Official Title of Study:

A Phase 4, Prospective, Open-label Study of Ozanimod to Explore the Safety, Efficacy, Quality of Life, and Biomarker Response in Participants with Moderate to Severe Ulcerative Colitis in Clinical Practice

NCT Number: NCT05369832

Document Date (Date in which document was last revised): 22-Aug-2022

# CLINICAL PROTOCOL IM047029

A Phase 4, Prospective, Open-label Study of Ozanimod to Explore the Safety, Efficacy, Quality of Life, and Biomarker Response in Participants with Moderate to Severe Ulcerative Colitis in Clinical Practice

**Brief Title:**

Open-label study of ozanimod in moderate to severe UC in clinical practice.

**Protocol Amendment 01**

[redacted]
Clinical Trial Physician-Medical Monitor
Bristol-Myers Squibb Company
3401 Princeton Pike Lawrenceville, NJ 08648
Phone [redacted]
email: [redacted]

[redacted]
Clinical Scientist
Bristol-Myers Squibb Company
3401 Princeton Pike Lawrenceville, NJ 08648
Phone [redacted]
email: [redacted]

**24-hr Emergency Telephone Number**
USA: 1-866-470-2267
International: +1-248-844-7390

**Celgene International II Sàrl**
Route de Perreux 1
2017 Boudry, Switzerland

## REGULATORY AGENCY IDENTIFIER NUMBER(S)

IND: 115243
EudraCT Number: 2022-001382-12
UTN: U1111-1276-5969

**study. Any permitted disclosures will be made only on a confidential "need to know" basis within your organization or to your independent ethics committee(s). Any other use, copying, disclosure or dissemination of this information is strictly prohibited unless expressly authorized in writing by BMS. Any supplemental information (eg, amendments) that may be added to this document is also confidential and proprietary to BMS and must be kept in confidence in the same manner as the contents of this document. Any person who receives this document without due authorization from BMS is requested to return it to BMS or promptly destroy it. References to BMS in this protocol may apply to partners to which BMS has transferred obligations (eg, a Contract Research Organization [CRO]).**

## DOCUMENT HISTORY

| Document | Date of Issue | Summary of Change |
|---|---|---|
| Protocol Amendment 01 | 22-Aug-2022 | • Removed the term "global" from the protocol title.<br>• Study duration reduced from 3 years to 2 years, correspondingly time points for additional endpoints common for both Cohort 1 and Cohort 2 after Week 26 (Table 4-3) have been adjusted.<br>• Revised number of participants in Cohort 1 from 200 to 150.<br>• Revised number of participants in Cohort 2 from 150 to 100.<br>• Revised Figure 5.1-1 (Study Design Schema) to reflect 2-year study duration and revised number of participants.<br>• Revised inclusion criterion 2b: Participants must have moderate to severely active UC, defined as a score of 4 through 9 on the 9-point modified Mayo score and an SF subscore ≥ 1 in order to enter the treatment period.<br>• Included a new inclusion criterion 5b: Biologic agents should be discontinued at least 8 weeks prior or at least 5 elimination half lives prior to study intervention initiation, whichever is shorter. Washout period may be waived with the demonstration of absent drug levels on a TDM assay.<br>• Renumbered inclusion criterion 5b to 5c and revised: Added 3 different criteria related to 6-marcaptourine/AZA or methortrexate.<br>• Revised inclusion criterion 7a-ii: WOCBP must have a negative pregnancy test during the screening process.<br>• Removed exclusion criterion 2g: UC involving the rectum only (UC proctitis).<br>• Deleted PK analysis throughout the protocol.<br>• In the SOA the following changes were made:<br>o Table 2-1: Deleted visit at Week 39 and 78; added Demographics and Subject Characteristics at baseline<br>o Table 2-2: Deleted the entire Year 3 time points.<br>o [redacted]<br>o [redacted]<br>o Revised notes for CBC and Differential Count, Biochemistry, Pregnancy Test, and Stool Collection.<br>o Revised legend notes, as needed.<br>• Revised Table 7.1-1: Packaging and labeling details of ozanimod have been updated. |

| Document | Date of Issue | Summary of Change |
|---|---|---|
| | | • Revised Table 7.7-1: Updated washout period for immunomodulatory drugs to 1 day and aligned details about biologic agents with inclusion criterion 5b.<br>• Study intervention discontinuation criterion (Section 8.1) related to laboratory abnormalities has been revised.<br>• Treatment interruption criteria (Section 8.1.1) has been revised.<br>• Laboratory test result abnormalities for ALC (Section 9.2.6) has been revised.<br>• [redacted]<br>• [redacted]<br>• Minor administrative and editorial changes were made throughout the protocol.<br>• Text in the protocol summary has been updated to maintain consistency and to align the text with that in the main body. |
| Original Protocol | 31-Mar-2022 | Not applicable |

**SPONSOR: CELGENE INTERNATIONAL II SÀRL**

**Celgene International II Sàrl Signature Page**

[redacted]

Signature DDMMYYYY

[redacted]

Printed Name of Celgene International II Sàrl

## OVERALL RATIONALE FOR PROTOCOL AMENDMENT 01:

The primary reason for Protocol Amendment 01 is to clarify study duration, participants in both cohorts, revision of inclusion/exclusion criteria, [redacted] References to Global were deleted throughout the protocol and in the title. Clarifying information and administrative changes were made.

These changes pertain to all participants.

| SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01 | | |
|---|---|---|
| **Section Number & Title** | **Description of Change** | **Brief Rationale** |
| All | Removed the term "global" from the protocol title. | Study has been reduced to USA-only. |
| All | Study duration reduced from 3 years to 2 years, correspondingly time points for additional endpoints common for both Cohort 1 and Cohort 2 after Week 26 (Table 4-3) have been adjusted. | Duration reduced due to operational feasibility assessment, whilst maintaining the scientific integrity of the study. |
| All | Revised number of participants in Cohort 1 from 200 to 150. | Duration reduced due to operational feasibility assessment, whilst maintaining scientific integrity of the study. |
| All | Revised number of participants in Cohort 2 from 150 to 100. | Duration reduced due to operational feasibility assessment, whilst maintaining scientific integrity of the study. |
| Section 5.1: Overall Design | Revised Figure 5.1-1<br>Revised Study Design Schema to reflect the 2-year study duration and revised number of participants. | Reflect above rationale. |

| SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01 | | |
|---|---|---|
| **Section Number & Title** | **Description of Change** | **Brief Rationale** |
| Section 6.1: Inclusion Criteria | Revised inclusion criterion 2b: Participants must have moderate to severely active UC, defined as a score of 4 through 9 on the 9-point modified Mayo score and an SF subscore ≥ 1 in order to enter the treatment period. | Broaden scope of study to include more moderate activity patients by reducing lower Mayo limit to 4-9 points (from 5-9 points). |
| Section 6.1: Inclusion Criteria | Added a new inclusion criterion 5c: Biologic agents should be discontinued at least 8 weeks prior or at least 5 elimination The washout prior to study intervention initiation, whichever is shorter. The washout period may be waived with the demonstration of absent drug levels on a TDM assay. | Given different half-lives of biologics, it is important to address and offer a washout of at least 5 elimination half-lives prior to intervention" for agents with short half-lives to be used sooner. |
| Section 6.1: Inclusion Criteria | Added 3 different criteria related to 6-marcaptourine/AZA or methortrexate. | Clarify use of 6-MP/azathioprine prior to study entry. |
| Section 6.1: Inclusion Criteria | Revised inclusion criterion 7a-ii: WOCBP must have a negative pregnancy test during the screening process. | Clarify timing for negative pregnancy test prior to initiating study treatment. |
| Section 6.2: Exclusion Criteria | Removed exclusion criterion 2g: UC involving the rectum only (UC proctitis). | Amendment to include proctitis patients in the trial. |
| All | Deleted PK analysis throughout the protocol. | Duration reduced due to operational feasibility assessment, whilst maintaining scientific integrity of the study. |

| SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01 | | |
|---|---|---|
| **Section Number & Title** | **Description of Change** | **Brief Rationale** |
| Section 2: Schedule of Activities | In the SOA the following changes were made:<br>Table 2-1: Deleted visit at Week 39 and 78; added Demographics and Subject Characteristics at baseline.<br>Table 2-2: Deleted the entire Year 3 time points.<br>[redacted]<br>Revised notes for CBC and Differential Count, Biochemistry, Pregnancy Test, and Stool Collection.<br>Revised legend notes, as needed. | Edit SOA to align with alterations as detailed above. |
| Section 7.1: Study Interventions Administered | Revised Table 7.1-1: Packaging and labeling details of ozanimod have been updated. | To align with singular (US) market. |
| Section 7.7.1: Prohibited and/or Restricted Treatments | Revised Table 7.7-1: Updated washout period for immunomodulatory drugs to 1 day and aligned details about biologic agents with inclusion criterion 5b. | To align with protocol from prior ozanimod trials, including True North trial. |
| Section 8.1: Discontinuation from Study Intervention | Study intervention discontinuation criterion (Section 8.1) related to laboratory abnormalities has been revised. | Clarify lab abnormalities that may lead to treatment discontinuation. |
| Section 8.1.1: Treatment interruption | Treatment interruption criteria (Section 8.1.1) has been revised. | Clarify recommended actions in the setting of interrupted treatment |

| SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01 | | |
|---|---|---|
| **Section Number & Title** | **Description of Change** | **Brief Rationale** |
| Section 9.2.6: Laboratory Test Result Abnormalities | Laboratory test result abnormalities for ALC (Section 9.2.6) has been revised. | Clarify any lab abnormalities that may be seen as reason to signify an AE |
| [redacted] | | |
| All | Minor administrative and editorial changes were made throughout the protocol. | Minor, therefore, have not been summarized. |
| Section 1: Protocol Summary | Text in the protocol summary has been updated to maintain consistency and to align the text with that in the main body. | As per rationale above. |

# TABLE OF CONTENTS

# 1 PROTOCOL SUMMARY

**Protocol Title:**

**A Phase 4, Prospective, Open-label Study of Ozanimod to Explore the Safety, Efficacy, Quality of Life, and Biomarker Response in Participants with Moderate to Severe Ulcerative Colitis in Clinical Practice**

**Brief Title: Open -label study of ozanimod in moderate to severe UC in clinical practice**

**Rationale:**

This prospective, open-label, Phase 4 study is designed to explore the safety, efficacy, effects on quality of life (QOL), and biomarker response of ozanimod (Zeposia®, RPC1063, BMS-986374) in participants with moderate to severely active ulcerative colitis (UC) in clinical practice.

The study population will be consistent with the product label, so that this study may generate data that are directly relevant to the labeled indication and that may be used to further inform the clinical use of ozanimod in this study population.

The study will include 2 cohorts:

- **Cohort 1:** Participants with moderate to severely active UC who have not been exposed to biologics or immunomodulators for the treatment of UC (ie, advanced therapy-naïve).
- **Cohort 2:** Participants with moderate to severely active UC who have been exposed to a single mechanism of action of biologics for the treatment of UC (ie, advanced therapy-exposed).

This study will generate additional data on the effect of ozanimod treatment, including (but not limited to) the following:

- Characterization of early response (improvement in signs and symptoms of UC within the first 4 weeks), including rectal bleeding (RB), stool frequency (SF), urgency, and abdominal symptoms.
- Characterization of the endoscopic and histologic response to ozanimod at Week 12 in an advanced therapy-naïve cohort.
- Characterization of the endoscopic and histologic response to ozanimod at Week 26 in an advanced therapy-exposed cohort.
- Characterization of the long-term safety of ozanimod over the duration of the study.
- Patient-reported outcome (PRO) measures, including impact on disease-specific QOL and symptoms, fatigue, patient satisfaction with treatment, and work productivity.
- Characterization of the effect of ozanimod treatment on biomarkers of disease activity used in clinical practice, [redacted]

## Objectives and Endpoints:

### Specific to Advanced Therapy-naïve Cohort (Cohort 1)

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To explore the efficacy of ozanimod in inducing clinical response in the advanced therapy-naïve cohort. | • Clinical response at Week 12, as measured by modified Mayo score. |
| **Secondary** | |
| • To explore the efficacy of ozanimod in the advanced therapy-naïve cohort. | • Clinical remission at Week 12, as measured by modified Mayo score.<br>• Endoscopic response at Week 12.<br>• Endoscopic improvement at Week 12.<br>• Histological improvement at Week 12. |
| • To explore the effects of ozanimod on disease-specific health-related quality of life (HRQOL) in the advanced therapy-naïve cohort. | • Change in the Inflammatory Bowel Disease Questionnaire (IBDQ) total score from baseline to Week 12.<br>• IBDQ response (change in total score [≥ 16 points] from baseline to Week 12).<br>• IBDQ remission (total score [≥ 170 points]) at Week 12. |

### Specific to Advanced Therapy-exposed Cohort (Cohort 2)

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To explore the efficacy of ozanimod in inducing clinical response in the advanced therapy-exposed cohort. | • Clinical response at Week 26, as measured by modified Mayo score. |
| **Secondary** | |
| • To explore the efficacy of ozanimod in the advanced therapy-exposed cohort. | • Clinical remission at Week 26, as measured by modified Mayo score.<br>• Endoscopic response at Week 26.<br>• Endoscopic improvement at Week 26.<br>• Endoscopic remission at Week 26.<br>• Histological improvement at Week 26.<br>• Histological remission at Week 26.<br>• Change in the IBDQ total score from baseline to Week 26.<br>• IBDQ response (change in total score [≥ 16 points] from baseline to Week 26).<br>• IBDQ remission (total score [≥ 170 points]) at Week 26.<br>• Corticosteroid-free clinical remission at Week 26, as measured by modified Mayo score. |

| Objectives | Endpoints |
|---|---|
| | • Histo-endoscopic mucosal improvement (HEMI) at Week 26 |

**Additional Objectives and Endpoints Common for both the Advanced Therapy-naïve Cohort (Cohort 1) and the Advanced Therapy-exposed Cohort (Cohort 2) after Week 26**

| Objectives | Endpoints |
|---|---|
| **Secondary** | |
| • To explore the safety and tolerability of ozanimod in the advanced therapy-naïve cohort and the advanced therapy-exposed cohort. | • Number and proportion of participants experiencing the following:<br>– Adverse events (AEs).<br>– Serious adverse events (SAEs).<br>– AEs and SAEs, including adverse event of interest (AEIs) and other select AEs, leading to discontinuation from study intervention and the study.<br>– Clinical laboratory values. |
| • To explore the long-term durability of response to ozanimod in the advanced therapy-naïve cohort and the advanced therapy-exposed cohort. | • Clinical remission by partial Mayo score at Weeks 52 and 104<br>• Corticosteroid-free clinical remission by partial Mayo score at Weeks 52 and 104.<br>• Clinical response by partial Mayo score at Weeks 52 and 104. |

**Overall Design:**

Study IM047-029 is a Phase 4, prospective, non-randomized, open-label, multicenter clinical study designed to explore the safety, efficacy, effects on QOL, and biomarker response of ozanimod 0.92 mg once daily (QD) per oral (PO) administration in participants with moderate to severely active UC in clinical practice.

This clinical study will evaluate ozanimod 0.92 mg QD PO in multiple UC disease subtypes, and with 2 specific cohorts as described above.

Participants will undergo screening evaluations to determine eligibility as indicated in the Schedule of Activities (SOA; see Table 2-1). Participants must meet the eligibility criteria in order to enter the treatment period (see Section 6). Participants must have moderate to severely active UC, defined as a score of 4 through 9 on the 9-point modified Mayo score, in order to enter the treatment period.

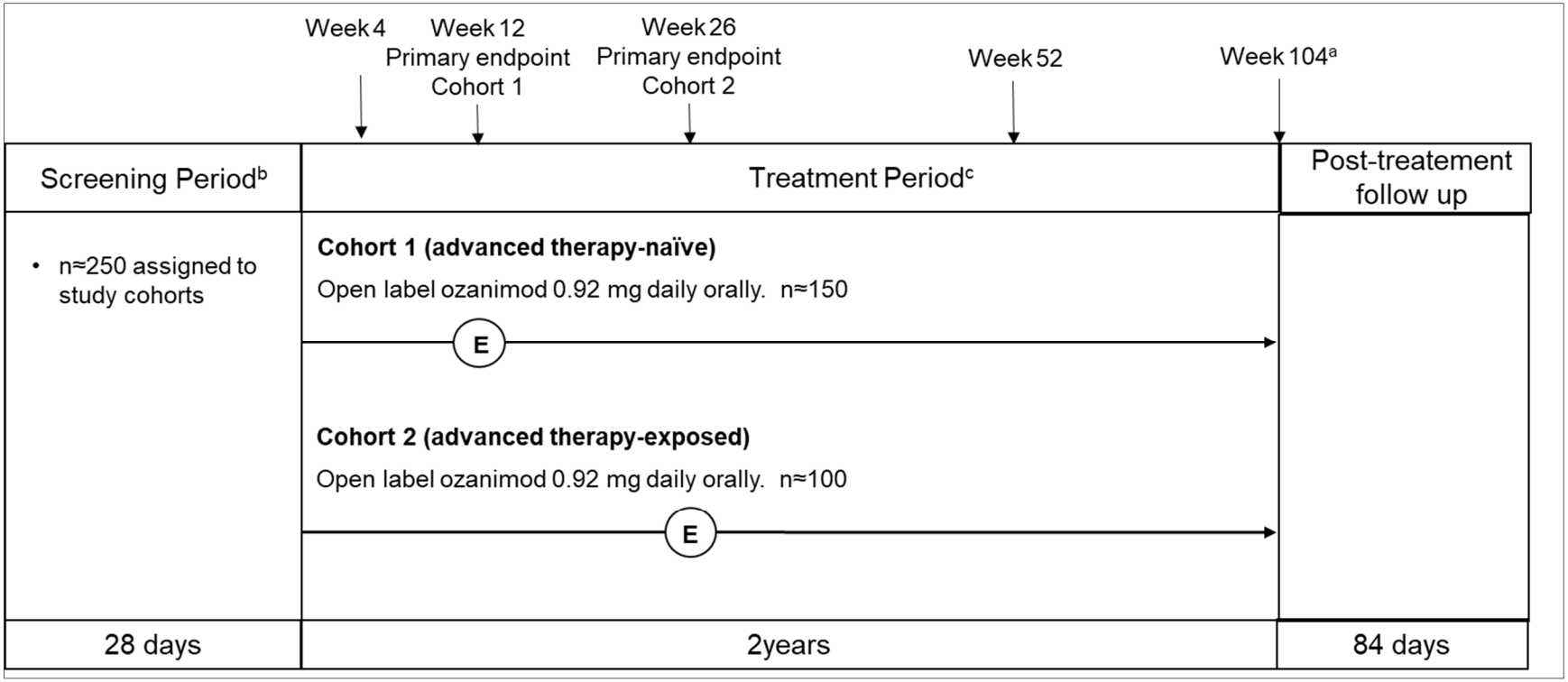
Eligibility assessments, physical examinations, additional screening tests, electronic diary dispensing and review, blood, stool, and urine sample collections, [redacted] endoscopies with biopsies, additional efficacy assessments, PRO and HRQOL assessments, healthcare resource utilization, investigational product (IP) supply, safety

assessments, and other study procedures will be performed as indicated in the SOA (see Table 2-1, Table 2-2).

All eligible participants will receive open-label ozanimod 0.92 mg QD PO, per product label, during the treatment period (see Table 7.1-1). Ozanimod titration will occur during the first 7 days of study intervention exposure, per label (see Table 7.1-2). Once the study intervention (ie, ozanimod) has been titrated up to 0.92 mg QD PO (Day 8), further dose escalation is not allowed.

The study design schematic is presented in Figure 1.

**Figure 1: Study Design Schema**




E, endoscopies and biopsies; EDC, electronic data capture; ES, endoscopic subscore; EOT, end of treatment.

[a] For participants who prematurely discontinue from the study, if possible, the EOT visit and follow-up visit should be conducted so that data can be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

[b] Screening endoscopy (colonoscopy or sigmoidoscopy) may be performed within 60 days prior to the first study intervention administration. Photographic evidence of ES ≥2 must be available for study inclusion, as per eligibility criteria. In the event that historic endoscopic data is used as a part of screening, historic histopathologic tissue will not be collected.

[c] Ozanimod titration will occur during the first 7 days of study intervention exposure, per label (Table 7.1-2). Participants will receive a phone call on Day 5 (when titrating their dose from 0.23 mg to 0.46 mg) and again on Day 8 (when titrating their dose from 0.46 mg to 0.92 mg) as a reminder about the dose adjustment. If required, an unscheduled visit can be planned anytime during the treatment period. Data regarding study procedures conducted at such unscheduled visits (eg, blood, stool, and urine tests; safety assessments) will be documented in the EDC tool.

**Number of Participants:**

It is estimated that approximately 250 screened participants in Cohort 1 (advanced therapy-naïve cohort) will be required to achieve 150 treated participants. Similarly, for Cohort 2 (advanced therapy-exposed cohort), it is estimated that approximately 165 participants will be required to achieve 100 treated participants. These enrollment estimates assume a screen failure rate of approximately 40% in each cohort.

If the screen failure rate is higher than expected, enrollment will remain open until the required number of treated participants in each cohort is achieved.

The sample size for this study is not based on statistical power for comparisons among treatment cohorts; it has been selected to minimize the width of the 95% confidence interval (CI) of the estimate of the clinical response rate (primary endpoint) for each.

**Study Population:**

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

**Key Inclusion Criteria**

- Participant must be over 18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place) at the time of signing the informed consent.
- A diagnosis of UC, with signs and symptoms consistent with UC for at least 3 months prior to the first study intervention administration.
- Moderate to severely active UC disease activity, defined as a modified Mayo score of 4 through 9, inclusive, with the following minimum subscores:
  - An SF subscore ≥ 1, AND
  - An RB subscore ≥ 1, AND
  - An endoscopic subscore (ES) ≥ 2 (endoscopy performed within 60 days of the first study intervention administration).
- In order to participate in Cohort 1 (advanced therapy-naïve cohort), a participant must meet the eligibility criteria outlined in this inclusion criterion (IC) and must not meet the eligibility criteria for Cohort 2.
  - Participants must be naïve to 6-mercaptopurine/azathioprine (AZA) and any biologics (see IC 5[a]) in Section 6.1 for list) for any other medical indication, as well as UC.
- In order to participate in Cohort 2 (advanced therapy-exposed cohort), a participant must have failed only one mechanism of action of biologics.
  - Documentation of an inadequate response, loss of response, or intolerance to a treatment course of one class of approved biologics (see IC 5[a]) in Section 6.1 for list) and should not have been treated with additional classes of approved biologics.
  - 6-mercaptopurine/AZA or methotrexate:
    - Participant may have been previously treated with 6-mercaptopurine/AZA or methotrexate.

- Participant may not take these agents concomitantly over the course of the study.
- These agents must be discontinued prior to day of starting study intervention.

- **Key Exclusion Criteria**
- Medical conditions, including the following:
  - Recent (within 6 months of screening) myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or New York Heart Association Class III/IV heart failure.
  - Presence of Mobitz type II second- or third-degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial block, unless the participant has a functioning pacemaker.
  - Severe untreated sleep apnea.
  - Current macular edema. (Note: Participants with diabetes, or a history of uveitis, retinal disease, or previous macular edema must have an ophthalmic evaluation of the fundus, including the macula, prior to the first study intervention administration.)
  - Current active infection, and/or any infection requiring oral antibiotics within 14 days of screening, or intravenous (IV) antibiotics within 30 days of screening.
  - Any major infection that required hospitalization.
  - Immunodeficient state (not including previously mentioned immunosuppressants) leading to increased risk of opportunistic infections.
  - A history of cancer within 5 years, including solid tumors and hematological malignancies (except basal cell carcinoma or squamous cell carcinoma of the skin that have been fully treated, or cervical dysplasia or carcinoma in situ that have been fully treated).
  - Severe hepatic impairment (Child-Pugh Class C).
- Participant has a current diagnosis of Crohn's disease (CD), indeterminate colitis, radiation colitis or ischemic colitis, a monogenic cause of UC-like intestinal inflammation, colonic diverticulitis, or an alternative diagnosis that explains their colonic inflammation.
- Current or recent (within 3 months of screening) evidence of fulminant colitis, toxic megacolon, or bowel perforation.
- Current need for, or anticipated need for, surgical intervention for UC during the course of the study.
- Extensive colonic resection or current stoma.
- Colonic dysplasia that has not been removed.
- Previous or current use of Janus kinase (JAK) inhibitors (eg, tofacitinib, filgotinib).
- Hypersensitivity to active ingredients or excipients of ozanimod.

**Intervention Cohorts and Duration:**

Intervention cohorts and study duration are described in the study rationale and overall design sections above.

**Study Intervention:**

| Study Intervention for IM047029 | |
|---|---|
| **Medication** | **Potency** |
| Ozanimod (Zeposia) | 0.23 mg, 0.46 mg, and 0.92 mg |

**Statistical Methods:**

Due to the open-label design of the study and the lack of a control group, all data will be summarized, and no hypothesis testing will be performed.

Baseline is defined as the last observed measurement prior to the first dose of study intervention on Day 1.

In general, descriptive summaries will be presented for the efficacy and safety variables collected. Continuous variables will be summarized using the number of participants (n), mean, standard deviation, minimum, median, and maximum. Categorical variables will be summarized using frequency counts and percentages and 95% CIs.

The primary endpoint for Cohort 1 is the proportion of participants who achieve a clinical response at Week 12. The clinical response rate at Week 12 will be estimated, and the corresponding 95% CI will be derived based on the Clopper Pearson method.

The primary endpoint for Cohort 2 is the proportion of participants who achieve clinical response at Week 26. An estimate of the clinical response rate at Week 26 will be provided along with the corresponding 95% CI derived based on the Clopper Pearson method.

The primary endpoint analysis will be performed when all participants in both cohorts have completed the primary endpoint visit (ie, Week 12 for Cohort 1 and Week 26 for Cohort 2). The statistical analysis plan (SAP) will describe the planned interim analyses in greater detail.

For proportion-based efficacy endpoints, patients with missing Week 12 efficacy data from Cohort 1 and/or participants with missing Week 26 efficacy data from Cohort 2 will be considered non-responders, and non-responder imputation will be used. Sensitivity analyses around missing data may involve missing data imputed using multiple imputation and may analyze observed cases with no imputation. Details of the sensitivity analysis will be provided in the SAP.

For continuous efficacy endpoints, observed cases will be analyzed with no imputation.

**Data Monitoring Committee:** No

**Other Committee:** No

**Brief Summary:**

The purpose of this study is to explore the safety, efficacy, effects on QOL, and biomarker response of ozanimod in participants with moderate to severely active UC in clinical practice. Study details include the following:

Study Duration: Approximately 2.4 years

Study Intervention Duration: 2 years

Study Visit Frequency: Participants will have clinic visits as follows:

- Year 1: Screening, Day 1, Week 4 (± 7 days), Week 12 (± 7 days), Week 26 (± 7 days), Week 52 (± 14 days).
- Years 2: Week 104 (± 14 days), Week 116 ( ± 14 days)

# 2 SCHEDULE OF ACTIVITIES

The Schedule of Activities (SOA) for the screening and initial on-treatment study period is provided in Table 2-1. The SOA for the on-treatment period beyond Week 52 is provided in Table 2-2.

**Table 2-1: Schedule of Activities for Year 1 (IM047029)**

| Procedure | Screening (Days -28 to -1) | Week 0 (Day 1) | Week 4 (Day 28) | Week 12 (Day 84) | Week 26 (Day 182) | Week 52 (Day 365) | Unscheduled[a] | Notes |
|---|---|---|---|---|---|---|---|---|
| **Visit Window (± n Days)** | | | 7 | 7 | 7 | 14 | | |
| **Eligibility Assessments** | | | | | | | | |
| Informed Consent | X | | | | | | | See APPENDIX 2 |
| Obtain Participant Number | X | | | | | | | |
| Medical History | X | | | | | | | |
| UC Disease History | X | | | | | | | |
| Prior Medications | X | X | | | | | | |
| Concomitant Medications | X | X | X | X | X | X | | Assessments after screening for change in concomitant medications (see Section 7.7) |
| UC Medications | X | X | X | X | X | X | | |
| Tobacco / e-cigarette Use | X | X | X | X | X | X | | Assessments after screening for change in use |
| Review Eligibility Criteria | X | | | | | | | See Section 6 for details |
| **Physical Examination** | | | | | | | | See Section 9.5.1 for details |
| Weight | X | X | | X | X | X | | |
| Height | X | | | | | | | |
| Vital Signs (HR, BP, Temperature [°C]) | X | X | X | X | X | X | | |
| Complete Physical Examination | X | | | X | X | X | | |

**Table 2-1: Schedule of Activities for Year 1 (IM047029)**

| Procedure | Screening (Days -28 to -1) | Week 0 (Day 1) | Week 4 (Day 28) | Week 12 (Day 84) | Week 26 (Day 182) | Week 52 (Day 365) | Unscheduled[a] | Notes |
|---|---|---|---|---|---|---|---|---|
| **Visit Window (± n Days)** | | | 7 | 7 | 7 | 14 | | |
| Interim Physical Examination | | X | X | | | | | |
| **Additional Screening Tests** | | | | | | | | |
| 12-lead ECG | X | | | | | | | See Section 9.5.3 for details |
| Examination of Ocular Fundus and Pulmonary Function[b] | X | | | | | | | |
| Cardiologist Clearance or 6-hour First Dose Observation[c] | X | X | | | | | | |
| **Electronic Diary (eCOA)** | | | | | | | | |
| Dispense and Train Participant on Electronic Daily Diary | X | | | | | | | |
| Demographics and Subject Characteristics | | X | | | | | | |
| Site Review of Electronic Daily Diary Compliance | | X | X | X | X | X | X | |
| **Blood and Urine Tests**[d] | | | | | | | | See Section 9.5.4 for details |
| CBC and Differential Count | X | X | X | X | X | X | X | Blood test results from anytime within 30 days prior to starting first |

**Table 2-1: Schedule of Activities for Year 1 (IM047029)**

| Procedure | Screening (Days -28 to -1) | Week 0 (Day 1) | Week 4 (Day 28) | Week 12 (Day 84) | Week 26 (Day 182) | Week 52 (Day 365) | Unscheduled[a] | Notes |
|---|---|---|---|---|---|---|---|---|
| **Visit Window (± n Days)** | | | 7 | 7 | 7 | 14 | | |
| Biochemistry[d] | X | X | X | X | X | X | X | dose of study intervention can be considered for screening process. Results must be documented, if obtained locally. |
| Varicella IgG | X | | | | | | | |
| | | | | | | | | |
| Pregnancy Test - Serum or Urine beta-hCG[e] | X | X | | | | | | See footnotes |
| FSH[f] | X | | | | | | | Optional. See footnotes |
| TDM Test[g] | X | | | | | | | Optional. See footnotes |
| | | | | | | | | |
| Diagnostic Test for SARS-CoV-2 | X | | | | | | | Participants must have a negative SARS-CoV-2 PCR test result prior to Day 1, in accordance with site standard practices |
| | | | | | | | | |
| **Stool Collection** | | | | | | | | |
| For *Clostridium difficile* Testing (and stool infectious screen) | X | | | | | | x[h] | Stool test results from anytime within 30 days prior to starting first dose of study intervention can be considered for screening process. Results must be documented, if obtained locally. |

**Table 2-1: Schedule of Activities for Year 1 (IM047029)**

| Procedure | Screening (Days -28 to -1) | Week 0 (Day 1) | Week 4 (Day 28) | Week 12 (Day 84) | Week 26 (Day 182) | Week 52 (Day 365) | Unscheduled[a] | Notes |
|---|---|---|---|---|---|---|---|---|
| **Visit Window (± n Days)** | | | 7 | 7 | 7 | 14 | | |
| For Culture, Ova, and Parasites[i] | X | | | | | | | or stool PCR - see footnotes |
| [redacted] | | | | | | | | |
| **Endoscopy and Biopsies[j]** | | | | | | | | |
| Cohort 1 (Advanced Therapy-naïve Cohort) | X | | | X | | | | Results from endoscopy (colonoscopy or sigmoidoscopy) performed within 60 days prior to first dose of study intervention may be considered for the screening process. Images must be documented to confirm severity. In the setting of historic (prior) endoscopy documentation, biopsy tissue will not be collected. |
| Cohort 2 (Advanced Therapy-exposed Cohort) | X | | | | X | | | Results from endoscopy performed within 60 days prior to first dose, may be considered for the screening process. Images must be documented to confirm severity.In the setting of historic (prior) endoscopy documentation, biopsy tissue will not be collected. |
| **Additional Efficacy Assessments[k]** | | | | | | | | |
| Site Calculates Modified Mayo Score | X | | | X[l] | X[m] | | | Required for eligibility assessment |

**Table 2-1: Schedule of Activities for Year 1 (IM047029)**

| Procedure | Screening (Days -28 to -1) | Week 0 (Day 1) | Week 4 (Day 28) | Week 12 (Day 84) | Week 26 (Day 182) | Week 52 (Day 365) | Unscheduled[a] | Notes |
|---|---|---|---|---|---|---|---|---|
| **Visit Window (± n Days)** | | | 7 | 7 | 7 | 14 | | |
| Baseline (prior to flare) SF | X | | | | | | | |
| PGA Collection | X | X | X | X | X | X | | Physician-reported |
| RB Subscore | X | X | X | X | X | X | | Recorded for 7 days prior to Day 1, daily for the first 12 weeks of the study, and 7 days prior to each study visit thereafter |
| SF Subscore | X | X | X | X | X | X | | |
| **HRQOL[n]** | | | | | | | | |
| [redacted] | | | | | | | | |
| IBDQ | | X | X | X | X | X | | |
| [redacted] | | | | | | | | |

**Table 2-1: Schedule of Activities for Year 1 (IM047029)**

| Procedure | Screening (Days -28 to -1) | Week 0 (Day 1) | Week 4 (Day 28) | Week 12 (Day 84) | Week 26 (Day 182) | Week 52 (Day 365) | Unscheduled[a] | Notes |
|---|---|---|---|---|---|---|---|---|
| **Visit Window (± n Days)** | | | 7 | 7 | 7 | 14 | | |
| **Healthcare Resource Utilization[o]** | | | | | | | | |
| [redacted] | | | | | | | | |
| **AE Reporting** | | | | | | | | |
| Monitor AEs | | X | X | X | X | X | X | |
| Monitor SAEs | X | X | X | X | X | X | X | |
| COVID AEs | X | X | X | X | X | X | X | |
| **IP Supply** | | | | | | | | |
| Dispense IP | | X[p] | X | X | X | X | X | |
| Review Participant Compliance with IP | | | X | X | X | X | X | |

AE, adverse event; BP, blood pressure; beta-hCG, beta-subunit of human chorionic gonadotropin; CBC, complete blood count; COVID, coronavirus disease; ECG, electrocardiogram; eCOA, electronic clinical outcome assessment; EDC, electronic data capture; [redacted] FDO, first dose observation; FSH, follicle-stimulating hormone; Hb, hemoglobin; HR, heart rate; HRQOL, health-related quality of life; [redacted] IBDQ, Inflammatory Bowel Disease Questionnaire; IFN, interferon; IgG, immunoglobulin G; LFT, liver function test; PCR, polymerase chain reaction; PCR, polymerase chain reaction; PGA, Physician's Global Assessment; RB, rectal bleeding; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SAE, serious adverse event; SF, stool frequency; TDM, therapeutic drug monitoring; [redacted] UC, ulcerative colitis; [redacted] WOCBP, women of childbearing potential; [redacted]

[a] If required, an unscheduled visit can be planned anytime during the treatment period. Data regarding study procedures conducted at such unscheduled visits (eg, blood, stool, and urine tests; safety assessments) will be documented in the EDC tool.

[b] Need for fundic examination and pulmonary function is dependent on specific risk factors outlined in the product label.

[c] Need for 6-hour FDO is dependent on specific cardiac risk factors outlined in the product label. A cardiologist's opinion is required in the setting of history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension, severe untreated sleep apnea, history of recurrent syncope or symptomatic bradycardia; pre-existing significant QT interval prolongation (QTc greater than 500 msec) or other risks for QT prolongation, and patients on medicinal products other than beta-blockers and calcium channel blockers that may potentiate bradycardia; patients on class Ia (eg, quinidine, disopyramide) or class III (eg, amiodarone, sotalol) antiarrhythmic medicinal products, which have been associated with cases of torsades de pointes in patients with bradycardia have not been studied with ozanimod.

[d] Complete list of clinical safety laboratory assessments is provided in Section 9.5.4.

[e] WOCBP only. Pregnancy test anytime within 7 days prior to day of study intervention initiation is permissable – if pregnancy test is done locally, it must be documented.

[f] Optional test of FSH level may be used to exclude childbearing potential in peri-menopausal females.

[g] For all biologics, the washout period is 8 weeks or 5 elimination half lives, which ever is shorter, but it may be waived with the demonstration of absent drug levels on TDM assay.

[redacted]

[i] Stool PCR panel may be performed as an alternative to stool culture if that is in routine clinical use at a site.

[j] Endoscopy- and biopsy-related procedure details will be provided to the sites in a separate document/manual.

[k] A brief description about additional efficacy assessments is provided in Section 9.1.

[l] Only for Cohort 1.

[m] Only for Cohort 2.

[n] A brief description about HRQOL assessments is provided in Section 9.1.2.2.

[o] A brief description about healthcare resource utilization assessments is provided in Section 9.10.

[p] Ozanimod titration will occur during the first 7 days of study intervention exposure, per label (Table 7.1-2). Participants will receive a phone call on Day 5 (when titrating their dose from 0.23 mg to 0.46 mg) and again on Day 8 (when titrating their dose from 0.46 mg to 0.92 mg) as a reminder about the dose adjustment.

**Table 2-2: Schedule of Activities for Year 2 (IM047029)**

| Procedure | Week 104 EOT/ET[a] (Day 728) | Week 116 PTFU (Day 812) | Unscheduled[b] | Notes |
|---|---|---|---|---|
| **Visit Window (± n Days)** | **14** | **14** | | |
| Concomitant Medications | X | X | | Assess for change in concomitant medications (see Section 7.7) |
| UC Medications | X | X | | |
| Tobacco / e-cigarette vape use | X | X | | Assess for change in use |
| **Physical Examination** | | | | See Section 9.5.1 for details |
| Weight | X | X | | |
| Vital Signs (HR, BP, Temperature [°C]) | X | X | | |
| Complete Physical Examination | X | | | |
| Interim Physical Examination | | X | | |
| **Electronic Diary (eCOA)** | | | | |
| Site Review of Electronic Daily Diary Compliance | X | X | X | |
| **Blood and Urine Tests**[c] | | | | See Section 9.5.4 for details |
| CBC and Differential Count | X | | X | |
| Biochemistry[d] | X | | X | |
| [redacted] | | | | |

**Table 2-2: Schedule of Activities for Year 2 (IM047029)**

| Procedure | Week 104 EOT/ET[a] (Day 728) | Week 116 PTFU (Day 812) | Unscheduled[b] | Notes |
|---|---|---|---|---|
| **Visit Window (± n Days)** | **14** | **14** | | |
| **Additional Efficacy Assessments[e]** | | | | |
| PGA Collection | X | X | | Physician-reported |
| RB Subscore | X | X | | Recorded for 7 days prior to each study visit |
| SF Subscore | X | X | | |
| **HRQOL[f]** | | | | |
| [redacted] | | | | |
| IBDQ | X | X | | |
| [redacted] | | | | |
| **Healthcare Resource Utilization[g]** | | | | |
| [redacted] | | | | |
| **AE Reporting** | | | | |
| Monitor AEs | X | X | X | |
| Monitor SAEs | X | X | X | |
| COVID AEs | X | X | X | |

**Table 2-2: Schedule of Activities for Year 2 (IM047029)**

| Procedure | Week 104 EOT/ET[a] (Day 728) | Week 116 PTFU (Day 812) | Unscheduled[b] | Notes |
|---|---|---|---|---|
| **Visit Window (± n Days)** | **14** | **14** | | |
| **IP Supply** | | | | |
| Dispense IP | | | X | |
| Review Participant Compliance with IP | X | | X | |

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; CBC, complete blood count; eCOA, electronic clinical outcome assessment; COVID, coronavirus disease; EDC, electronic data capture; [redacted] EOT, end of treatment; ET, early termination; [redacted] HR, heart rate; HRQOL, health-related quality of life; [redacted] IBDQ, Inflammatory Bowel Disease Questionnaire; INR, international normalized ratio; IP, investigational product; PGA, Physician's Global Assessment; PTFU, post-treatment follow-up; RB, rectal bleeding; [redacted] SAE, serious adverse event; SF, stool frequency; [redacted] UC, ulcerative colitis; [redacted] ULN, upper limit of normal; [redacted]

[a] For participants who prematurely discontinue from the study, if possible, the EOT visit and follow-up visit should be conducted so that data can be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

[b] If required, an unscheduled visit can be planned anytime during the treatment period. Data regarding study procedures conducted at such unscheduled visits (eg, blood, stool, and urine tests; safety assessments) will be documented in the EDC tool.

[c] Complete list of clinical safety laboratory assessments is provided in Section 9.5.4.

[d] Per physician discretion, INR may be collected if ALT or AST > 3 × ULN.

[e] A brief description about additional efficacy assessments is provided in Sections 9.1.

[f] A brief description about HRQOL assessments is provided in Section 9.1.2.2.

[g] A brief description about healthcare resource utilization assessments is provided in Section 9.10.

# 3 INTRODUCTION

Ozanimod (RPC1063, BMS-986374) is a sphingosine 1-phosphate (S1P) receptor modulator that has been approved in the US, Europe, and other countries for the treatment of ulcerative colitis (UC) and multiple sclerosis (MS). The US Food and Drug Administration (FDA) approval of ozanimod (trade name Zeposia®) for the treatment of moderate to severely active UC was received in May 2021 and was based on data from the pivotal Phase 3 True North study (RPC01-3101) and supported by data from the Phase 2 Touchstone Study (RPC01-202), which evaluated ozanimod as an induction and maintenance therapy vs placebo in adult patients with moderate to severe UC.[1,2]

## 3.1 Study Rationale

This prospective, open-label, Phase 4 study is designed to explore the safety, efficacy, effects on quality of life (QOL), and biomarker response of ozanimod in participants with moderate to severely active UC in clinical practice.

The study population will be consistent with the product label, so that this study may generate data that are directly relevant to the labeled indication and that may be used to further inform the clinical use of ozanimod in this study population.

The study will include 2 cohorts:

- **Cohort 1:** Participants with moderate to severely active UC who have not been exposed to biologics or immunomodulators for the treatment of UC (ie, advanced therapy-naïve).
- **Cohort 2:** Participants with moderate to severely active UC who have been exposed to a single mechanism of action of biologics for the treatment of UC (ie, advanced therapy-exposed).

This study will generate additional data on the effect of ozanimod treatment, including (but not limited to) the following:

- Characterization of early response (improvement in signs and symptoms of UC within the first 4 weeks), including rectal bleeding (RB), stool frequency (SF), urgency, and abdominal symptoms.
- Characterization of the endoscopic and histologic response to ozanimod at Week 12 in an advanced therapy-naïve cohort.
- Characterization of the endoscopic and histologic response to ozanimod at Week 26 in an advanced therapy-exposed cohort.
- Characterization of the long-term safety of ozanimod over the duration of the study.
- Patient-reported outcome (PRO) measures, including impact on disease-specific QOL and symptoms, fatigue, patient satisfaction with treatment, and work productivity.
- Characterization of the effect of ozanimod treatment on biomarkers of disease activity used in clinical practice, [redacted]

## 3.2 Background

### *3.2.1 Ulcerative Colitis*

UC is a chronic gastrointestinal (GI) inflammatory disorder that involves the surface mucosa, the crypt epithelium, and the submucosa of the colon.[3,4] The etiology of UC is multifactorial, but likely includes a dysregulated mucosal immune response against commensal nonpathogenic bacteria of the colon, resulting in bowel inflammation.[5]

Patients with UC suffer from diarrhea, RB, weight loss, abdominal pain, and fever.[3,4] The pathology of UC is characterized by a life-long chronic course of exacerbations and remissions. In the case of severe UC, the bowel wall may become thinned, the mucosa denuded, and the inflammation may extend to the serosa, leading to dilation, toxic megacolon, and perforation.[6] Toxic megacolon, although uncommon, may require an urgent colectomy to avoid perforation, peritonitis, and sepsis. Within 10 years of diagnosis, 19.9% of patients with UC have undergone colectomy.[7]

In addition, patients with UC have an increased risk of carcinoma when compared with the general population. The estimated risk of colorectal carcinoma increases as the duration and extent of disease increases, from 2% in patients with UC for 10 years, to 8% in patients with UC for 20 years, and to 18% in patients with UC for 30 years.[8,9]

The overall goal of treatment for patients with active UC is to induce and maintain both remission and mucosal healing.[10] Treatment of UC consists of anti-inflammatory and immunosuppressive therapies that are chosen to maximize efficacy while minimizing toxicity. The therapy chosen is therefore dependent on the patient's disease severity and their response to therapy.[10,11] Although agents used to treat mild to moderate UC are generally well -tolerated, as the severity of UC disease increases, so too do the potential toxicities related to the medications required to manage the disease. Treatment for mild to moderate UC typically starts with topical agents (5-aminosalicylate [5-ASA] or corticosteroids administered via suppository or enema). In patients unresponsive to local therapy or in those with more severe or more extensive disease, oral 5-ASA, such as mesalamine, olsalazine, sulfasalazine, and balsalazide, with or without antibiotics, is commonly required.[10,12] Initially, up to 90% of patients with mild to moderate UC can maintain their remission status using oral administration of 5-ASA, which is generally safe and well -tolerated.[10]

For those patients who do not respond or lose response to treatment with 5-ASA or for those with more severe and extensive disease at presentation, corticosteroids are generally the first-line treatment for inducing disease remission. Although effective in inducing disease remission, treatment with corticosteroids is associated with multiple adverse effects, including weight gain, insomnia, mood swings, osteoporosis, scalp hair loss or facial hair growth, moon face, cataracts, acne, hypertension, diabetes, appearance of stretch marks, and increased susceptibility to infections and bruising.

For those patients who are unresponsive to, or intolerant of corticosteroids, immunomodulators, including azathioprine (AZA), 6-mercaptopurine, and cyclosporine[12] are used to induce and/or

maintain remission.[11] However, these medications have multiple limitations, including toxicities. The use of 6-mercaptopurine and AZA can result in neutropenia, pancytopenia, pancreatitis, nephrotoxicity, hepatotoxicity, and, in rare cases, Epstein–Barr virus (EBV) and non-EBV-associated lymphoma, as well as the uniformly fatal hepatosplenic T cell lymphoma.[13,14,15] A Cochrane systematic review concluded that available medical trials do not support the use of methotrexate for short- or long-term remission of active UC.[16]

Updated guidance on treating UC in adult patients emphasizes the role of biologic agents, including infliximab, adalimumab, golimumab (anti-tumor necrosis factor [TNF] therapies), vedolizumab (anti-integrin antibody), tofacitinib (Janus kinase [JAK] inhibitor), and ustekinumab (anti-interleukin [IL]–12/23 antibody).[17,18] However, up to one-fifth of patients receiving anti-TNF agents may not demonstrate an initial response,[17] and an additional 10% to 20% may lose response every year despite an initial benefit.[19,20] The anti-TNF agents also come with the potential risk of infusion reactions or injection site reactions, infections, malignancy, autoimmunity, and psoriasis known for that medication class. Although tofacitinib is administered orally, the US FDA has approved new warnings on an increased risk of blood clots and death with the dose of tofacitinib that is used in patients with UC.[21] Therefore, there remains an unmet need for a UC treatment that is effective, well-tolerated, and orally active. In this scenario, the US FDA approval of ozanimod, a selective S1P receptor modulator, as once daily (QD) per oral (PO) treatment in adults with moderate to severely active UC could help to fill a treatment gap in this disease.

### 3.2.2 Ozanimod

Ozanimod is a small molecule compound that selectively binds with high affinity to S1P receptors 1 and 5. In vitro, ozanimod has little activity on the other S1P receptors, showing half-maximal $EC_{50}$ > 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 GI Peyer's patches), which can result in reversible systemic reduction in circulating lymphocytes.[22] Given the immune-mediated inflammation in UC, 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.

An open-label, pharmacokinetic (PK)/pharmacodynamic (PD) study in patients with MS examined the effect of ozanimod on circulating leukocyte subsets.[23] Ozanimod 0.92 mg demonstrated greater reduction in CD4+ (helper) T cells than CD8+ (cytotoxic) T cells. Additionally, CD4+ and CD8+ central memory T cells were reduced more than CD4+ and CD8+ effector memory T cells, respectively. There was minimal impact on monocytes and natural killer cells. It was hypothesized that the differential impact on leukocyte subpopulations may provide inhibition of inflammation that may lead to pathophysiology in MS, while allowing for maintenance of immune function.

Leukocyte subpopulations in patients with UC who have received ozanimod have not yet been studied.

Ozanimod is extensively metabolized in humans to form a number of circulating active metabolites, including 2 major active metabolites (CC112273 [also referred to as RP112273] and CC1084037 [also referred to as RP100798]); other active metabolites, including RP101988, RP101075, RP112289, and RP101442; and one circulating inactive metabolite, RP101124. 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 subjects, approximately 94% of circulating total active drug exposure was represented by ozanimod (6%), CC112273 (73%), and CC1084037 (15%).

### *3.2.3 Ozanimod in UC*

In the True North study, a total of 645 participants were randomly assigned 2:1 to either ozanimod 0.92 mg QD PO (n = 429) or placebo (n = 216). The primary induction endpoint of clinical remission at Week 10 (18% vs 6%; P<0.0001, for ozanimod vs placebo, respectively) was met, as were the key secondary endpoints, including clinical response (48% vs 26%; P<0.0001), endoscopic improvement (27% vs 12%; P<0.0001), and endoscopic-histologic mucosal improvement (13% vs 4%; P<0.001). Decreases in RB and SF subscores were observed as early as Week 2 (ie, one week after participants completed the required 7-day dosage titration) in participants treated with ozanimod.

A total of 457 participants who received ozanimod in the induction period or in an open-label arm and achieved clinical response at Week 10 were re-randomized 1:1 and were treated with either ozanimod 0.92 mg QD PO (n = 230) or placebo (n = 227) for 42 weeks, for a total of 52 weeks of treatment. The primary endpoint of clinical remission at Week 52 was met (37% vs 19%; P<0.0001), as were the key secondary endpoints, including clinical response (60% vs 41%; P<0.0001), endoscopic improvement (46% vs 26%; P<0.001), corticosteroid-free clinical remission (32% vs 17%; P<0.001), and endoscopic-histologic mucosal improvement (30% vs 14%; P<0.001).

The safety and tolerability results from the induction and maintenance periods of the True North study demonstrated that ozanimod at a dose of 0.92 mg daily for 8 weeks or for 52 weeks, respectively, was well -tolerated and had an acceptable safety profile in patients with moderate to severely active UC. There was no evidence of new patterns of treatment-emergent adverse events (TEAEs), increased incidence of TEAEs, or unique TEAEs with longer exposure to ozanimod. Overall, these results were consistent with safety findings that have previously been reported regarding ozanimod therapy in Phase 3 trials involving patients with MS.

A detailed description of the efficacy and safety of ozanimod is provided in the product label.

## 3.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably anticipated adverse events (AEs) of ozanimod may be found in the product label.

### 3.3.1 Risk Assessment

**Table 3.3.1-1: Risk Assessment**

| Potential Risk of Clinical Significance | Summary of Data/ Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Study Intervention(s)** | | |
| Infections (eg, herpes viral infection, cryptococcal infection, PML) | Per Zeposia product label | Per Zeposia product label |
| Prior and concomitant treatment with anti-neoplastic, immunosuppressive, or immune-modulating therapies | Per Zeposia product label | Per Zeposia product label |
| Vaccinations | Per Zeposia product label | Per Zeposia product label |
| Bradyarrhythmia and AV conduction delays | Per Zeposia product label | Per Zeposia product label |
| Liver injury | Per Zeposia product label | Per Zeposia product label |
| Fetal risk | Per Zeposia product label | Per Zeposia product label |
| Increased blood pressure | Per Zeposia product label | Per Zeposia product label |
| Respiratory effects | Per Zeposia product label | Per Zeposia product label |
| Macular edema (eg, in patients with a history of uveitis or diabetes mellitus) | Per Zeposia product label | Per Zeposia product label |
| Posterior reversible encephalopathy syndrome | Per Zeposia product label | Per Zeposia product label |
| Unintended additive immunosuppressive effects from prior treatment with immunosuppressive or immune-modulating drugs | Per Zeposia product label | Per Zeposia product label |
| Immune system effects after stopping ozanimod | Per Zeposia product label | Per Zeposia product label |
| **Study Procedures** | | |
| Endoscopy and biopsies | While endoscopy is considered to be a very safe procedure, rare complications may include perforation, bleeding, and infection. Risk of bleeding complications after an endoscopy is increased if the procedure involves biopsy | Per institutional protocol/investigator discretion |
| **Other (if Applicable)** | | |
| SARS-CoV-2 infection | Current ongoing pandemic | Vaccination prior to enrollment is encouraged. The risk of enrolling participants with active SARS-CoV-2 infection will be minimized by testing at screening. General risk mitigation against SARS-CoV-2 |

**Table 3.3.1-1: Risk Assessment**

| Potential Risk of Clinical Significance | Summary of Data/ Rationale for Risk | Mitigation Strategy |
|---|---|---|
| | | infection will be implemented in accordance with the site's monitoring and prevention control measures. [redacted] |

AV, atrioventricular; PML, progressive multifocal leukoencephalopathy; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

### *3.3.2 Benefit Assessment*

Ozanimod has been approved in the US, Europe, and other countries for the treatment of moderate to severely active UC. Data from the Phase 3 True North study suggests that ozanimod is efficacious in the treatment of moderate to severe UC, with an acceptable safety profile. In the True North study, a significantly greater proportion of patients who received ozanimod achieved the primary induction endpoint (ie, clinical remission) as well as key secondary endpoints (ie, clinical response, endoscopic improvement, and endoscopic-histologic mucosal improvement) compared with those who received placebo. Longer exposure to ozanimod did not lead to any new safety concerns.

As this is an open-label study, participants are not at risk of receiving placebo, and ozanimod therapy is expected to potentially induce clinical remission, endoscopic response and improvement, histological improvement, and health-related quality of life (HRQOL) in this target patient population.

### *3.3.3 Overall Benefit/Risk Conclusion*

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with ozanimod are justified by the anticipated benefits that may be afforded to participants with moderate to severe UC.

The Sponsor will evaluate the risk/benefit profile of the study on an ongoing basis. This evaluation will be based on all available data with particular attention to i) AEs or other safety trends in this or any other clinical study of ozanimod whose character, severity, and/or frequency suggest that participants would be exposed to an unreasonable and significant risk of illness or injury; (ii) new nonclinical data suggesting unreasonable and significant risk of illness or injury.

If such evaluation suggests that the risk/benefit profile of the study has become unfavorable to participants, the Sponsor will pause enrollment and/or treatment until further evaluation of data can take place on potential actions. Such actions may include (but are not limited to) study continuation, substantial amendment, or termination of the study.

# 4 OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are listed in the following 3 tables:

- Table 4-1: Objectives and endpoints that are specific to Cohort 1.
- Table 4-2: Objectives and endpoints that are specific to Cohort 2.
- Table 4-3: Objectives and endpoints that are common for both Cohort 1 and Cohort 2.

Additional endpoints and analyses will be described in the statistical analysis plan (SAP), the Endoscopy Image Review Charter, and/or the Histopathology Image Review Charter (as applicable). Selected endpoint definitions are provided in APPENDIX 6.

**Table 4-1: Objectives and Endpoints Specific to Advanced Therapy-naïve Cohort (Cohort 1)**

| Objectives | Endpoints |
|---|---|
| **Primary** | **Primary** |
| • To explore the efficacy of ozanimod in inducing clinical response in the advanced therapy-naïve cohort. | • Clinical response at Week 12, as measured by modified Mayo score. |
| **Secondary** | **Secondary** |
| • To explore the efficacy of ozanimod in the advanced therapy-naïve cohort. | • Clinical remission at Week 12, as measured by modified Mayo score.<br>• Endoscopic response at Week 12.<br>• Endoscopic improvement at Week 12.<br>• Histological improvement at Week 12. |
| • To explore the effects of ozanimod on disease-specific HRQOL in the advanced therapy-naïve cohort. | • Change in the IBDQ total score from baseline to Week 12.<br>• IBDQ response (change in total score [≥ 16 points] from baseline to Week 12).<br>• IBDQ remission (total score [≥ 170 points]) at Week 12. |
| [redacted] | [redacted] |

[redacted] IBDQ, Inflammatory Bowel Disease Questionnaire.

**Table 4-2: Objectives and Endpoints Specific to Advanced Therapy-exposed Cohort (Cohort 2)**

| Objectives | Endpoints |
|---|---|
| **Primary**<br>• To explore the efficacy of ozanimod in inducing clinical response in the advanced therapy-exposed cohort. | **Primary**<br>• Clinical response at Week 26, as measured by modified Mayo score. |
| **Secondary**<br>• To explore the efficacy of ozanimod in the advanced therapy-exposed cohort. | **Secondary**<br>• Clinical remission at Week 26, as measured by modified Mayo score.<br>• Endoscopic response at Week 26.<br>• Endoscopic improvement at Week 26.<br>• Endoscopic remission at Week 26.<br>• Histological improvement at Week 26.<br>• Histological remission at Week 26.<br>• Change in the IBDQ total score from baseline to Week 26.<br>• IBDQ response (change in total score [≥ 16 points] from baseline to Week 26).<br>• IBDQ remission (total score [≥ 170 points]) at Week 26.<br>• Corticosteroid-free clinical remission at Week 26, as measured by modified Mayo score.<br>• HEMI at Week 26. |
| [redacted] | |

HEMI, histo-endoscopic mucosal improvement; IBDQ, Inflammatory Bowel Disease Questionnaire.

**Table 4-3: Additional Objectives and Endpoints Common for both the Advanced Therapy-naïve Cohort (Cohort 1) and the Advanced Therapy-exposed Cohort (Cohort 2) after Week 26**

| Objectives | Endpoints |
|---|---|
| **Secondary** | **Secondary** |
| • To explore the safety and tolerability of ozanimod in the advanced therapy-naïve cohort and the advanced therapy-exposed cohort. | • Number and proportion of participants experiencing the following:<br>– AEs.<br>– SAEs.<br>– AEs and SAEs, including AEIs and other select AEs, leading to discontinuation from the study intervention and the study.<br>– Clinical laboratory values. |
| • To explore the long-term durability of response to ozanimod in the advanced therapy-naïve cohort and the advanced therapy-exposed cohort. | • Clinical remission by partial Mayo score at Weeks 52 and 104.<br>• Corticosteroid-free clinical remission by partial Mayo score at Weeks 52 and 104.<br>• Clinical response by partial Mayo score at Weeks 52 and 104. |
| [redacted] | |

**Table 4-3: Additional Objectives and Endpoints Common for both the Advanced Therapy-naïve Cohort (Cohort 1) and the Advanced Therapy-exposed Cohort (Cohort 2) after Week 26**

| Objectives | Endpoints |
|---|---|
| [redacted] | [redacted] |

AEI, adverse event of interest; [redacted] SAE, serious adverse event; [redacted]

# 5 STUDY DESIGN

## 5.1 Overall Design

Study IM047029 is a Phase 4, prospective, non-randomized, open-label, multicenter clinical study designed to explore the safety, efficacy, effects on QOL, and biomarker response of ozanimod 0.92 mg QD PO administration in participants with moderate to severely active UC in clinical practice.

This clinical study will evaluate ozanimod 0.92 mg QD PO in multiple UC disease subtypes, and with 2 specific cohorts as described in Section 3.1 and Figure 5.1-1.

Participants will undergo screening evaluations to determine eligibility as indicated in the SOA; see Table 2-1). Participants must meet the eligibility criteria outlined in Section 6 in order to enter the treatment period. Participants must have moderate to severely active UC, defined as a score of 4 through 9 on the 9-point modified Mayo score, in order to enter the treatment period.

Assessments of medical and UC disease history, prior medications, concomitant and UC medications, tobacco/e-cigarette use, baseline (prior to flare) SF, physical examinations, 12-lead electrocardiograms (12-lead ECGs), blood, stool, and urine sample collections, endoscopies with biopsies, Physician's Global Assessment (PGA) ratings, PRO and HRQOL instruments, and other study procedures will be performed as indicated in the SOA (Table 2-1, Table 2-2). Additional risk-based assessment of cardiac conduction abnormalities, pulmonary function, and/or visual

acuity (including evaluation of the fundus and macula) may also be performed during screening and as appropriate thereafter.

Disease activity assessment for the purpose of eligibility and evaluation of the primary endpoints in both cohorts will be performed using the modified Mayo score instrument (APPENDIX 3). The modified Mayo score will be calculated using data from the following sources: baseline (prior to flare) SF (patient-reported and recorded by the investigator), daily assessments of SF and RB (PROs recorded in the participant's electronic daily diary), and assessment of mucosal inflammation at endoscopy. The PGA of disease activity (physician-reported) will also be captured at various time points (Table 2-1, Table 2-2).

Screening will include the assessment of pre-existing cardiac conduction abnormalities by 12-lead ECG. Investigators should consider cardiology consultation if conduction abnormalities are identified on the 12-lead ECGs, or if the participant is receiving concomitant medications (see Table 7.7-2) that have the potential to decrease their heart rate (HR).

Participants who have a history of uveitis, diabetes mellitus, macular edema or other retinal disease will have ophthalmic evaluation of the fundus, including the macula, prior to study intervention, in order to exclude macular edema.

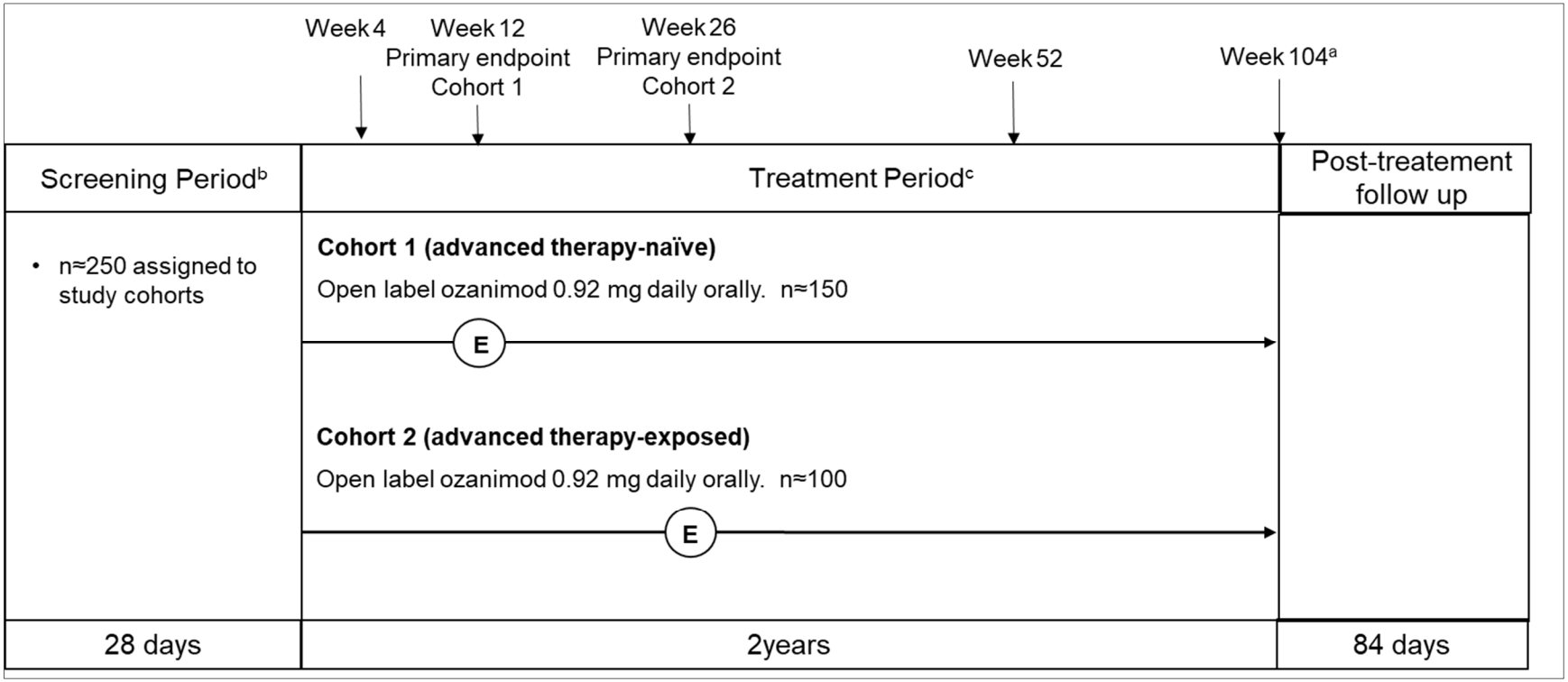
Antibodies to varicella zoster virus (VZV) will be tested during the screening period. Participants must have documentation of positive VZV immunoglobulin G (IgG) antibody status at screening or complete VZV vaccination prior to the first study intervention administration.

1) No live or live-attenuated vaccine within 4 weeks prior to study intervention administration. Pregnancy will be excluded in women of childbearing potential (WOCBP) prior to the first study intervention administration.

All eligible participants will receive open-label ozanimod 0.92 mg QD PO, per product label, during the treatment period (Table 7.1-1). Ozanimod titration will occur during the first 7 days of study intervention exposure, per label (Table 7.1-2). Once study intervention (ie, ozanimod) has been titrated up to 0.92 mg QD PO (Day 8), further dose escalation is not allowed.

The study design schematic is presented in Figure 5.1-1.

**Figure 5.1-1: Study Design Schema**




E, endoscopies and biopsies; ES, endoscopic subscore; EOT, end of treatment.

[a] For participants who prematurely discontinue from the study, if possible, the EOT visit and follow-up visit should be conducted so that data can be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

[b] Screening endoscopy (colonoscopy or sigmoidoscopy) may be performed within 60 days prior to the first study intervention administration. Photographic evidence of ES ≥2 must be available for study inclusion, as per eligibility criteria. In the event that historic endoscopic data is used as a part of screening, historic histopathologic tissue will not be needed to be collected.

[c] Ozanimod titration will occur during the first 7 days of study intervention exposure, per label (Table 7.1-2). Participants will receive a phone call on Day 5 (when titrating their dose from 0.23 mg to 0.46 mg) and again on Day 8 (when titrating their dose from 0.46 mg to 0.92 mg) as a reminder about the dose adjustment. If required, an unscheduled visit can be planned anytime during the treatment period. Data regarding study procedures conducted at such unscheduled visits (eg, blood, stool, and urine tests; safety assessments) will be documented in the EDC tool.

### *5.1.1 Data Monitoring Committee and Other Committees*

A Data Monitoring Committee or other review committee will not be used in the study.

## 5.2 Number of Participants

It is estimated that approximately 250 screened participants in Cohort 1 (advanced therapy-naïve cohort) will be required to achieve 150 treated participants. Similarly, for Cohort 2 (advanced therapy-exposed cohort), it is estimated that approximately 165 participants will be required to achieve 100 treated participants. These enrollment estimates assume a screen failure rate of approximately 40% in each cohort.

If the screen failure rate is higher than expected, enrollment will remain open until the required number of treated participants in each cohort is achieved.

## 5.3 End of Study Definition

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

The end of the trial is defined as the last participant's last visit or scheduled procedure shown in the SOA (Table 2-2) for the last participant.

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.

A participant is considered to have completed the study if he/she has completed the last procedure shown in the SOA (Table 2-2).

## 5.4 Scientific Rationale for Study Design

Ozanimod is approved in the US for the treatment of moderate to severely active UC in adults. This approval was based on safety and efficacy data from the induction and maintenance periods of the Phase 3 True North study (NCT02435992)[24] and supported by safety and efficacy data from the Phase 2 Touchstone study (NCT01647516)[25] and by safety data from 2 randomized, double-blind, double-dummy, active comparator-controlled clinical trials in patients with relapsing forms of MS (NCT02294058 and NCT02047734).[26,27,28,29] The eligibility criteria for the cohorts within this clinical protocol will be consistent with the approved product label (in the US and other countries, as applicable). The cohorts within this clinical protocol will generate novel data on safety, efficacy, effects on QOL, and biomarker response of ozanimod, as listed in Section 3.1. Consequently, this study will extend the evidence base supporting ozanimod, and these data may be used to further inform the clinical use of ozanimod in the approved UC patient population.

The results of the True North and Touchstone studies demonstrate that equivalence between ozanimod and placebo is no longer present for the multiplicity of controlled endpoints evaluated in those clinical trials.[28,29] Consequently, Cohort 1 and Cohort 2 will not use placebo control.

The primary endpoint of Cohort 1 and Cohort 2 is assessed using the modified Mayo score instrument, which is a composite of the Mayo score SF, RB, and endoscopic findings subscores.

Consistent with regulatory draft guidance, the instrument is modified from the original description of the Mayo score by the exclusion of friability from an ES of 1 (ES = 1), and the exclusion of the Mayo score's PGA.[3,30,31] Permutations of the Mayo score are listed in APPENDIX 3. Clinical response, the primary endpoint of Cohort 1 and Cohort 2, has been accepted as a primary endpoint in clinical trials that have supported prior approvals of treatments for UC.[31] Additional endpoints based on permutations of the Mayo score that will be evaluated in Cohort 1 and Cohort 2 are listed in Table 4-1, Table 4-2, and Table 4-3.

Additional instruments to be assessed in Cohort 1 and Cohort 2 will include (but not be limited to) the following: Geboes score, [redacted] Inflammatory Bowel Disease Questionnaire (IBDQ), [redacted] (Section 2).

Taken together, the data collected using the instruments described above will facilitate a comprehensive exploration of the effect of ozanimod on UC disease activity (clinical, endoscopic, and histologic), additional UC symptoms, QOL, fatigue, work productivity, and treatment satisfaction.

### 5.5 Justification for Dose

Ozanimod 0.92 mg QD PO has been approved in the US, Europe, and other countries for the treatment of moderate to severely active UC, following a 7-day titration with 0.23 mg and 0.46 mg QD PO.[1,2]

## 6 STUDY POPULATION

Prospective approval of protocol deviations to the 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**

a) Participants must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written informed consent form (ICF) 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) A diagnosis of UC, with signs and symptoms consistent with UC for at least 3 months prior to the first study intervention administration.

b) Moderate to severely active UC disease activity, defined as a modified Mayo score of 4 through 9, inclusive, with the following minimum subscores:

i) An SF subscore ≥ 1,

AND

ii) An RB subscore ≥ 1,

AND

iii) An ES ≥ 2 (endoscopy performed within 60 days of the first study intervention administration).

c) Must be up to date with screening for colorectal neoplasia and surveillance for dysplasia, according to local standard of care.

d) Must have documentation of positive VZV IgG antibody status at screening or complete VZV vaccination prior to the first study intervention administration.

e) Report of a previous colonoscopy that documents extent of disease (Note: If performed in the prior 60 days, this data may be used for study inclusion.)

f) UC disease distribution (including ulcerative proctitis) extending proximal to the rectum (ie, approximately ≥ 5 cm from anal margin).

**3) Age of Participant**

a) Participant must be over 18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place) at the time of signing the informed consent.

**4) Cohort 1 (Advanced Therapy-naïve Cohort): Disease Distribution and Prior UC Medication Exposure**

*In order to participate in Cohort 1, a participant must meet the eligibility criteria outlined in this inclusion criterion (IC) and must not meet the eligibility criteria outlined in IC 5.*

a) Participants must be naïve to 6-mecaptopurine/AZA and any biologics (see IC 5[a] for list) for any other medical indication, as well as UC.

**5) Cohort 2 (Advanced Therapy-exposed Cohort): Disease Distribution and Prior UC Medication Exposure**

*In order to participate in Cohort 2, a participant must have failed only one mechanism of action of biologics.*

a) Documentation of an inadequate response, loss of response, or intolerance to a treatment course of <u>one class</u> of <u>approved</u> biologics (and should not have been treated with additional classes of approved biologics), including:

i) Anti-TNF agents (eg, infliximab, adalimumab, golimumab, certolizumab, anti-TNF biosimilars).

ii) Anti-integrin inhibitors (eg, vedolizumab).

iii) Anti-IL-12p40 biologics (eg, ustekinumab).

iv) Anti-IL-23p19 biologics (eg, mirikizumab, risankizumab).

v) Other biologics that may become approved for clinical use in this UC study during the course of the study (please discuss with Medical Monitor).

b) Not Applicable Per Protocol Amendment 01: Patient may have been previously treated with 6-mercaptopurine/AZA, but not concomitantly over the course of the study, and not for at least 30 days prior to the first study intervention administration.

c) Biologic agents should be discontinued at least 8 weeks prior or at least 5 elimination half lives prior to study intervention initiation, whichever is shorter. Washout period may be waived with the demonstration of absent drug levels on a therapeutic drug monitoring (TDM) assay.

d) 6-mercaptopurine/AZA or methotrexate:

i) Participant may have been previously treated: with 6-mercaptopurine/AZA or methotrexate.

ii) Participant may not take these agents concomitantly over the course of the study.

iii) These agents must be discontinued prior to day of starting study intervention.

**6) Dose Stabilization and Prohibited Concomitant Medications**

a) Compliance with the washout periods for prohibited concomitant medications, as listed in Table 7.7-1.

b) Must meet the dose stabilization criteria for permitted concomitant medications, as listed in Table 7.7-3.

**7) Reproductive Status**

- Investigators shall counsel WOCBP 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) Women who are not of childbearing potential are exempt from contraceptive requirements. Evidence to support this status must be included in source documents.

ii) WOCBP must have a negative highly sensitive serum or urine pregnancy test (minimum sensitivity of 25 IU/L or equivalent units of human chorionic gonadotropin [hCG]) during the baseline as outline in the SOA (Section 2).

- The investigator is responsible for the review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

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

iv) WOCBP 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 one of the following conditions applies:

(1) Is not a WOCBP.

OR

(2) Is a WOCBP 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, 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) Recent (within 6 months of screening) myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or New York Heart Association Class III/IV heart failure.

b) Presence of Mobitz type II second- or third-degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial block, unless the participant has a functioning pacemaker.

c) Severe untreated sleep apnea.

d) Current macular edema. (Note: Participants with diabetes, or a history of uveitis, retinal disease, or previous macular edema must have an ophthalmic evaluation of the fundus, including the macula, prior to the first study intervention administration.)

e) Current active infection, and/or any infection requiring oral antibiotics within 14 days of screening, or intravenous (IV) antibiotics within 30 days of screening.

f) Any major infection that required hospitalization.

g) Immunodeficient state (not including previously mentioned immunosuppressants) leading to increased risk of opportunistic infections.

h) A history of cancer within 5 years, including solid tumors and hematological malignancies (except basal cell carcinoma or squamous cell carcinoma of the skin that have been fully treated, or cervical dysplasia or carcinoma in situ that have been fully treated).

i) Severe hepatic impairment (Child-Pugh Class C).

**2) UC-related Exclusion Criteria**

a) Participant has a current diagnosis of Crohn's disease (CD), indeterminate colitis, radiation colitis or ischemic colitis, a monogenic cause of UC-like intestinal inflammation, colonic diverticulitis, or an alternative diagnosis that explains their colonic inflammation.

b) Current or recent (within 3 months of screening) evidence of fulminant colitis, toxic megacolon, or bowel perforation.

c) Current need for, or anticipated need for, surgical intervention for UC during the course of the study.

d) Extensive colonic resection or current stoma.

e) Colonic dysplasia that has not been removed.

f) Previous or current use of JAK inhibitors (eg, tofacitinib, filgotinib).

g) **Not applicable per Protocol Amendment 1:** UC involving the rectum only (UC proctitis).

h) Women who are pregnant, planning on becoming pregnant during the study, breastfeeding, or who have a positive serum or urine beta-hCG test during screening or on Day 1.

**3) Not applicable per Protocol Amendment 1: Reproductive Satus**

a) Women who are pregnant, planning on becoming pregnant during the study, breastfeeding, or who have a positive serum or urine beta-hCG test during screening or on Day 1.

**4) Prior/Concomitant Therapy**

a) Prior participation in an ozanimod clinical trial.
b) Prior exposure to ozanimod or other S1P receptor modulators.
c) Current immunomodulators for the treatment of UC.
d) Previous or current JAK inhibitors for the treatment of UC.
e) Current biologics for the treatment of UC.
f) Current use of a monoamine oxidase inhibitor.
g) Live or live-attenuated vaccine within 4 weeks prior to study intervention administration.
h) Current or recent (without B cell recovery) use of alemtuzumab.
i) Current use of beta interferon.
j) Current use of glatiramer acetate.

*Note: A detailed summary of prohibited concomitant medications and washout periods is listed in* Table 7.7-1.

**5) Physical and Laboratory Test Findings**

If any of the following stool or blood tests were performed in the prior 30 days and can be documented, this data may be used for study inclusion.

a) Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, 12-lead ECGs, or clinical laboratory determinations beyond what is consistent with the target population.
b) Positive stool test for *Clostridium difficile*. If positive, participants may be rescreened after appropriate treatment and retested no earlier than 7 days after completion of treatment.
c) Positive stool test for pathogenic bacteria, ova, or parasites. If positive, participants may be rescreened after completion of treatment.
d) Clinically significant abnormalities in laboratory testing during the screening period.
e) Severe anemia (ie, hemoglobin [Hb] <8 g/dL) at screening visit.
f) Liver function impairment or persisting elevations of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 × upper limit of normal (ULN), or direct bilirubin > 1.5 × ULN.

**6) Allergies and Adverse Drug Reaction**

a) Hypersensitivity to active ingredients or excipients of ozanimod.

**7) 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 Bristol-Myers Squibb [BMS] approval is required.)
b) Inability to comply with study procedures, including study visits, venipunctures, endoscopies, etc.
c) Participation in another clinical trial concurrent with this study.
d) Any other sound medical, psychiatric, and/or social reason as determined by the investigator.

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. Further criteria will follow the product label.

## 6.3 Lifestyle Restrictions

Female participants (WOCBP only) should use highly effective contraception during the treatment period and for 90 days after discontinuing study intervention.

Aged, fermented, cured, smoked, and pickled foods containing large amounts of exogenous amines (eg, aged cheese, pickled herring) may cause release of norepinephrine, resulting in a rise of blood pressure (tyramine reaction). Consequently, participants will be counselled to avoid foods containing a large amount of tyramine during the treatment period.

## 6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently entered in the study/included in the analysis population.

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 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 serious adverse events (SAEs).

### *6.4.1 Retesting During Screening or Lead-in Period*

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 treated). If re-enrolled, the participant must be re-consented and given a distinct patient identification number (PID).

Retesting of laboratory parameters and/or other assessments within any single screening or lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

The most current result prior to the 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 Table 2-1, the SOA for Year 1, may be repeated in an effort to find all possible well-qualified participants. Discussion with the Medical Monitor is needed to identify whether repeat testing of any particular parameter is clinically relevant.

# 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 investigational (medicinal) product (IP/IMP) as indicated in Table 7.1-1.

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 that already have a marketing authorization but are used or assembled (formulated or packaged) differently from the authorized form, used for an unauthorized indication, or used to gain further information about the authorized form.

## 7.1 Study Interventions Administered

Details of the IP used for both cohorts are provided in Table 7.1-1:

**Table 7.1-1: Study Interventions**

| | **Study Intervention Details (for Cohort 1 and Cohort 2)** |
|---|---|
| Intervention Name | Ozanimod (Zeposia) |
| Type | Drug |
| Dose Formulation | Capsule |
| Unit Dose Strength(s) | 0.23 mg, 0.46 mg, and 0.92 mg |
| Dosage Level(s) | Days 1–4: 1 × 0.23 mg (QD)<br>Days 5–7: 1 × 0.46 mg (QD)<br>Day 8 and thereafter : 1 × 0.92 mg (QD) |
| Route of Administration | Oral |
| Use | Active |
| Sourcing | Provided by the Sponsor |
| Packaging and Labeling | Ozanimod will be packaged and labelled per country requirements. |
| Current/Former Name(s) or Alias(es) | RPC1063, BMS-986374 |

Table 7.1-2Participants will receive a phone call on Day 5 (when titrating their dose from 0.23 mg to 0.46 mg) and again on Day 8 (when titrating their dose from 0.46 mg to 0.92 mg) as a reminder about the dose adjustment (see Table 2-1).

**Table 7.1-2: Ozanimod Dose Titration Regimen**

| **Days** | **Regimen** |
|---|---|
| Days 1–4 | 0.23 mg QD PO |
| Days 5–7 | 0.46 mg QD PO |
| Day 8 and thereafter | 0.92 mg QD PO |

## 7.2 Method of Study Intervention Assignment

Study using interactive response technology (IRT): All participants will be centrally assigned using IRT. Before the study is initiated, each user will receive log-in information and directions on how to access the IRT.

The study intervention will be dispensed at the study visits as listed in the SOA (Section 2).

During the screening visit, the investigative site will access the screening option of the IRT designated by BMS for the assignment of a 5-digit participant number that will be unique across all sites. Enrolled participants, including those who are not dosed, will be assigned sequential participant numbers starting with [redacted]. The PID will ultimately comprise the site number and participant number. For example, the first participant screened (ie, enrolled) at site number 1 will have a PID of [redacted]. Once it is determined that the participant meets the eligibility criteria, he or she will be assigned to the applicable cohort during the screening visit.

## 7.3 Blinding

This is an open-label study. Participants, site personnel (eg, monitors and investigators), and Sponsor personnel will not be blinded to therapy.

## 7.4 Dosage Modification

Additional dose modification after the 7-day titration is not allowed.

## 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 the designee, where permitted, to ensure that the 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) 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.

Documentation of IP 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, etc.

- The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study intervention received and that 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).
- Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual.

## 7.6 Treatment Compliance

Study intervention compliance will be periodically (see Table 2-1 and Table 2-2) monitored for drug accountability. Drug accountability should be reviewed by the site study staff at each visit to

confirm treatment compliance. Sites should discuss discrepancies with the participants at each on-treatment study visit.

When participants self-administer study intervention(s) at home, compliance with the study intervention will be assessed at each visit. Compliance will be assessed by counting returned capsules during site visits and will be documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

A record of the quantity of study intervention dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates of intervention delays and/or dose reductions, will also be recorded in the eCRF.

## 7.7 Concomitant Therapy

### *7.7.1 Prohibited and/or Restricted Treatments*

Prohibited and/or restricted medications taken prior to study intervention administration in the study are described below. Medications taken prior to study intervention administration must be recorded on the eCRF.

- Prior exposure to ozanimod is prohibited.
- Exposure to any investigational drug or placebo within 4 weeks of study intervention administration is prohibited.
- Prohibited concomitant medications are listed in Table 7.7-1.

**Table 7.7-1: Summary of Prohibited Concomitant Medications**

| | |
|---|---|
| **Immunomodulatory Drugs** | • eg, Thiopurines, methotrexate, cyclosporin, tacrolimus.<br>• Prohibited, with a required washout period of at least 1 day. |
| **Advanced Therapies for the Treatment of UC** | • Biologic agents and small molecules.<br>• Prohibited with required washout periods prior to study initiation of at least 8 weeks or 5 elimination half lives, whichever is shorter.<br>• Washout period may be waived with the demonstration of absent drug levels on a TDM assay. |
| **Monoamine Oxidase Inhibitors** | • Prohibited during ozanimod treatment.<br>• 14-day washout period prior to the first study intervention administration. |
| **Live or Live-attenuated Vaccines** | • Prohibited during ozanimod treatment.<br>• 30-day washout period prior to the first study intervention administration.<br>• Avoid use for up to 3 months after discontinuation of the study intervention. |

**Table 7.7-1: Summary of Prohibited Concomitant Medications**

| | |
|---|---|
| **Therapy for Current Active or Any Major Infections** | • Patients who require antibiotic treatment (oral or IV) for current active or any major infections are excluded. |
| **Alemtuzumab** | • Prohibited during ozanimod treatment.<br>• Confirm B cell recovery prior to the first study intervention administration. |
| **Beta Interferon** | • Prohibited during ozanimod treatment. |
| **Glatiramer Acetate** | • Prohibited during ozanimod treatment. |

Restricted concomitant medications and foods are listed in Table 7.7-2.

**Table 7.7-2: Summary of Restricted Concomitant Medications and Foods**

| | |
|---|---|
| **NSAIDs** | • May be used as clinically indicated during the study.<br>• Oral NSAIDs may be associated with GI toxicity, including mucosal injury. Consequently, their use is not recommended. |
| **Inactivated or Subunit Vaccines** | • May be used as clinically indicated during the study.<br>• The effect of ozanimod treatment on responses to vaccination is not known. |
| **Antiarrhythmic Drugs with Known Arrhythmogenic Properties** | • Ozanimod has not been studied in patients taking QT-prolonging drugs.<br>• Class Ia (eg, quinidine, procainamide) and Class III (eg, amiodarone, sotalol) antiarrhythmic drugs have been associated with cases of torsades de pointes in patients with bradycardia.<br>• Advice from a cardiologist should be sought prior to the initiation of treatment with ozanimod. |
| **Combination Beta Blocker and a Calcium Channel Blocker** | • Co-administration of ozanimod with both a beta blocker and a calcium channel blocker has not been studied. However, there is potential for additive effects on HR.<br>• Advice from a cardiologist should be sought prior to the initiation of treatment with ozanimod. |
| **Adrenergic and Serotoninergic Drugs** | • Co-administration of ozanimod with drugs or over-the-counter medications that can increase norepinephrine or serotonin (eg, opioid drugs, SSRIs, SNRIs, tricyclic antidepressants, tyramine) will be per product label.<br>• Monitor participants for hypertension with concomitant use. |
| **Foods Containing a Large Amount of Tyramine** | • Participants should be advised to avoid foods containing a large amount of tyramine during the treatment period.<br>• Aged, fermented, cured, smoked, and pickled foods containing large amounts of exogenous amines (eg, aged cheese, pickled herring) may cause the release of norepinephrine, resulting in an increase in blood pressure (tyramine reaction). |
| **Strong CYP2C8 Inducers** | • Use of strong CYP2C8 inducers (eg, rifampicin) should be avoided. |

**Table 7.7-2: Summary of Restricted Concomitant Medications and Foods**

| | |
|---|---|
| | • Co-administration of ozanimod with strong CYP2C8 inducers reduces the exposure of the major active metabolites of ozanimod, which may decrease the efficacy of ozanimod. |

CYP2C8, cytochrome P4502C8; NSAID, non-steroidal anti-inflammatory drugs; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Dose stabilization rules for permitted concomitant medications are listed in Table 7.7-3.

**Table 7.7-3: Summary of Dose Stabilization Rules for Permitted Concomitant Medications**

| | |
|---|---|
| **Oral and Rectal 5-ASAs** | • Oral and rectal 5-ASAs are permitted.<br>• Stable doses are encouraged after the first study intervention administration, particularly up to the assessment of the primary endpoint. |
| **Rectal Corticosteroids** | • Rectal corticosteroids are permitted as clinically indicated.<br>• After assessment of the primary endpoint, rectal corticosteroids are only allowed for a maximum of 3 months per year (eg, rectal corticosteroids are permitted during induction, and one other course is permitted as indicated within Year 1; only one 3-month course is permitted per year thereafter). |
| **Oral Prednisone** | • Cannot be on oral prednisone continuously for more than 28 days prior to Day 1.<br>• Oral prednisone ≤40 mg QD PO (or equivalent) is permitted at Day 1, if clinically indicated, and is permitted at that dose for no more than 14 days prior.<br>• Tapering schedule will be as follows: Reduce dose by 5 mg weekly until 20 mg is reached, then reduce by 2.5 mg weekly to 0 mg. Tapering can occur more rapidly at the investigator's discretion. Patient should be on prednisone continuously for no more than 12 weeks.<br>• One rescue course of prednisone (up to 40 mg QD PO with subsequent tapering, as described above) will be permitted per year, not including prednisone use in the first 12 weeks of the study. The maximum duration of each course is 12 weeks. |
| **Oral Budesonide** | • Budesonide ≤9 mg QD PO is permitted at Day 1, if clinically indicated.<br>• Dose should be stable for 14 days prior to the first study intervention administration.<br>• One rescue course of budesonide will be permitted each year with a maximum course duration of 12 weeks and tapering at the investigator's discretion.<br>• The investigator may switch between prednisone and budesonide for the rescue treatment. The maximum duration of 12 weeks applies, irrespective of steroid switching. |

#### *7.7.2 Other Restrictions and Precautions*

Participants are prohibited from joining another interventional clinical trial while they are participating in this study.

##### *7.7.2.1 Treatment Failure Rules*

Treatment failure rules will be applied to the primary analyses of all efficacy endpoints. Participants will be considered to have failed treatment if any of the following occur:

- Any protocol-prohibited change in medications, including:
  - Post-baseline initiation of or increase in total daily dose to a level higher than the 40 mg maximum permitted dose of corticosteroid to treat UC.
  - Prolonged course of systemic corticosteroids (ie, > 12 consecutive weeks) for treatment of UC.
  - Initiation of an immune-suppressing therapy, including 6-mercaptopurine, AZA, methotrexate, anti-TNF agents, anti-integrin, anti-IL-12/23 agents, or JAK inhibitors.
- A colectomy (partial or total) or an ostomy.
- Discontinuation of the study intervention due to lack of therapeutic effect before primary or secondary efficacy evaluations.

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

At the end of the study, BMS will not continue to provide BMS-supplied study interventions to participants or investigators unless BMS chooses to extend the study. The investigator should ensure that the participant receives the appropriate standard of care to treat the condition under study.

## 8 DISCONTINUATION CRITERIA

### 8.1 Discontinuation From Study Intervention

Participants MUST discontinue IP for any of the following reasons:

- Participant's or investigator'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 the 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.
- Any clinical AE, laboratory abnormality, intercurrent illness, or other appropriate reason(s), which, in the opinion of the investigator, indicates that continued administration of study intervention 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.)

- Pregnancy (refer to Section 9.2.5).
- Significant non-compliance with the protocol (eg, procedures, assessments, medications). The investigator should discuss such issues with the Medical Monitor.
- Participant meets one of the following criteria for laboratory abnormalities in 2 sequential laboratory measurements taken up to 14 days apart:
  - Hb < 7.0 g/dL or a decrease of >30% from baseline
  - Lymphocyte count < $0.2 \times 10^9$/L (< 200/$mm^3$) – see Section 9.2.6 for temporary discontinuation guidance.
- Participant meets any of the following criteria for liver-related laboratory abnormalities. If these abnormalities are identified, repeat testing should occur within 48 to 72 hours, and these results should be discussed with the BMS Medical Monitor or designee. Additional recommendations on the recognition and investigation of potential drug-induced liver injury (DILI) are given in Section 9.2.7.
  - ALT or AST > 8 × ULN on a single occasion.
  - ALT or AST > 5 × ULN for more than 2 weeks.
  - ALT or AST > 3 × ULN and total bilirubin > 2 × ULN or international normalized ratio (INR) > 1.5.
  - ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

Refer to the SOA for the data that will 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 the 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, as applicable, and entered on the appropriate eCRF page.

### *8.1.1 Treatment Interruption*

Participants should be instructed that if they forget to take a dose, they can take it within 4 hours of the normal dosing time; otherwise, they should take their next dose at the regular time on the following day. If the participant vomits the 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. Participants will record whether they took the daily dose of medication in an electronic diary that will be reviewed periodically by the site staff and the site monitor.

If a dose is missed during the first 2 weeks of treatment, re-iniate treatment using dose escalation regimen. If a dose of study intervention is missed after the first 2 weeks of treatment, continue with the treatment as planned. If more than 7 consecutive days between Day 15 and Day 28 of treatment, or more than 14 consecutive days after Day 28 of treatment, re-initiate treatment using the dose escalation regimen. The Medical Monitor should be contacted to discuss completing the dose escalation schedule.

### *8.1.2 Post-study Intervention Study Follow-up*

Participants who discontinue study intervention may continue to be followed.

## 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 the 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 investigator should explain the withdrawal of consent in detail in the medical records, including whether the withdrawal is from further treatment with study intervention only or whether it is also from study procedures and/or post-treatment study follow-up, and should enter this 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 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, the end of treatment and follow-up visits should be conducted, if possible, as shown in the SOA. See the SOA (Table 2-1 and Table 2-2) for the data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- 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.

### 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 the participant 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 a lack of response by the 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 the date and cause of death.
- If the investigator's use of a 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 the SOA (Section 2).
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the SOA (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 study intervention administration on Day 1. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures that are conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes, provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the SOA (Section 2).

## 9.1 Efficacy Assessments

### *9.1.1 Efficacy Assessments for the Study*

Study evaluations will take place in accordance with the SOA (Section 2). Endoscopy- and biopsy-related procedure details will be provided to the sites in a separate document/manual. A brief description about additional efficacy assessments is provided in Sections 5.1 and 5.4.

### *9.1.2 Other Efficacy Assessments for the Study*

#### *9.1.2.1 Histology Assessment*

A histology assessment will be done using the Geboes score. This instrument has been used to characterize the histological appearance of the mucosa in registrational UC studies.[32]

#### *9.1.2.2 Health-related Quality of Life*

HRQOL will be captured using the following questionnaires: [redacted] IBDQ, [redacted].

[redacted] The IBDQ was developed to measure the patient's experience of inflammatory bowel diseases (UC and CD). It consists of 32 questions divided into 4 dimensions: bowel symptoms (10 items), systemic symptoms (5 items), emotional function (12 items), and social function (5 items). Each question ranges from 1 "worst situation" to 7 "best situation"; and the total score ranges from 32 to 224, with higher scores representing better QOL.[34,35] [redacted]

The timing of HRQOL collection is provided in the SOA (Section 2).

## 9.2 Adverse Events

The definitions of an AE or an SAE can be found in APPENDIX 5.

AEs will be reported by the participants

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 5 for SAE reporting.

### 9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE and coronavirus disease (COVID) AE information should begin at screening until the follow-up visit, at the time points specified in the SOA (Section 2).

All SAEs must be collected from the time of signing the ICF, including those thought to be associated with protocol-specified procedures, and within 30 days 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 a protocol-specified procedure (eg, endoscopy, biopsy).

- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded in the appropriate section of the eCRF.
- All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in APPENDIX 5.
- The investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of the 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 to be 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 5.

#### 9.2.1.1 Adverse Events of Interest

Because of the characteristics of the disease under study and ozanimod in particular, some AEs are considered adverse event of interest (AEI). AEIs may be serious or nonserious. Such events may require further investigation to better characterize and understand them. In the ozanimod clinical development program, potential AEIs that may be a result of S1P1 modulation will be closely monitored during the study. These AEIs include bradycardia, heart conduction abnormalities (second degree and higher AV block), macular edema, malignancy, serious or opportunistic infection, pulmonary effects, hepatic effects, posterior reversible encephalopathy syndrome, progressive multifocal leukoencephalopathy (PML), and events associated with orthostatic hypotension (eg, dizziness, lightheadedness, syncope, seizure). The Sponsor may request additional medical information concerning AEIs that are nonserious.

- Bradycardia and heart conduction abnormalities (eg, symptomatic bradycardia, 2nd degree AV block, QT prolongation) will be screened for per the SOA (Section 2). First dose observation or cardiologist opinion will be per the SOA (Section 2). Investigators should be particularly cautious with participants with pulse rates < 55 beats per minute prior to administration of ozanimod. Atropine IV is recommended as first-line treatment for bradycardia, up to a

maximum daily dose of 3 mg. In general, common guidelines for treatment of bradycardia (eg, advanced cardiac life support) should be followed as appropriate.

- Macular edema
  - For participants with symptoms of new-onset macular edema that develop following initiation of treatment, a general ophthalmologic examination, including eye history, visual acuity, and dilated ophthalmoscopy must be performed.
  - Ozanimod must be discontinued in any participant who has a confirmed diagnosis of new-onset macular edema.
  - Participants with a diagnosis of macular edema must be followed up monthly and more frequently, if needed, based on the ophthalmologist's clinical judgment.
- Malignancy: Participants should be carefully monitored for malignancies (including dermatologic malignancy). The investigator will complete dermatological examinations to monitor the potential development of new cutaneous malignancies during the study. Participants with any suspicious finding noted during the examination will be referred to an appropriately qualified dermatologist for evaluation and treatment, if warranted.
- Serious or opportunistic infection: Tuberculosis, serious bacterial infections, systemic fungal infections, viral infections, such as herpes infections (including herpes zoster and disseminated herpes simplex), and protozoan infections will be considered AEIs.
- Pulmonary effects: If a participant discontinues due to a respiratory AE, the investigator should ensure that the participant has had adequate evaluations, as clinically indicated by a pulmonologist (consider pulmonary function tests, chest X-ray, or high-resolution computed tomography, based on findings of the other examinations), at the time of the AE.
- Hepatic effects: If participants have elevations in liver function tests (LFTs; ALT or/and AST) $\geq 3 \times$ ULN, a retest should be performed as soon as possible but no later than 14 days after the original test. Upon confirmation of the abnormality, retests should be performed weekly until the elevated LFT decreases to below $3 \times$ ULN. At any time, if any of the following occur and there are no apparent alternative causes for the finding, the study intervention must be permanently discontinued:
  - ALT or AST $> 8 \times$ ULN or
  - ALT or AST $> 5 \times$ ULN with confirmation within 2 weeks or
  - ALT or AST $> 3 \times$ ULN and (total bilirubin $> 2 \times$ ULN or INR $> 1.5$) or
  - ALT or AST $> 3 \times$ ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($> 5\%$).
- The investigator should establish causality.
- After discontinuation due to elevation of ALT or AST $> 5 \times$ ULN or concurrent elevations of ALT or AST $> 3 \times$ ULN and bilirubin $> 2 \times$ ULN, further liver function evaluations should be performed (for example, coagulation panel and alkaline phosphatase) in consultation with the Medical Monitor.
- Posterior reversible encephalopathy syndrome (PRES) is a syndrome characterized by sudden onset of severe headache, confusion, seizures, and visual loss. If a participant develops any unexpected neurological or psychiatric symptoms/signs (eg, cognitive deficits, behavioral changes, cortical visual disturbances, or any other neurological cortical symptoms/signs), any

symptom/sign suggestive of an increase of intracranial pressure, or accelerated neurological deterioration, the physician should promptly schedule a complete physical and neurological examination and should consider magnetic resonance imaging (MRI). If PRES is suspected, treatment with study intervention should be discontinued.

- PML: In the event of any neurological decline while on ozanimod, the participant should be urgently evaluated by a neurologist.
  - PML is an opportunistic viral infection of the brain caused by the John Cunningham virus that typically occurs in patients who are immunocompromised and may lead to death or severe disability. John Cunningham virus infection resulting in PML has been associated with some risk factors (eg, polytherapy with immunosuppressants, severely immunocompromised patients). PML has been observed in patients treated with immunomodulators, including ozanimod.
  - Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.
  - Investigators should be vigilant for clinical symptoms or other findings that may be suggestive of PML. If PML is suspected, a neurologist consultation should be obtained, and an MRI scan should be requested. Treatment with ozanimod should be suspended until PML has been excluded. If confirmed, treatment with ozanimod should be discontinued.

### *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 5).
- 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. Completion of supplemental eCRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

All SAEs 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 5.

### 9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification of SAEs by the investigator to the Sponsor 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 product label 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 SUSAR (suspected, unexpected serious adverse reaction) is a subtype of SAE 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 for at least intervention after study product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event. Then, they must 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 5.

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 with 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.

- Reductions in absolute lymphocyte count (ALC) levels for participants in this study are an expected primary PD effect. If ALC < 200 cells/µL results are observed during the study, the investigator will be notified and asked to repeat the laboratory tests within 14 days. If the repeat ALC is confirmed below the 200 cells/µL limit, the investigator will temporarily discontinue study intervention. Laboratory testing will be repeated weekly until the ALC is > 500 cells/µL. For participants who have a confirmed ALC below the 200 cells/µL limit and decide to permanently discontinue study intervention, central laboratory testing will continue every 14 days (± 3 days) after the end of treatment 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. Reductions in ALC, in general, need not be reported as AEs unless there are clinical consequences. The decision to report decreased ALC as an AE is at the investigator's discretion.
- 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 term would be used by the reporting investigator rather than the laboratory term (eg, anemia vs low Hb value).

### *9.2.7 Potential DILI*

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs meeting the defined criteria must be reported as SAEs (see Section 9.2 and APPENDIX 5 for reporting details).

A potential DILI is defined as:

- Aminotransferase (AT; ALT or AST) elevation > 3 × ULN

  AND
- Total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

  AND
- No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

### *9.2.8 Other Safety Considerations*

Any significant worsening of conditions noted during interim or final physical examinations, 12-lead ECG, X-ray filming, 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.

## 9.3 Expedited Reporting of SUSARs

For regulatory reporting, the BMS Drug Safety team is responsible for determining the expectedness of reported events that are suspected to be related to ozanimod based on the product label. Upon assessment and confirmation, SUSARs will be distributed per agreed contractual obligations between BMS and PPD.

- Reporting to global regulatory authorities/agencies will be handled by the BMS Drug Safety team.
- Reporting to Ethics Committees will be handled as follows:
  - For countries where reporting obligations to the IEC/IRB are delegated to PPD, the pharmacovigilance (PVG) team will ensure distribution to the appropriate IEC/IRB.

– For countries where reporting obligations to the IEC/IRB fall under the responsibility of the principal investigators (PIs), the PPD PVG team will distribute the reports to the PIs via PPD's LifeSphere system. The PIs will retrieve the safety reports from LifeSphere and perform onward submission to their corresponding IECs/IRBs per current local regulations.

This also applies for distribution of aggregate reports (eg, 6-monthly SUSAR line listings and Development Safety Update Report), based on the delegation of reporting tasks between PPD and BMS.

## 9.4 Overdose

An overdose is any dose of IP given to a participant or taken by a participant that exceeds the dose described in the protocol. Any overdose, with or without associated AEs, must be promptly reported to the Medical Monitor or other designated Drug Safety Center. The overdose should be recorded in the study exposure eCRF. AEs associated with an overdose should be reported in relevant AE/SAE sections in the eCRF.

In the event of an overdose, the investigator should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AEs/SAEs and laboratory abnormalities, as deemed appropriate by investigator.
- Document the quantity of the excess dose, as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

## 9.5 Safety

Planned time points for all safety assessments are listed in the SOA (Section 2).

### *9.5.1 Physical Examinations*

Physical examinations will be performed at the time points specified in the SOA (Section 2). Physical examinations will be performed by an investigator-designated medical doctor or advanced practitioner (eg nurse practitioner, physician assistant). Findings must be recorded in the appropriate section of the eCRF.

### *9.5.2 Vital Signs*

Vital signs will be measured at the time points specified in the SOA (Section 2).

### *9.5.3 12-lead ECG*

12-lead ECG will be performed at screening, as specified in the SOA (Section 2). ECG will be read locally. Clinically significant 12-lead ECG findings must be recorded in the appropriate section of the eCRF and should be discussed with the BMS Medical Monitor or designee.

### 9.5.4 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.
- Refer to Table 9.5.4-1 for details related to the clinical safety laboratory assessments and to the SOA (Section 2) for their time points.

A central laboratory will perform the analyses and will provide reference ranges for these tests.

Results of the clinical laboratory tests must be available prior to the first dose of study intervention on Day 1.

**Table 9.5.4-1: Clinical Safety Laboratory Assessments**

| | |
|---|---|
| **CBC and Differential Count** | |
| Hb | |
| Hematocrit | |
| Total leukocyte count, including differential | |
| Platelet count | |
| **Biochemistry** | |
| ALT<br>AST<br>Total bilirubin<br>Direct bilirubin<br>Alkaline phosphatase<br>Lactate dehydrogenase<br>Creatinine<br>BUN<br>Uric acid<br>Fasting glucose | Total protein<br>Albumin<br>Sodium<br>Potassium<br>Chloride<br>Calcium<br>Phosphorus<br>Magnesium |
| **Urinalysis** | |
| Protein | |
| Glucose | |
| Blood | |
| Leukocyte esterase | |
| Specific gravity | |
| pH | |
| Microscopic examination of the sediment if blood, protein, or leukocytes esterase are positive on the dipstick | |
| **Other Analyses** | |
| Pregnancy test (screening only; serum or urine)<br>Varicella IgG (screening only)<br>[redacted] | |

**Table 9.5.4-1: Clinical Safety Laboratory Assessments**

| |
|---|
| Urine beta-hCG test (WOCBP only) |
| FSH (optional; screening only [may be used to exclude childbearing potential in peri-menopausal females]) |

BUN, blood urea nitrogen; CBC, complete blood count; FSH, follicle-stimulating hormone; [redacted] IgG, immunoglobulin G.

[redacted]

[redacted]

## 9.8 Additional Research

Additional research related to the study intervention and/or disease may be performed. The results of this additional research could help to improve the diagnosis and/or the treatment of this disease in the future. This research [redacted]

[redacted]

## 9.9 Other Assessments

Not applicable.

## 9.10 Healthcare Resource Utilization

Healthcare resource utilization data associated with medical encounters will be collected in the eCRF by the investigator and study site personnel for all participants throughout the study (see Table 2-1 and Table 2-2). Protocol-mandated procedures, tests, and encounters will be excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters [redacted], including surgeries and other selected procedures (inpatient and outpatient).
- Duration of hospitalization (total length of stay in days, including duration by wards; eg, intensive care unit).

# 10 STATISTICAL CONSIDERATIONS

## 10.1 Statistical Hypotheses

Due to the open-label design of the study and the lack of a control group, all data will be summarized, and no hypothesis testing will be performed.

## 10.2 Sample Size Determination

The sample size for this study is not based on statistical power for comparisons among treatment cohorts; it has been selected to minimize the width of the 95% confidence interval (CI) of the estimate of the clinical response rate (primary endpoint) for each cohort.

An estimated total of 250 participants will be enrolled to achieve a total sample of 150 treated participants in Cohort 1, and approximately 165 participants will be enrolled to achieve a total sample of 100 treated participants in Cohort 2. The methods for determining each cohort's sample size are described below.

**Cohort 1 (Advanced Therapy-naïve Cohort)**

Due to the lack of published data evaluating the proportion of subjects achieving clinical response at Week 12, sample size estimates are based on clinical response rates at Week 10 in the biologic-naïve population from Study RPC01-3101 (ie, patients who have not been exposed to at least one biologic prior to study entry). Based on those results, it is anticipated that at least 50% of Cohort 1 will achieve clinical response at Week 12. Under these assumptions, a sample size of 150 participants would estimate exact binomial 95% CIs ranging between 41.7% and 58.3%.

**Cohort 2 (Advanced Therapy-exposed Cohort)**

The proportion of patients with clinical response in Cohort 2 is estimated to be 35% to 45% at Week 26 based on the clinical response rate at Weeks 10 and 52, as well as symptomatic response (as a surrogate variable) in the biologic-exposed population of Study RPC01-3101 (ie, patients who have been exposed to at least one biologic prior to study entry). Assuming a 45% clinical response rate at Week 26, a sample size of 100 participants is needed to provide a half-width of

the 95% CI of 10.5% (ie, 95% CI: 35%, 55.3%) using the exact CI formula for binomial probabilities.

## 10.3 Analysis Sets

For the purposes of analysis, the populations are defined as follows:

| Population | Description |
|---|---|
| Enrolled | All participants who signed an ICF and were registered into IRT. |
| Cohort 1 Treated Analysis Population | All Cohort 1 participants who received at least one dose of study intervention. This population will be used for both the efficacy and safety analyses for Cohort 1. |
| Cohort 2 Treated Analysis Population | All Cohort 2 participants who received at least one dose of study intervention. This population will be used for both the efficacy and safety analyses for Cohort 2. |
| **Defined Analysis Data Sets** | **Description** |
| Analysis set for primary estimand (Cohort 1) | All Cohort 1–treated participants. Participants who discontinued study intervention and/or received prohibited concomitant medications prior to Week 12 will be considered non-responders. |
| Analysis set for primary estimand (Cohort 2) | All Cohort 2–treated participants. Participants who discontinued study intervention and/or received prohibited concomitant medications prior to Week 26 will be considered non-responders. |

## 10.4 Statistical Analyses

Detailed methodology for the summary and statistical analyses of the data collected in this study will be documented in an SAP, which will be written and finalized prior to the study database lock. The plans outlined in this protocol may be modified in the SAP; however, any major modifications of the key endpoint definitions and/or related analyses will also be reflected in a protocol amendment.

### *10.4.1 General Considerations*

Baseline is defined as the last observed measurement prior to the first dose of study intervention on Day 1.

In general, descriptive summaries will be presented for the efficacy and safety variables collected. Continuous variables will be summarized using the number of participants (n), mean, standard deviation, minimum, median, and maximum. Categorical variables will be summarized using frequency counts and percentages, and 95% CIs. Analyses will be performed separately for each cohort, unless otherwise stated.

### *10.4.2 Disposition, Demographics, and Baseline Characteristics*

Participant disposition, including the number of participants screened and dosed, will be summarized for the enrolled population. Participant demographics will be summarized for the treated population and will include age, sex, race, ethnicity, height, weight, and body mass index.

Baseline characteristics will be summarized for the treated population and will include age at UC symptom onset, age at UC diagnosis, years since UC symptom onset, years since UC diagnosis,

prior anti-TNF use, corticosteroid use at screening, concomitant UC medication use at baseline, each component of the Mayo score, the complete Mayo score, the partial Mayo score, and the 9-point Mayo score.

### *10.4.3 Primary Endpoint*

The primary endpoint for each cohort, their corresponding descriptions, and prespecified time points are listed in Table 10.4.3-1.

The primary endpoint for Cohort 1 is the proportion of participants who achieve a clinical response at Week 12. The clinical response rate at Week 12 will be estimated, and the corresponding 95% CI will be derived based on the Clopper Pearson method.

The primary endpoint for Cohort 2 is the proportion of participants who achieve a clinical response at Week 26. An estimate of the clinical response rate at Week 26 will be provided, along with the corresponding 95% CI derived based on the Clopper Pearson method.

For proportion-based efficacy endpoints, patients with missing Week 12 efficacy data from Cohort 1 and/or participants with missing Week 26 efficacy data from Cohort 2 will be considered non-responders, and non-responder imputation will be used. Sensitivity analyses around missing data may involve missing data imputed using multiple imputation and may analyze observed cases with no imputation. Details of the sensitivity analysis will be provided in the SAP.

For continuous efficacy endpoints, observed cases will be analyzed with no imputation.

**Table 10.4.3-1: Endpoints**

| **Primary** | **Description** | **Timeframe** |
|---|---|---|
| Clinical Response (modified Mayo score) | Proportion of participants achieving the following:<br>• Decrease from baseline in the modified Mayo score of ≥ 2 points, and<br>• Decrease from baseline in the modified Mayo score of ≥ 35%, and<br>• Decrease in RB subscore of ≥ 1 point or absolute RB subscore ≤ 1. | Week 12 (Cohort 1)<br>Week 26 (Cohort 2) |
| **Secondary** | **Description** | **Timeframe** |
| Clinical Remission (modified Mayo score) | Proportion of treated participants achieving the following in each component of the modified Mayo score:<br>• SF subscore ≤ 1, with ≥ 1-point decrease from baseline, and<br>• RB subscore = 0, and<br>• ES ≤ 1. | Week 12 (Cohort 1)<br>Week 26 (Cohort 2) |
| Endoscopic Response | Proportion of treated participants with a decrease from baseline of ≥ 1 point in Mayo ES | Week 12 (Cohort 1)<br>Week 26 (Cohort 2) |
| Endoscopic Improvement | Proportion of treated participants with Mayo ES ≤ 1 | Week 12 (Cohort 1)<br>Week 26 (Cohort 2) |

**Table 10.4.3-1: Endpoints**

| | | |
|---|---|---|
| Endoscopic Remission | Proportion of treated participants with Mayo ES = 0 | Week 26 (Cohort 2) |
| IBDQ Response | Proportion of participants with a change from baseline in total score of ≥ 16 points | Week 12 (Cohort 1)<br>Week 26 (Cohort 2) |
| IBDQ Remission | Proportion of patients with a total score ≥ 170 points | Week 12 (Cohort 1)<br>Week 26 (Cohort 2) |
| Corticosteroid-free Clinical Remission (modified Mayo score) | Proportion of treated participants with:<br>• Clinical remission (modified Mayo score) and<br>• No oral systemic steroid use in prior 90 days | Week 26 (Cohort 2) |
| HEMI | Proportion of participants with endoscopy subscore of ≤ 1 point and a Geboes index score < 3.1 | Week 26 (Cohort 2) |
| [redacted] | | |

HEMI, histo-endoscopic mucosal improvement.

### *10.4.4 Secondary Endpoints*

All secondary endpoints, their corresponding descriptions, and prespecified time points are listed in Table 10.4.3-1 for each cohort.

For all binary response secondary endpoints in each cohort, the response rate at the prespecified time point will be estimated and a corresponding 95% CI will be derived based on the Clopper Pearson method. Details of the analysis for each secondary endpoint will be specified in the SAP.

[redacted]

### *10.4.6 Other Safety Analyses*

All safety analyses will be carried out for the treated population.

AEs will be monitored during the study, and the data will be analyzed with respect to incidence, severity, and the potential relationship of the AEs and study intervention. AEs with onset on or after the first dose of study intervention, or with onset prior to the first dose of study intervention that increase in severity on or after the first dose of study intervention will be considered treatment-emergent. TEAEs will be summarized for the safety population by system organ class (SOC) and preferred term, and presented in descending order of frequency within each SOC. SAEs, including AEIs, and AEs leading to discontinuation of study intervention will be summarized similarly.

Laboratory parameters will also be summarized. For each laboratory test, individual participant values outside the standard reference range will be flagged and listed. Shift tables will be produced showing the frequency of shifts from baseline to the lowest and to the highest on-trial value in and out of the normal range, as well as by visit. Changes from baseline to each visit for each laboratory parameter will also be summarized.

The change from baseline to each visit for each of the vital sign variables will be summarized. Abnormal vital sign values will be flagged and listed.

### *10.4.7 Other Analyses*

Additional endpoints collected during the study, such as [redacted] IBDQ (QOL), [redacted] will be summarized. All collected values will be listed for all participants.

[redacted]

## 10.5 Interim Analyses

Pre-planned interim analyses may be performed when all participants in both cohorts have completed the primary endpoint visit (ie, Week 12 for Cohort 1 and Week 26 for Cohort 2), and again when all participants in both cohorts have completed the 52-week visit. The final study analysis will be performed when all participants have completed the 116-week study (including the safety follow-up visit) or discontinued early from the study. Additionally, optional datacuts at other time points will be planned, if required. Details of all planned analyses will be provided in the SAP.

# 11 REFERENCES

1 ZEPOSIA® (ozanimod) US Prescribing Information. Celgene Corporation Summit, NJ. December 2021.

2 ZEPOSIA® Annex I Summary of Product Characteristics. Celgene Distribution B.V., Winthontlaan 6 N 3526 KV Utrecht Netherlands. May 2020.

3 Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987;317(26):1625-9.

4 Stenson WF. Inflammatory bowel disease. In: Goldman L, Bennett JC, editors. Cecil textbook of medicine. Philadelphia: W.B. Saunders; 2000. pp. 722-29.

5 Ordás I, Eckmann L, Talamini M, et al. Ulcerative colitis. Lancet. 2012;380(9853):1606-19.

6 Glickman RM. Inflammatory bowel disease: ulcerative colitis and Crohn's disease. In: Fauci AS, Braunwald E, editors. Harrison's principles of internal medicine. New York: McGraw-Hill; 1998. pp. 1633-45.

7 Van Limbergen J, Russell RK, Drummond HE, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. Gastroenterology 2008;135(4):1114-22.

8 Bernstein CN, Blanchard JF, Kliewer E, Wajda A. Cancer risk in patients with inflammatory bowel disease: a population-based study. Cancer 2001;91(4):854-62.

9 Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut 2001;48(4):526-35.

10 Ng SC, Kamm MA. Therapeutic strategies for the management of ulcerative colitis. Inflamm Bowel Dis 2009;15(6):935-50.

11 Kornbluth A, Sachar DB, Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. Am J Gasteroenterol 2010;105(3):501-23.

12 Rosenberg LN, Peppercorn MA. Efficacy and safety of drugs for ulcerative colitis. Expert Opinion Drug Saf 2010;9(4):573-92.

13 Carter MJ, Lobo AJ, Travis SP. Guidelines for the management of inflammatory bowel disease in adults. Gut 2004;53(Suppl 5):1-6.

14 Chaparro M, Trapero-Marugan M, Moreno-Otero R, Gisbert JP. Azathioprine plus ribavirin treatment and pancytopenia. Aliment Pharmacol Ther 2009;30(9):962-3.

15 Bousvaros A. Use of immunomodulators and biologic therapies in children with inflammatory bowel disease. Expert Rev Clin Immunol 2010;6(4):659-66.

[16] Chande N, Wang Y, MacDonald JK, McDonald JW. Methotrexate for induction of remission in ulcerative colitis. Cochrane Database Syst Rev 2014;(8)CD006618.

[17] Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG clinical guideline: ulcerative colitis in adults. Am J Gastroenterol 2019;114(3):384-413.

[18] Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. Gastroenterology 2020;158(5):1450-61.

[19] Gisbert JP, Panés J. Loss of response and requirement of infliximab dose intensification in Crohn's disease: a review. Am J Gastroenterol. 2009;104(3):760-7.

[20] Billioud V, Sandborn WJ, Peyrin-Biroulet L. Loss of response and need for adalimumab dose intensification in Crohn's disease: a systematic review. Am J Gateroenterol 2011;106(4):674-84.

[21] XELJANZ® (tofacitinib) US Prescribing Information. Pfizer Labs, NY. May 2018.

[22] Mandala S, Hajdu R, Bergstrom J, et al. Alteration of lymphocyte trafficking by sphingosine-1-phosphate receptor agonists. Science 2002;296(5566):346-9.

[23] Harris S, Tran JQ, Southworth H, et al. Effect of the sphingosine-1-phosphate receptor modulator ozanimod on leukocyte subtypes in relapsing MS. Neurol Neuroimmunol Neuroinflamm 2020;7(5)e839.

[24] Celgene. A phase 3, multicenter, randomized, double-blind, placebo-controlled trial of oral RPC1063 as induction and maintenance therapy for moderate to severe ulcerative colitis [Internet]. clinicaltrials.gov; 2021 Sep [cited 2022 Mar 25]. Report No.: NCT02435992. Available from: https://clinicaltrials.gov/ct2/show/NCT02435992.

[25] Celgene. A phase 2, multi-center, randomized, double-blind, placebo controlled parallel-group study to evaluate the clinical efficacy and safety of induction therapy with RPC1063 in patients with moderately to severely active ulcerative colitis [Internet]. clinicaltrials.gov; 2021 May [cited 2021 Nov 1]. Report No.: NCT01647516. Available from: https://clinicaltrials.gov/ct2/show/NCT01647516.

[26] Celgene. A phase 2/3, multi-center, randomized, double-blind, placebo-controlled (Part A) and double-blind, double-dummy, active-controlled (Part B), parallel group study to evaluate the efficacy and safety of RPC1063 administered orally to relapsing multiple sclerosis patients [Internet]. clinicaltrials.gov; 2021 Feb [cited 2022 Mar 25]. Report No.: NCT02047734. Available from: https://clinicaltrials.gov/ct2/show/NCT02047734.

[27] Celgene. A phase 3, multi-center, randomized, double-blind, double-dummy, active controlled, parallel group study to evaluate the efficacy and safety of RPC1063 administered orally to relapsing multiple sclerosis patients [Internet]. clinicaltrials.gov; 2020 Nov [cited 2021 Nov 1]. Report No.: NCT02294058. Available from: https://clinicaltrials.gov/ct2/show/NCT02294058.

[28] Sandborn WJ, Feagan BG, Wolf DC, et al. Ozanimod induction and maintenance treatment for ulcerative colitis. N Engl J Med 2016;374(18):1754-62.

[29] Sandborn WJ, Feagan BG, D'Haens G, et al. Ozanimod as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2021;385(14):1280-91.

[30] Scherl EJ, Pruitt R, Gordon GL, et al. Safety and efficacy of a new 3.3 g b.i.d. tablet formulation in patients with mild-to-moderately-active ulcerative colitis: a multicenter, randomized, double-blind, placebo-controlled study. Am J Gastroenterol 2009;104(6):1452-9.

[31] Draft Guidance for Industry, Ulcerative Colitis: Clinical Trial Endpoints. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). 2016.

[32] Geboes K, Riddell R, Ost A, et al. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. Gut 2000;47(3):404-9.

[redacted]

[34] Guyatt G, Mitchell A, Irvine EJ, et al. A new measure of health status for clinical trials in inflammatory bowel disease. Gastroenterology 1989;96(3):804-10.

[35] Mitchell A, Guyatt G, Singer J, et al. Quality of life in patients with inflammatory bowel disease. J Clin Gastroenterol 1988;10(3):306-10.

[redacted]

# 12 APPENDICES

## APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

| Term | Definition |
|---|---|
| 5-ASA | 5-aminosalicylate |
| AE | adverse event |
| AEI | adverse event of interest |
| ALC | absolute lymphocyte count |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AT | aminotransferase |
| AV | atrioventricular |
| AZA | azathioprine |
| BMS | Bristol-Myers Squibb |
| CD | Crohn's disease |
| CI | confidence interval |
| COVID | coronavirus disease |
| CSR | clinical study report |
| CTAg | Clinical Trial Agreement |
| DILI | drug-induced liver injury |
| EBV | Epstein–Barr virus |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| [redacted] | [redacted] |
| ES | endoscopic subscore |
| EU | European Union |
| [redacted] | [redacted] |
| FDA | Food and Drug Administration |
| FSH | follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GI | gastrointestinal |
| Hb | hemoglobin |

| Term | Definition |
|---|---|
| hCG | human chorionic gonadotropin |
| HEMI | histo-endoscopic mucosal improvement |
| HIPAA | Health Insurance Portability and Accountability Act |
| HR | heart rate |
| HRQOL | health-related quality of life |
| HRT | hormone replacement therapy |
| [redacted] | [redacted] |
| IBDQ | Inflammatory Bowel Disease Questionnaire |
| IC | inclusion criterion |
| ICF | informed consent form |
| ICH | International Council on Harmonisation |
| ICMJE | International Committee of Medical Journal Editors |
| IEC | Independent Ethics Committee |
| IgG | immunoglobulin G |
| IL | interleukin |
| IMP | investigational medicinal product |
| INR | international normalized ratio |
| IP | investigational product |
| IRB | Institutional Review Board |
| IRT | interactive response technology |
| IT | information technology |
| IUS | intrauterine system |
| IV | intravenous |
| JAK | Janus kinase |
| LAM | lactational amenorrhea method |
| LFT | liver function test |
| MRI | magnetic resonance imaging |
| MS | multiple sclerosis |
| PD | pharmacodynamics |
| PGA | Physician's Global Assessment |

| Term | Definition |
|---|---|
| [redacted] | [redacted] |
| PI | principal investigator |
| PID | patient identification number |
| PML | progressive multifocal leukoencephalopathy |
| PO | per oral |
| PRES | posterior reversible encephalopathy syndrome |
| PRO | patient-reported outcome |
| PVG | pharmacovigilance |
| QD | once daily |
| QOL | quality of life |
| RB | rectal bleeding |
| S1P | sphingosine 1-phosphate |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| SF | stool frequency |
| SOA | Schedule of Activities |
| SOC | system organ class |
| SUSAR | suspected, unexpected serious adverse reaction |
| TEAE | treatment-emergent adverse event |
| TNF | tumor necrosis factor |
| [redacted] | [redacted] |
| UC | ulcerative colitis |
| [redacted] | [redacted] |
| ULN | upper limit of normal |
| VZV | varicella zoster virus |
| WOCBP | women of childbearing potential |
| [redacted] | [redacted] |

# 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 eCRF.

## 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 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 ICF will receive approval/favorable opinion by the IEC/IRB, 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, 1 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, 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 institutional 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 (EU) Directive 2001/20/EC
- European Regulation 536/2014 for clinical studies (if applicable)
- European Medical Device Regulation 2017/745 for clinical device research (if applicable)
- the IRB/IEC
- 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, 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 the following:

- IRB/IEC
- Regulatory authority(ies), if applicable according to 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, by the local Health Authority, must be sent to 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 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 and answer all questions regarding the study.
- Inform the participant that his/her participation is voluntary. The participant will be required to sign a statement of informed consent that meets the requirements of 21 CFR Part 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 the participant to inquire about the details of the study.
- Obtain an ICF signed and personally dated by the participant and by the person who conducted the informed consent discussion.
- Include a statement in the participant's medical record that written informed consent was obtained before the 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 the participant to the most current version of the ICF(s) during his/her participation.

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 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.

Participants who are unable to give their written informed consent (eg, due to stroke or participants with severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The participant must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this participant become capable, he or she should personally sign and date the ICF as soon as possible. The explicit wish of a participant who is unable to give his or her written consent, but who is capable of forming an opinion and assessing

information to refuse participation in, or to be withdrawn from, the clinical study at any time, should be considered by the investigator.

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 PVG activities on key-coded health data transferred by BMS across national borders are 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 (CTAgs) 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 (IT) 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 case report form or entered in the 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.
- Definition of what constitutes source data and its origin can be found in the source data location list/map or equivalent document.

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, 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, 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 (but are not limited to) the following:<br>• Amount received and placed in storage area<br>• Amount currently in storage area<br>• Label identification number or batch number<br>• Amount dispensed to and returned by each participant, including unique participant identifiers<br>• Amount transferred to another area/site for dispensing or storage<br>• Non-study disposition (eg, lost, wasted)<br>• Amount destroyed at study site, if applicable<br>• Amount returned to BMS<br>• Dates and initials of person responsible for IP<br>• Dispensing/accountability per the Delegation of Authority Form |

Note: 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 eCRF 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. Electronic case report forms may be requested for AEs and/or laboratory test result abnormalities that are reported or identified during 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 eCRFs.

The completed eCRF 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. The investigator must retain a copy of the eCRFs, 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 non-compliance 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.

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 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 must contact BMS prior to destroying any records associated with the study.

BMS or its designee will notify the investigator 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/IEC). Notice of such transfer will be given in writing to BMS or its designee.

## RETURN OF STUDY INTERVENTION

For this study, study intervention, such as partially used study intervention titration blistercard or bottles, may be destroyed on-site.

| If | Then |
|---|---|
| Study interventions supplied by BMS (or vendors) | Any unused study interventions can only be destroyed after being inspected and reconciled by the responsible Study Monitor, unless study intervention titration blistercards or bottles must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxic or biologic agents).<br><br>Partially used study interventions and/or titration blistercard or bottles may be destroyed after proper reconciliation and documentation. However, unused IMP must be reconciled by the site monitor/clinical research associate prior to destruction.<br><br>If study interventions will be returned, the return will be arranged by the responsible study monitor. |

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 study intervention.
- 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 blistercard or bottle, including the date disposed of, quantity disposed, and identification of the person disposing the blistercards or bottles. 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 study period.

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

If conditions for destruction cannot be met, the responsible study monitor will make arrangements for return of study interventions provided by BMS (or its vendors).

## STUDY AND SITE 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, the following:

For study termination:

- Discontinuation of further development of study intervention
- For site termination:
- 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 or no recruitment (evaluated after a reasonable amount of time) 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 ensure appropriate participant therapy and/or follow-up.

## DISSEMINATION OF CLINICAL STUDY DATA

To benefit potential study participants, patients, health care 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 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.

In the EU, the summary of results and summary for laypersons will be submitted within 1 year of global end of trial.

## 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:

- External PI designated at protocol development
- National coordinating investigator

- Study Steering Committee chair or designee
- Participant recruitment (eg, among the top quartile of enrollers)
- Involvement in study design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)

## 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 CTAg governing (study site or investigator) 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 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 PI, sub-investigator, or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications by the Sponsor or its designees is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE; www.icmje.org). Authorship selection is based on 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)
2) Drafting the work or revising it critically for important intellectual content
3) Final approval of the version to be published
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 the Sponsor 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.

Participants must be informed that their study-related data (including but not limited to), such as endoscopy images, may be used for the publication of results, if required.

## APPENDIX 3 SELECTED INSTRUMENT DEFINITIONS (BASED ON PERMUTATIONS OF THE MAYO SCORE)

[redacted]

| | |
|---|---|
| **Modified Mayo Score** | Sum of the following components of the Mayo score (Range 0-9):<br>• SF subscore: Range 0-3<br>• RB subscore: Range 0-3<br>• ES: Range 0-3<br>ES is modified from the original description: Friability is not included in ES = 1. |
| **Partial Mayo Score** | Sum of the following components of the Mayo score (Range 0-9):<br>• SF subscore: Range 0-3<br>• RB subscore: Range 0-3<br>• PGA: Range 0-3 |

[redacted]

# APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

Appendix 4 provides general information and definitions related to WOCBP and methods of contraception that can be applied to most clinical trials. For information specific to this study regarding acceptable contraception requirements for female participants, refer to Section 6.1 of the protocol. Only the contraception methods described in Section 6.1 are acceptable for this study.

## DEFINITIONS

### Woman of Childbearing Potential

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
- Pre-menopausal female with one 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.

- Post-menopausal female
  - A post-menopausal state is defined as 12 months of amenorrhea in a woman over the age of 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 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 judgment 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 time point at which the study intervention (IMP and other study interventions, ie, non-IMP/auxiliary medicinal product required for study) or any active major metabolites have decreased to a concentration that is no longer considered relevant for human teratogenicity or fetotoxicity. This should be evaluated in the context of safety margins from the no-observed-adverse-effect level or the time required for 5 half-lives of the study intervention 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>**<br>*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 in which hormonal contraception is permitted by the study protocol.)[b]<br>– Oral (birth control pills)<br>– Intravaginal (rings)<br>– Transdermal<br>• Combined (estrogen- and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study intervention. |
| • Progestogen-only hormonal contraception associated with inhibition of ovulation. (This method of contraception can only be used by WOCBP participants in studies in which hormonal contraception is permitted by the study protocol.)[b]<br>– Oral<br>– Injectable<br>• Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study intervention. |
| **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 in which hormonal contraception is permitted by the study protocol.)[b]<br>• Intrauterine device.<br>• Intrauterine system (IUS). (This method of contraception can only be used by WOCBP participants in studies in which hormonal contraception is permitted by the study protocol.)[b,c]<br>• 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 intervention. 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 intervention.
- 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 of the protocol.
- 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, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactation 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 intervention, 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] IUS 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.<br>• Vaginal sponge with spermicide.<br>• 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 in which hormonal contraception is prohibited.) |
| **Unacceptable Methods of Contraception** |
| • Periodic abstinence (calendar, symptothermal, post-ovulation methods)<br>• Withdrawal (coitus interruptus)<br>• Spermicide only<br>• 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: Pregnancy of the protocol and APPENDIX 4.

# APPENDIX 5 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

## ADVERSE EVENTS

| **AE Definition** |
|---|
| An AE is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition occurring in a clinical investigation participant after signing of informed consent, whether or not considered related to the study intervention. |
| An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory test result), symptom, or disease temporally associated with the study intervention. |
| **Events Meeting the AE Definition** |
| • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECGs, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal laboratory test results or other safety assessment findings 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.<br>• Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.<br>• New conditions detected or diagnosed after study intervention administration, even though the condition may have been present before the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br>• 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/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.<br>• 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 the definition above, then it cannot be an SAE, even if serious conditions are met.

## SERIOUS ADVERSE EVENTS

| **A 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 that hypothetically might have caused death if it were more severe). |
| Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below).<br><br>NOTE:<br><br>The following hospitalizations are not considered SAEs in BMS clinical studies:<br><br>• A visit to the emergency department or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event).<br>• Elective surgery that was planned prior to signing consent.<br>• Admissions per protocol for a planned medical/surgical procedure.<br>• Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy).<br>• Medical/surgical admission other than to remedy ill health and planned prior to enrollment in the study. Appropriate documentation is required in these cases.<br>• 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).<br>• 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 results 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 department or at home for allergic bronchospasm and blood dyscrasias or convulsions that do not result in hospitalization. Potential DILI is also considered an important medical event. (See Section 9.2.7: Potential DILI of the protocol for the definition of a potential DILI.) |

Pregnancy and DILI must follow the same transmission timing and processes to BMS as those used for SAEs. (See Section 9.2.5: Pregnancy of the protocol 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 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 one 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 one of the pre-defined 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.)<br><br>If an ongoing SAE changes in its intensity or relationship to study intervention or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or the designee) using the same procedure used for transmitting the initial SAE report.<br><br>All AEs/SAEs must be followed to resolution or stabilization. |

## REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study intervention, and pregnancies must be reported to BMS (or the designee) promptly and not to exceed 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 eCRF.
  - The paper SAE Report Form is intended only as a back-up option when the EDC system is unavailable/not functioning for transmission of the eCRF to BMS (or the designee).
    - In this case, the paper form is transmitted via email or confirmed fax 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 fax transmission.

**SAE Email Address: SAE reporting contact information will be provided locally**

**SAE Fax Number: SAE reporting contact information will be provided locally**.

**SAE Telephone Contact** (required for SAE and pregnancy reporting): **SAE reporting contact information will be provided locally**.

## APPENDIX 6 SELECTED ENDPOINT DEFINITIONS

| | | |
|---|---|---|
| **Clinical Response** (modified Mayo score, primary endpoint) | | Achieving the following changes from baseline in the modified Mayo score:<br>• A decrease from baseline in the modified Mayo score ≥ 2 points, and<br>• A decrease from baseline in the modified Mayo score ≥ 35% , and<br>• A decrease from baseline in RB subscore ≥ 1 point or absolute RB subscore ≤ 1. |
| [redacted] | | |
| **Clinical Remission** (modified Mayo score) | | A modified Mayo score with the following:<br>• SF subscore ≤ 1, with ≥ 1 point decrease from baseline, *and*<br>• RB subscore = 0, *and*<br>• ES ≤ 1 |
| [redacted] | | |
| **Clinical Remission** (partial Mayo) | | Partial Mayo score ≤ 2.5 |
| **Endoscopic Response** | | A decrease from baseline of ≥ 1 point in Mayo ES |
| **Endoscopic Improvement** | | Mayo ES ≤ 1 |

| | | |
|---|---|---|
| **Endoscopic Remission** | | Mayo ES = 0 |
| **Histological Improvement** | • | • Achieving a Geboes score < 3.1 |
| **Histologic Remission** | | Achieving Geboes score < 2 |
| **HEMI** | | Mayo ES ≤ 1 *and* a Geboes score < 3.1 |
| **Corticosteroid-free Clinical Remission** (modified Mayo score) | | Clinical remission (by modified Mayo criteria), and no oral systemic steroid use in prior 90 days. |
| **Corticosteroid-free Clinical Remission** (partial Mayo score) | | Clinical remission (by partial Mayo criteria), and no oral systemic steroid use in prior 90 days. |
| [redacted] | | |