of ≥ 50%; PCDAI, Pediatric Crohn's Disease Activity Index; SES-CD, Simple Endoscopic Score for Crohn's Disease.

[redacted]

Population-Level Summary

For each of the primary and secondary efficacy endpoints, the analysis will be based on the ITT population in which [redacted] will be pooled. The estimated proportion along with its associated 2-sided 95% Wald CI using a normal approximation for a single sample proportion will be constructed.

[redacted]

11 REFERENCES

[redacted]

2 Sandborn WJ, Feagan BG, Wolf D, et al. Ozanimod induction and maintenance treatment for ulcerative colitis. N Engl J Med 2016;374:1754-62.

3 Sandborn W, D'Haens GR, Wolf DC, et al. Ozanimod as induction therapy in moderate to severe ulcerative colitis: results from the Phase III, randomized, double-blind, placebo-controlled true north study. 2020; 8(10): 1258-1275.

4 Lakatos PL. Recent trends in the epidemiology of inflammatory bowel diseases: up or down? World J Gastroenterol 2006;12:6102-8.

5 Schwartz DA, Loftus EV Jr, Tremaine W, et al. The natural history of fistulizing Crohn's disease in Olmsted County, Minnesota. Gastroenterology 2002;122:875-80.

6 Peyrin-Biroulet L, Loftus EV Jr, Colombel JF, et al. The natural history of adult Crohn's disease in population-based cohorts. Am J Gastroenterol 2010;105:289-97.

7 Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002;359:1541-9.

8 Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007;132:52-65.

9 Sandborn WJ, Feagan BG, Stoinov S, et al. Certolizumab pegol for the treatment of Crohn's disease. N Engl J Med 2007;357:228-38.

10 Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med 2013;369:711-21.

11 Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. N Engl J Med 2016;375:1946-60.

12 Rosen MJ, Dhawan A, Saeed SA. Inflammatory bowel disease in children and adolescents. JAMA Pediatr 2015;169:1053–60.

13 Müller KE, Lakatos PL, Arató A, et al. Incidence, Paris classification, and follow-up in a nationwide incident cohort of pediatric patients with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2013;57:576-82.

14 Gupta N, Bostrom AG, Kirschner BS, et al. Incidence of stricturing and penetrating complications of Crohn's disease diagnosed in pediatric patients. Inflamm Bowel Dis. 2010;16:638-44.

15 Dubinsky MC, Lin YC, Dutridge D, et al. Serum immune responses predict rapid disease progression among children with Crohn's disease: immune responses predict disease progression. Am J Gastroenterol 2006;101:360-7.

16 Pfefferkorn MD, Marshalleck FE, Saeed SA, et al. NASPGHAN clinical report on the evaluation and treatment of pediatric patients with internal penetrating Crohn disease: intraabdominal abscess with and without fistula. J Pediatr Gastroenterol Nutr 2013;57:394-400.

17 Vasseur F, Gower-Rousseau C, Vernier-Massouille G, et al. Nutritional status and growth in pediatric Crohn's disease: a population-based study. Am J Gastroenterol 2010;105:1893 1900.

18 Narula N, Dhillon A, Zhang D, et al. Enteral nutritional therapy for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2018; 4:CD000542.

19 Cameron FL, Wilson ML, Basheer N, et al. Anti-TNF therapy for paediatric IBD: the Scottish national experience. Arch Dis Child 2015;100:399-405.

20 Drozdowicz LB, Bostwick JM. Psychiatric adverse effects of pediatric corticosteroid use. Mayo Clin Proc 2014, 89:817-34.

21 Centers for Disease Control. Clinical growth charts [cited 2020 Jan 17]. Available from URL: https://www.cdc.gov/growthcharts/clinical_charts.htm.

[redacted]

25 European Medicines Agency. Guideline on the development of new medicinal products for the treatment of Crohn's disease. 28 June 2018 CPMP/EWP/2284/99 Rev. 2, Committee for Medicinal Products for Human Use (CHMP).

[redacted]

28 Centers for Disease Control. Vaccines and Preventable Diseases For Healthcare Professionals. Varicella. 28-Apr-2021. Available from URL: https://www.cdc.gov/vaccines/vpd/varicella/hcp/index.html

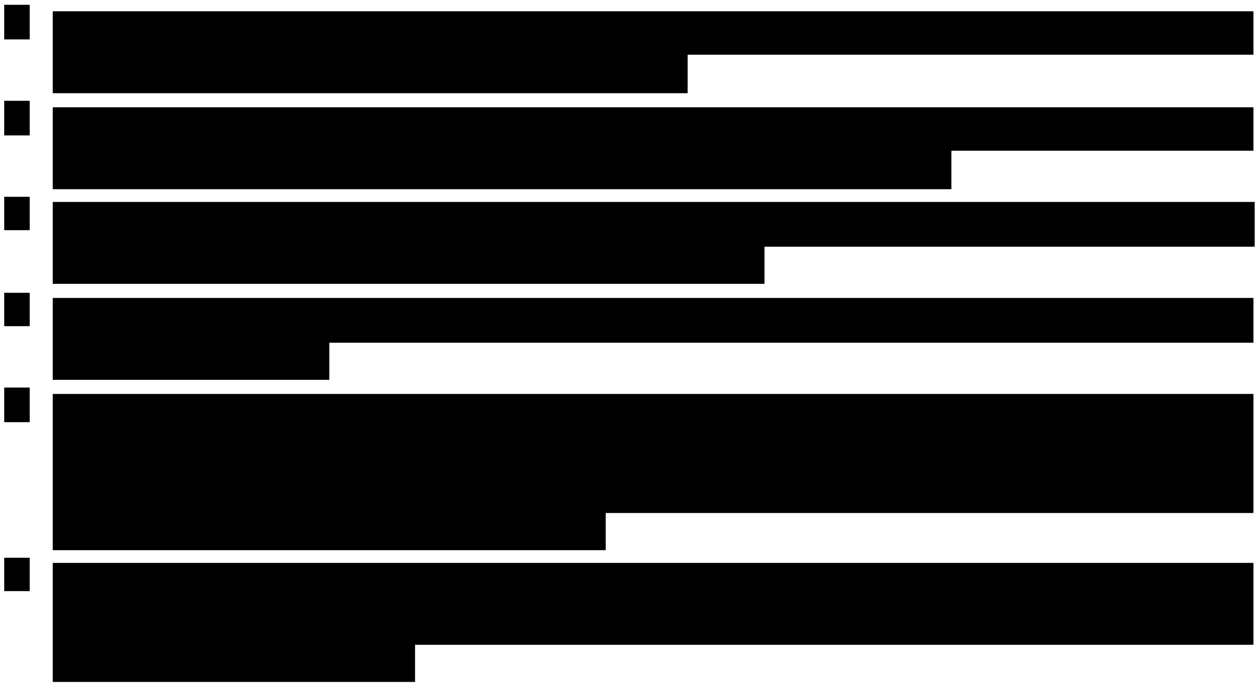
29 Hughes H, Kahl L. The Harriet Lane handbook: a manual for pediatriac house officers. 21st ed. Philadelphia (PA): Elsevier; 2018.

30 Hyams JS, Ferry GD, Mandel FS, et al. Development and validation of a pediatric Crohn's disease activity index. J Pediatr Gastroenterol Nutr 1991;12:439-47.

31 Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc 2004;60:505-12.

32 Khanna R, Zou G, D'Haens G, et al. A retrospective analysis: the development of patient reported outcome measures for the assessment of Crohn's disease activity. Aliment Pharmacol Ther 2015;41:77-86.

33 Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol 1997;32:920-4.



40 European Commission. Ethical considerations for clincial trials on medicinal products conducted with minors. 2017. Available from URL: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-10/2017_09_18_ethical_consid_ct_with_minors.pdf

41 Howie SRC. Blood sample volumes in child health research: review of safe limits. Bull World Health Organ 2011;89:46-53.

42 Otley A, Loonen H, Parekh N, et al. Assessing activity of pediatric Crohn's disease: which index to use? Gastroenterol 1999; 116:527-31.

[43] Sands BE, Feagan BG, Sandborn WJ, et al. (GED-0301) for active Crohn's disease: results of a Phase 3 study. Am J Gastroenterol 2020;115:738-45.

[44] U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Humira (adalimumab). BLA 125057/45 approval package. 03-Oct-2005. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/bla/2005/125057Orig1s045.pdf. Accessed 09-Feb-2022.

[45] Wang Y, Jadhav PR, Lala M, et al. Clarification on precision criteria to derive sample size when designing pediatric pharmacokinetic studies. J Clin Pharmacol 2012;52:1601-6.

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
5-ASA	5-aminosalicylic acid
β-hCG	β-subunit human chorionic gonadotropin
AE	adverse event
AESI	adverse event of special interest
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ARR	annualized relapse rate
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AV	atrioventricular
AZA	azathioprine
BCRP	breast cancer resistance protein
BMI	body mass index
BP	blood pressure
BPM	beats per minute
BMS	Bristol-Myers Squibb
C difficile	Clostridium difficile
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CDC	Center for Disease Control
CI	confidence interval
COVID-19	coronavirus disease 2019
[redacted]	[redacted]
CV	coefficient of variation
DILI	drug-induced liver injury
DM	diabetes mellitus
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
[redacted]	[redacted]
ECG	electrocardiogram
eCRF	electronic Case Report Form
EEN	exclusive enteral nutrition

Term	Definition
ER-50	decrease from baseline of ≥ 50%
ESR	erythrocyte sedimentation rate
ET	early termination
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
FOCBP	female of childbearing potential
[redacted]	[redacted]
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
[redacted]	[redacted]
GI	gastrointestinal
HAV	hepatitis A virus
HbA1c	hemoglobin A1c
HBc	hepatitis B core
HBs	hepatitis B surface
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN β-1a	interferon β-1a
IgG	immunoglobulin G
IgM	immunoglobulin M
IL	interleukin
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board

Term	Definition
[redacted]	[redacted]
IRT	Interactive Response Technology
ITT	intent-to-treat
IV	intravenous
IVIg	intravenous immune globulin
JCV	John Cunningham virus
LAR	legally acceptable representative
LFT	liver function test
LH	luteinizing hormone
LTE	long-term extension
6-MP	6 mercaptopurine
MRI	magnetic resonance imaging
MS	multiple sclerosis
MTX	methotrexate
N	number of participants or observations
NSAID	nonsteroidal anti-inflammatory drug
[redacted]	[redacted]
OLE	open-label extension
OLP	open-label period
PD	pharmacodynamics
PCDAI	Pediatric Crohn's Disease Activity Index
[redacted]	[redacted]
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PRES	posterior reversible encephalopathy syndrome
[redacted]	[redacted]
[redacted]	[redacted]
S1P	sphingosine 1-phosphate
SAE	serious adverse event
SAP	Statistical Analysis Plan
[redacted]	[redacted]
[redacted]	[redacted] deviation
SE	standard error

Term	Definition
SES-CD	Simple Endoscopic Score for Crohn's Disease
SFU	safety follow-up
TEAE	treatment-emergent adverse event
TB	tuberculosis
TBV	total blood volume
TDM	therapeutic drug monitoring
TNF	tumor necrosis factor
UC	ulcerative colitis
ULN	upper limit of normal
VZV	varicella zoster virus
WBC	white blood cell
YO	years-old

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The terms "participant" and "subject" refer to a person who has consented to participate in the clinical research study. Typically, the term "participant" is used in the protocol and the term "subject" is used in the Case Report Form (CRF).

REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws, regulations, and requirements

The study will be conducted in compliance with the protocol. The protocol, any revisions/amendments, and the participant informed consent form (ICF) will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable regulations prior to initiation of the study.

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a Quality Issue (eg, protocol deviation) that is likely to affect, to a significant degree, one or more of the following: (1) the rights, physical safety or mental integrity of one or more participants; (2) the scientific value of the clinical trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP regulation(s) or trial protocol(s).

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, Investigator's Brochure, product labeling information, ICF, participant recruitment materials (eg, advertisements), and any other written information to be provided to participants.

The investigator, Sponsor, or designee should provide the IRB/IEC with reports, updates, and other information (eg, expedited safety reports, amendments, administrative letters) annually, or more frequently, in accordance with regulatory requirements or institution procedures.

The investigator is responsible for providing oversight of the conduct of the study at the site and adherence to requirements of the following where applicable:

- ICH guidelines,
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- European Union Directive 2001/20/EC; or
- European Regulation 536/2014 for clinical studies (if applicable),
- European Medical Device Regulation 2017/745 for clinical device research (if applicable),
- the IRB/IEC
- and all other applicable local regulations.

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and, if applicable, also by the local Health Authority), except where necessary to eliminate an immediate hazard(s) to study participants.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s), the deviation or change will be submitted as soon as possible to:

- IRB/IEC
- Regulatory authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and, if applicable, also by the local Health Authority, must be sent to Bristol-Myers Squibb (BMS).

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the ICF must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from participants currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new participants prior to enrollment.

FINANCIAL DISCLOSURE

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information, in accordance with regulations, to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

Investigators must ensure that participants are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

The Sponsor or designee will provide the investigator with an appropriate sample ICF, which will include all elements required by the ICH GCP, and applicable regulatory requirements. The sample ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

The investigator or his/her representative must:

- Obtain IRB/IEC written approval/favorable opinion of the written ICF and any other information to be provided to the participant prior to the beginning of the study and after any revisions are completed for new information.
- Provide a copy of the ICF and written information about the study in the language in which the participant is proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Explain the nature of the study to the participant or his/her legally acceptable representativeand answer all questions regarding the study.
- Inform participant that his/her participation is voluntary. Participant or his/her legally acceptable representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- Allow time necessary for participant or his/her legally acceptable representative to inquire about the details of the study.

Obtain an ICF signed and personally dated by participant or his/her legally acceptable representativeand by the person who conducted the informed consent discussion.

- Include a statement in participant's medical record that written informed consent was obtained before participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Re-consent participant to the most current version of the ICF(s) during his/her participation in the study, as applicable.

Revise the ICF whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or his/her legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the participant's signed ICF, and, in the US, the participant's signed HIPAA Authorization.

The ICF must also include a statement that BMS and local and foreign regulatory authorities have direct access to participant records.

In situations where consent cannot be given by participants, their legally acceptable representatives (as per country regulation) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the participant volunteers to participate.

If informed consent is initially given by a participant's legally acceptable representative or legal guardian and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the ICF approved for the study prior to clinical study participation. The explicit wish of a minor, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time, should be considered by the investigator.

Minors who are judged to be of an age of reason must also give their written consent. Minors who reach the age of majority (legal adulthood) during the clinical trial must give their written consent.

The rights, safety, and well-being of the study participants are the most important considerations and should prevail over interests of science and society.

BMS COMMITMENT TO DIVERSITY IN CLINICAL TRIALS

The mission of BMS is to transform patients' lives through science by discovering, developing, and delivering innovative medicines that help them prevail over serious diseases.

BMS is committed to doing its part to ensure that patients have a fair and just opportunity to achieve optimal health outcomes.

BMS is working to improve the recruitment of a diverse participant population with the goal that the clinical trial becomes more reflective of the real-world population and the people impacted by the diseases studied.

DATA PROTECTION, DATA PRIVACY, AND DATA SECURITY

BMS collects and processes personal data of study participants, patients, health care providers, and researchers for biopharmaceutical research and development to advance innovative, high-quality medicines that address the medical needs of patients. BMS ensures the privacy, protection, and confidentiality of such personal data to comply with applicable laws. To achieve these goals, BMS has internal policies that indicate measures and controls for processing personal data. BMS adheres to these standards to ensure that collection and processing of personal data are limited and proportionate to the purpose for which BMS collects such personal data. This purpose is clearly and unambiguously notified to the individual at the time of collection of personal data. In the true spirit of science, BMS is dedicated to sharing clinical trial information and data with participants, medical/research communities, the media, policy makers, and the general public. This is done in a manner that safeguards participant privacy and informed consent while respecting the integrity of national regulatory systems. Clinical trial data, health-related research, and pharmacovigilance activities on key-coded health data transferred by BMS across national borders is done in compliance with the relevant data protection laws in the country and GCP requirements.

BMS protects Personal Information with adequate and appropriate security controls as indicated under the data protection laws. To align with the recommended security standards, BMS has adopted internal security standards and policies to protect personal data at every stage of its processing.

To supplement these standards, BMS enters into Clinical Trial Agreements with confidentiality obligations to ensure proper handling and protection of personal data by third parties accessing and handling personal data.

BMS takes unauthorized access and disclosure of Personal Information very seriously. BMS has adopted the security standards that include National Institute of Standards and Technology Cybersecurity Framework for studies in the US. BMS aligns with these standards to continuously assess and improve its ability to protect, detect, and respond to cyber attacks and other unauthorized attempts to access personal data. These standards also aid in mitigating possible adverse effects. Furthermore, BMS Information Technology has defined 6 principles to protect our digital resources and information:

1) Responsibilities of IT Personnel

2) Securing the BMS Digital Infrastructure

3) Identity and Access Management

4) External Partner Connections

5) Cyber Threat Detection and Response

6) Internal Cyber Incident Investigation

SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the electronic CRF (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

- The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definitions of what constitutes source data can be found

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original, and attributable, whether the data are handwritten on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical records/electronic health

records, adverse event (AE) tracking/reporting, protocol-required assessments, and/or drug accountability records.

When paper records from such systems are used in place of an electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

STUDY INTERVENTION RECORDS

Records for study intervention (whether supplied by BMS, its vendors, or the site) must substantiate study intervention integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence/biocomparability, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form
Sourced by site and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the standard operating procedures/standards of the sourcing pharmacy

BMS or its designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

CASE REPORT FORMS

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents, or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the Sponsor or designee electronic data capture (EDC) tool, eCRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance Form, respectively. If the electronic SAE form is not available, a paper SAE form can be used.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF and SAE/pregnancy CRFs must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. Sub-investigators in Japan may not be delegated the CRF approval task. The investigator must retain a copy of the CRFs, including records of the changes and corrections.

Each individual electronically signing eCRFs must meet Sponsor or designee training requirements and must only access the BMS EDC tool using the unique user account provided by the Sponsor or designee. User accounts are not to be shared or reassigned to other individuals.

MONITORING

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, remote, or on-site monitoring) are provided in the monitoring plan.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site, they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

Certain CRF pages and/or electronic files may serve as the source documents.

In addition, the study may be evaluated by the Sponsor or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to the Sponsor or designee.

RECORDS RETENTION

The investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS or its designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or its designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed-upon designee (eg, another investigator, study site, IRB). Notice of such transfer will be given in writing to BMS or its designee.

RETURN OF STUDY TREATMENT

For this study, study treatments (those supplied by BMS or a vendor or sourced by the investigator), such as partially used study treatment containers, vials, and syringes, may be destroyed on site.

If	Then
Study treatments supplied by BMS (including its vendors)	Any unused study interventions supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor, unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). Partially used study interventions and/or empty containers may be destroyed after proper reconciliation and documentation. But unused IMP must be reconciled by site monitor/Clinical Research Associate prior to destruction. If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors; eg, study treatments	It is the investigator's or designee's responsibility to dispose of all containers

If	Then
sourced from the site's stock or commercial supply or a specialty pharmacy)	according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal of study interventions, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal (eg, incinerator, licensed sanitary landfill, or licensed waste-disposal vendor) must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Study Monitor to review throughout the clinical trial period.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met, the responsible Study Monitor will make arrangements for return of study treatments provided by BMS (or its vendors). Destruction of non-study treatments sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

STUDY AND SITE START AND CLOSURE

The Sponsor/designee reserves the right to close the study site or to terminate the study at any time for any reason at the sole discretion of the Sponsor. 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, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or 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 IECs/IRBs, the regulatory authorities, and any contract research organization(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.

DISSEMINATION OF CLINICAL STUDY DATA

In order to benefit potential study participants, patients, healthcare providers and researchers, and to help BMS honor its commitments to study participants, BMS will make information about clinical research studies and a summary of their results available to the public as per regulatory and BMS requirements. BMS will post study information on local, national or regional databases in compliance with national and international standards for disclosure. BMS may also voluntarily disclose information to applicable databases.

CLINICAL STUDY REPORT

A Signatory Investigator must be selected to sign the Clinical Study Report (CSR).

For each CSR related to this protocol, the following criteria will be used to select the Signatory Investigator:

SCIENTIFIC PUBLICATIONS

The data collected during this study are confidential and proprietary to the Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the Clinical Trial Agreement (CTAg) governing participation in the study. These requirements include, but are not limited to, submitting proposed publications to the Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTAg.

Scientific publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any Principal Investigator, sub-investigator, or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable participants with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND

3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who make the most significant contributions, as defined above, will be considered by BMS for authorship of the primary publication. Sub-investigators will generally not be considered for authorship in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

For secondary analyses and related publications, author list and author order may vary from primary to reflect additional contributions.

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:

An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation participant administered study treatment that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, electrocardiograms, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/serious adverse event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term.

Events NOT Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE, even if serious conditions are met.

SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death.
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below). NOTE: The following hospitalizations are not considered SAEs in Bristol-Myers Squibb (BMS) clinical studies: • A visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event). • Elective surgery, planned prior to signing consent. • Admissions as per protocol for a planned medical/surgical procedure. • Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy). • Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases. • Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason). • Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols).
Results in persistent or significant disability/incapacity.
Is a congenital anomaly/birth defect.
Is an important medical event (defined as a medical event[s] that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm and blood dyscrasias or convulsions that do not result in hospitalization. Potential drug-induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 for the definition of potential DILI.)

Pregnancy and DILI must follow the same transmission timing and processes to BMS as used for SAEs. (See Section 9.2.5 for reporting pregnancies.)

EVALUATING AES AND SAES

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- 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 study intervention administration, will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or product information for marketed products in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up 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.

- **Assessment of Intensity**

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Follow-up of AEs and SAEs

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term[s] initially reported.)

If an ongoing SAE changes in its intensity or relationship to study treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to BMS (or designee) immediately within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE data reporting is through the electronic case report form (eCRF).
  - The paper SAE Report Form is intended only as a back-up option when the electronic data capture system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile transmission.
    - When paper forms are used, the original paper forms are to remain on site.
- Pregnancies must be recorded on paper Pregnancy Surveillance Forms and transmitted via email or confirmed facsimile transmission.

SAE Email Address: [redacted]

SAE Facsimile Number: *Will be provided by local site monitor.*

SAE Telephone Contact (required for SAE and pregnancy reporting): *Will be provided by local site monitor.*

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

Appendix 4 provides general information and definitions related to Woman of Childbearing Potential and methods of contraception that can be applied to most clinical trials. For information specific to this study regarding acceptable contraception requirements for female and male participants, refer to the Methods of Contraception table in this appendix. Only the contraception methods that are highly effective (with a failure rate of < 1% per year), with low user dependency, are acceptable for this study.

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle-stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause.

Note: Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. Suggested guidelines for the duration of the washout periods for HRT types are presented below. Investigators should use their judgement in checking serum FSH levels.

- 1-week minimum for vaginal hormonal products (rings, creams, gels)
- 4-week minimum for transdermal products
- 8-week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal.

End of Relevant Systemic Exposure

End of relevant systemic exposure is the timepoint where the Investigational Medicinal Product (IMP) or any active major metabolites have decreased to a concentration that is no longer considered to be relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed-adverse-effect level or the time required for 5 half-lives of the IMP to pass.

METHODS OF CONTRACEPTION

Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are <u>User Dependent</u> *Failure rate of < 1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b] – Oral (birth control pills) – Intravaginal (rings) – Transdermal • Combined (estrogen-and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy.
• Progestogen-only hormonal contraception associated with inhibition of ovulation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b] – Oral – Injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy.
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b] • Intrauterine device.

- Intrauterine hormone-releasing system (IUS). (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b,c]
- Bilateral tubal occlusion.

- Vasectomized partner

Having a vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

- Sexual abstinence.

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

- Continuous abstinence must begin at least 30 days prior to initiation of study therapy.
- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participant chooses to forego complete abstinence.
- Periodic abstinence (including, but not limited to, calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study.

NOTES:

[a] Typical use failure rates may differ from failure rates when contraceptive methods are used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. For information specific to this study regarding permissibility of hormonal contraception, refer to .Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol.

[c] IUSs are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness. For information specific to this study regarding permissibility of hormonal contraception, refer to .Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol.

Less Than Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of > 1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously. • Diaphragm with spermicide. • Cervical cap with spermicide. • Vaginal sponge with spermicide. • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action. (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited.)
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, postovulation methods). • Withdrawal (coitus interruptus). • Spermicide only. • LAM.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of pregnancy information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5 and Appendix 3.

APPENDIX 5 CRITERIA TO DEFINE INADEQUATE RESPONSE (PRIMARY), LOSS OF RESPONSE (SECONDARY), AND INTOLERANCE TO PREVIOUS STANDARD OF CARE MEDICATION(S)

For any medication or treatment regimen that satisfies the inclusion criteria and is not described here, please contact the Clinical Trial Physician or designee.

It will be documented when the subject has had inadequate response, loss of response, or been intolerant to (eg, unable to achieve doses, dose levels, or treatment durations either because of treatment-related side effects and/or laboratory abnormalities) prior therapy.

Medication Class	Qualifying Criteria
Oral 5-ASAs	Any ONE (or more) of the following: Signs and symptoms of persistently active disease despite a history of at least one 4-week regimen at highest dose or per institutional practice Documented history of intolerance to oral 5-ASAs where subject developed adverse reactions including, but not limited to, headaches, nausea/vomiting, anorexia, abdominal pain, diarrhea, pericarditis, or pancreatitis
Corticosteroids (eg, oral prednisone, budesonide MMX, intravenous corticosteroids)	Any ONE (or more) of the following: Signs and symptoms of persistently active disease despite a history of at least one induction regimen of a corticosteroid for the treatment of CD for at least 2 weeks or per institutional practice Inability to stop steroids within 3 months without recurrent active disease Experienced a relapse requiring steroids within 3 months of stopping steroids At least 2 failed attempts to taper corticosteroids below a dose that is equivalent to oral prednisone 10 mg/day (or equivalent) or budesonide 3 mg/day (or equivalent) on 2 separate occasions (dosage regimen can be adjusted to accommodate mg/kg/day dosing as appropriate) Documented history of intolerance to corticosteroids where subject developed adverse reactions including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, cataracts, refractory steroid acne, or infection
Immunomodulators (eg, azathioprine, 6-mercaptopurine, cyclosporine, methotrexate)	Any ONE (or more) of the following: Signs and symptoms of persistently active disease despite a history of at least one 8-12 week regimen of immunomodulator given at a standard maintenance dose or per institutional practice History of intolerance to at least 1 immunomodulator where subject developed adverse reactions including, but not limited to, nausea/vomiting, abdominal pain, pancreatitis, liver function test abnormalities, lymphopenia, myelosuppression, or pancreatitis
Biologic therapy (eg, ustekinumab, abatacept, infliximab, etanercept, adalimumab, anakinra, rituximab, and vedolizumab)	Any ONE (or more) of the following: Signs and symptoms of persistently active disease despite an adequate study of induction treatment per country's approved label (if applicable) or per institutional practice Recurrence of symptoms during maintenance dosing following prior clinical benefit History of intolerance to at least 1 biologic therapy where subject developed adverse reactions including, but not limited to, infusion-related reaction, demyelination, congestive heart failure, development of anti-drug antibodies, infection, arthralgia, or liver test abnormalities

Medication Class	Qualifying Criteria
Other systemic immunomodulatory treatments for CD	Any ONE (or more) of the following: Signs and symptoms of persistently active disease despite an adequate study of induction treatment per country's approved label (if applicable) or per institutional practice Recurrence of symptoms during maintenance dosing following prior clinical benefit History of intolerance where participant developed adverse reaction(s)

APPENDIX 6 PEDIATRIC CROHN'S DISEASE ACTIVITY INDEX (PCDAI)

HISTORY (Recall, 1 week)

Abdominal pain: None _____(0)
Mild - Brief, does not interfere with activities _____(5)
Mod/severe-daily, longer lasting, affects activities, nocturnal _____(10)

Stools: (per day)
0-1 liquid stools, no blood _____(0)
Up to 2 semi-formed with small blood, or 2-5 liquid _____(5)
Gross bleeding, or ≥ 6 liquid, or nocturnal diarrhea _____(10)

Patient Functioning, General Well-Being (Recall, 1 week)

No limitation of activities, well _____(0)
Occasional difficulty in maintaining age appropriate activities, below par _____(5)
Frequent limitation of activity, very poor _____(10)

LABORATORY

HCT (%)	≤10 yrs:	>33	___(0)	11-14M:	≥35	___(0)
		28-32	___(2.5)		30-34	___(2.5)
		<28	___(5)		<30	___(5)
	11-19F:	≥34	___(0)	15-19M:	≥37	___(0)
		29-33	___(2.5)		32-36	___(2.5)
		<29	___(5)		<32	___(5)

ESR (mm/hr) <20 _____(0)
20-50 _____(2.5)
>50 _____(5)

Albumin (g/dL) ≥3.5 _____(0)
3.1-3.4 _____(5)
≤3.0 _____(10)

EXAMINATION

Weight

Weight gain or voluntary weight stable/loss _____(0)
Involuntary weight stable, weight loss 1-9% _____(5)
Weight loss ≥ 10% _____(10)

Height

At Diagnosis:
<1 channel decrease _____(0)
≥1, <2 channel decrease _____(5)
>2 channel decrease _____(10)
or

Follow-up:*
Height velocity ≥-1SD _____(0)
Height velocity <-1SD, >-2SD _____(5)
Height velocity ≤-2SD _____(10)

Abdomen

No tenderness, no mass _____(0)
Tenderness, or mass without tenderness _____(5)
Tenderness, involuntary guarding, definite mass _____(10)

Perirectal disease

None, asymptomatic tags _____(0)
1-2 indolent fistula, scant drainage, no tenderness _____(5)
Active fistula, drainage, tenderness, or abscess _____(10)

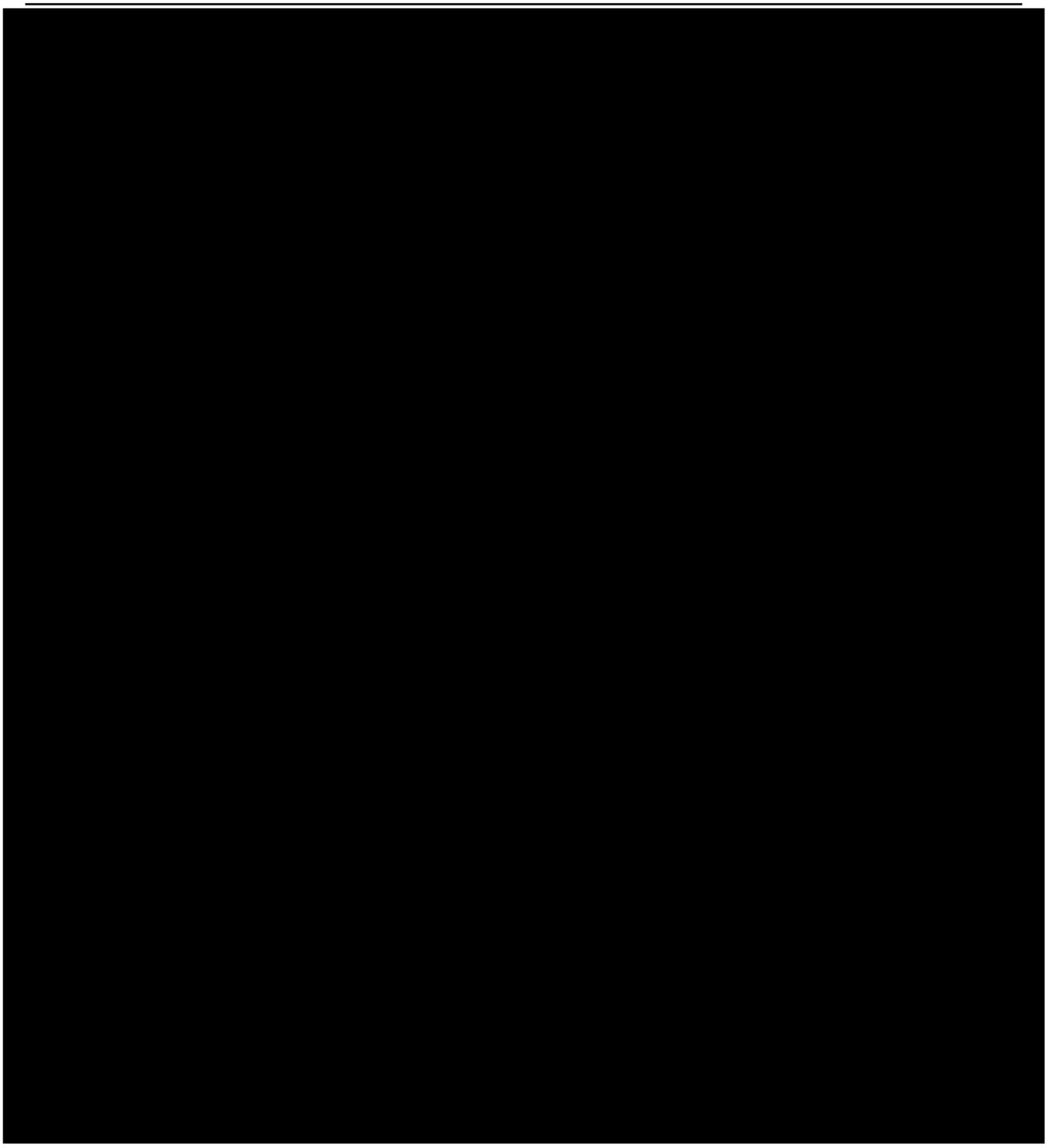
Extra-intestinal Manifestations

(Fever ≥38.5 for 3 days over past week, definite arthritis, uveitis, E.nodosum, P. gangrenosum)
None _____(0)
One _____(5)
≥ Two _____(10)

TOTAL SCORE _____

Source: Hyams JS, Ferry GD, Mandel FS, et al. Development and validation of a pediatric Crohn's disease activity index. J Pediatr Gastroenterol Nutr 1991;12:439-47.

Note: The abdominal pain, stool frequency and general wellbeing scores from the week prior to each study visit will be used to calculate the PCDAI. If the subject is undergoing a planned colonoscopy, the day(s) of bowel preparation should be excluded from consideration.



APPENDIX 9 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 01, 22-Dec-2022

The main rationale for this amendment is to update the inclusion criteria to (a) allow for positive varicella zoster virus (VZV) antibody titers to help fulfill the vaccination requirement and (b) update the drug clearance period for prior biologics from 8 weeks to 4 weeks. The table below highlights the key changes made to the protocol. Additional revisions as outlined below, including to sections of the Protocol Summary, have been made to ensure alignment throughout the protocol.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01

Section Number & Title	Description of Change	Brief Rationale
Title Page	• Added Celgene International II Sàrl telephone number • Updated Clinical Trial Physician contact details	• Administrative changes

[redacted]

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01

Section Number & Title	Description of Change	Brief Rationale
[redacted]		
Section 3.1.1: Summary of Nonclinical Studies	• Revised text regarding juvenile toxicity studies	• Updated based on additional data available and to align with the Investigator's Brochure
Section 3.3.1: Risk Assessment	[redacted]	[redacted]

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01

Section Number & Title	Description of Change	Brief Rationale
Section 5.1: Overall Design	• Removed the following statement: "The final decision to discontinue the participant early for entry into the LTE Period will be left to the discretion of the investigator."	• Treatment discontinuation parameters must be followed per the Sponsor guidance in the best interest of the participant
	• Moved study discontinuation language to the study discontinuation section	• Statement moved to appropriate section within the protocol for clarity
Section 6.1: Inclusion Criteria	• Inclusion criterion (IC) #2b: Modified text regarding local histopathology sample collection	• To allow for the collection of local histology samples for disease confirmation
	• IC #2f: Added documentation of positive VZV IgG antibody	• In addition to documentation of varicella vaccination, positive VZV antibody titers are also considered an acceptable form of immunity and can be used to help fulfill the vaccination requirement for eligibility
	• IC #4: Removed text regarding counseling of male participants that are sexually active with females of childbearing potential	• Counseling is unnecessary, as there are no safety concerns regarding reproductive status of male participants following studies on male reproductive effects
Section 6.2: Exclusion Criteria	• Exclusion criterion (EC) #1j: Added a positive urine pregnancy testing on Day 1	• Clarified that participants are not eligible for participation if pregnant on Day 1
	• EC #1p: Added documented evidence of surveillance for polyps, dysplasia, or malignancy in the last 2 years or per local and national medical guidelines	• Clarified cancer surveillance guidelines, given the risk of colorectal cancer in this population
	• EC #3c: Shortened the time required between treatment with a biologic agent and the first dose of study treatment	• Given the risks associated with immune suppression and treatment parameters used in clinical practice, the proposed timeframe optimizes the treatment-free period between the previous line of therapy and the current study
Section 6.4.1	• Added language to allow for use of prior colonoscopies	• To align with inclusion criteria
Section 7.2: Method of Study Intervention Assignment	• Added the option for an age range for consent/assent, per local or country guidelines	• Age ranges for informed consent form and assent signatures may be governed by local or country regulations
Section 7.3: Blinding	• Removed text regarding shipping of randomization schedules to, blinding, and involvement in study conduct of pharmacist or other individual responsible for the dispensing of blinded study treatment	• Sites are not required to have any unblinded site staff
Section 7.7.1: Steroid Taper	• Revised instructions for steroid tapering	• Steroid taper can be initiated prior to the end of induction given the potential safety issues with steroid use in children

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01

Section Number & Title	Description of Change	Brief Rationale
Section 7.7.2: Prohibited and/or Restricted Treatments	• Added post-baseline initiation or increase in systemic corticosteroids during Induction or Maintenance Periods, and increase in systemic corticosteroids > 40 mg/day prednisone or equivalent during LTE	• For consistency throughout protocol
	• Clarified that systemic immunomodulatory agents are prohibited and/or restricted during the study	• To clarify that topical use is allowed during the study
	• Added systemic corticosteroid doses for specific weight groups	• Clarification
Section 8.1: Discontinuation From Study Intervention	• Removed requirement for treatment discontinuation for participants meeting any of the criteria for treatment failure during the Induction Period	• Participants who meet treatment failure criteria may continue in the Open-label Extension (OLE) Period of the study
	• Removed the following sentence: "Participants receiving any medical or surgical intervention for the treatment of Crohn's Disease that meet the criteria for treatment failure [redacted] during the Induction period will be discontinued from the study and will not be eligible for the LTE Period."	• Participants who meet treatment failure criteria may continue in the OLE Period of the study
	• Added systemic corticosteroid doses for specific weight groups	• Clarification
Section 9: Study Assessments and Procedures	• Clarified that therapeutic drug monitoring (TDM) will be performed locally	• TDM can be used to confirm drug levels (for prior biologic use) and will be performed locally by the site
	• Modified to lengthen the window for endoscopy for the assessment of efficacy at [redacted]	• To allow for flexibility in scheduling
	• Clarified that follow-up is required for all participants who received ≥ 1 dose of study treatment	• Clarification of participants who require follow-up visits
	• [redacted]	• Clarification of the criteria by which participants may enter the LTE Period
	• Added systemic corticosteroid doses for specific weight groups	• Clarification
Section 9.2.5	• Removed requirement tracking pregnancies in female partners of male participants	• Estimation of semen levels and vaginal absorption were performed, and clinically meaningful exposures were not achieved. In addition, the Sponsor has not observed any increased risk in the pregnancy outcomes for female partners of male subjects.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01

Section Number & Title	Description of Change	Brief Rationale
[redacted]		
Section 9.4.11: Clinical Safety Laboratory Assessments	• Revised the roles of central and local laboratories and related requirements	• Data from the central laboratory will be used for analysis, but local laboratories may be used, if needed, under specific circumstances
Section 9.4.11.1: Hematology	• Added that alerts for out-of-range values will be flagged for the site while keeping the numerical results blinded	• Although white blood cell counts and differentials are blinded given the pharmacodynamic effect of ozanimod on absolute lymphocyte counts, sites will be alerted to follow-up on out-of-range values
	• Added instruction to contact the Clinical Trial Physician/Medical Monitor if the participant's hemoglobin level is ≤ 7.0 g/dL during the study	• The stipulation for hemoglobin level to be maintained above 7.0 d/dL has been previously noted in the eligibility criteria. The instruction to contact the Clinical Trial Physician/Medical Monitor for discussion has been added to this section to reinforce the need to monitor participants throughout the study for safety reasons.
Section 9.4.11.3: Serology	• Added testing for VZV antibody titer	• Titers can be tested to fulfill the vaccination requirement for eligibility
[redacted]		

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Appendix 2: Study Governance Considerations	• Added 2 new sections: "BMS Commitment to Diversity in Clinical Trials" and "Data Protection, Data Privacy, and Data Security"	• To align the protocol with BMS' commitment to diversity and the European Union Clinical Trials Register
Throughout the protocol	• Clarified that randomization and Day [redacted] are the same • Changed the term "subject" to "participant" • Added "oral" to budesonide and beclomethasone references for clarity • Minor editorial and formatting changes that do not affect content	• Clarifications