Official Title of Study:

A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Efficacy, and Biomarker Response of BMS-986165 in Subjects with Moderate to Severe Ulcerative Colitis

PROTOCOL(S) IM011-127

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CLINICAL PROTOCOL IM011127

A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Efficacy, and Biomarker Response of BMS-986165 in Subjects with Moderate to Severe Ulcerative Colitis

Short Title: Safety, Efficacy, and Biomarker Response of BMS-986165 in Subjects with Moderate to Severe Ulcerative Colitis

Protocol Amendment Number 02

Incorporates Administrative Letter 01

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DOCUMENT HISTORY

Document	Date of Issue	Approver(s)	Summary of Changes
Protocol Amendment 02	24-Feb-2022	[redacted]	Changes include the following: 1. Removed the BMS-986165 6 mg BID treatment arm 2. Clarified future treatment regimen for subjects currently receiving treatment in the BMS-986165 6 mg BID arm 3. Updated prior UC medication Inclusion Criterion to require inadequate response, loss of response, or intolerance to a treatment course of ≥ 1 of the standard of care UC medications; added an Inclusion Criterion to require at least 1 prior treatment course of corticosteroids for UC; and added corticosteroids (must have had 2 exposures separated by a corticosteroid-free period) [redacted] to the list of these standard of care UC medications 4. Added potential inclusion of subjects in the study who discontinue treatment with biologics due to inadequate funding (previously located in Appendix 5) 5. Added an enrollment target number of subjects [redacted] and included washout parameters for the medication class [redacted]

Document	Date of Issue	Approver(s)	Summary of Changes
			[redacted] 12. Added study treatment interruption rule for skin AEs and clarified dose interruption criteria for medical procedures in OLE period in Section 8.1.1 13. Moved study treatment interruption information from Section 7.4 to Section 8.1.1 14. Added definitions/exploratory efficacy endpoints for durable clinical response and durable endoscopic response, and added definition for corticosteroid-free remission 15. Added Exclusion Criterion for subjects receiving CMV colitis treatment within 12 weeks of randomization 16. Added Exclusion Criterion for subjects with a positive diagnostic test for SARS-CoV-2 during screening and added instruction that the screening SARS-CoV-2 diagnostic test must be performed and confirmed negative prior to randomization

Document	Date of Issue	Approver(s)	Summary of Changes
			17. Added to the guidance for rescreening of subjects with a positive SARS-CoV-2 test who had COVID-19 symptoms 18. Clarified reporting time requirements for AEs related to SARS-CoV-2 19. Removed Exclusion Criterion exception previously allowing subjects with Gilbert's syndrome to enroll in the study 20. Clarified potential acceptability of prophylactic use of antimicrobial agents during the study 21. Added calculation of modified Mayo score at Week 52 and symptomatic Mayo score for treatment response at Week 20 22. Clarified process for rescreening when qualifying endoscopy is completed, including determining stool frequency and rectal bleeding scores for eligibility. Additionally, for all rescreening, added a 45-day window after original screening during which select laboratory assessments do not need to be repeated if rescreening is required 23. Incorporated changes from Administrative Letter 01 and added guidance regarding the preference for usage of the central laboratory versus local laboratories for performing safety assessments 24. Added potential to extend 14-day window for randomization after the initial screening endoscopy by an additional 3 days with BMS Medical Monitor/designee approval (rescreening only) 25. Removed details of potential exposure-response analyses and replaced with reference to separate analysis plan as needed 26. Removed reference to "legally acceptable" representatives in relation to signing the ICF only

Document	Date of Issue	Approver(s)	Summary of Changes
			27. Clarified in Section 10.4.4 that an interim analysis of data would potentially be conducted in addition to the primary efficacy analysis to be conducted, and added corresponding required steps related to SAP finalization and interim analysis plan approval if an interim analysis is to be conducted 28. Updated Appendix 4 according to the 25-Nov-2020 Protocol Model Document Appendix template 29. Updated Appendix 13 according to current enterprise COVID-19 language
Protocol Administrative Letter 01	04-Jun-2021	[redacted]	Aligned the laboratory to be used for Clostridioides difficile testing in Table 11 with Section 9.4.3.
Protocol Amendment 01	06-May-2021	[redacted]	Changes include the following: 1. Added information, instructions, and measures to be taken in relation to SARS-CoV-2 infection 2. Added clarification regarding additional research sample collection and use 3. Removed prohibition of medical marijuana 4. Added assessments of mean corpuscular volume and mean corpuscular hemoglobin to the list of hematology laboratory tests to be conducted. 5. Removed the endoscopic global severity score. This was included in error, and is not being collected in the study. 6. Clarified the definitions of steroid-dependent and steroid-resistant UC, to aid eCRF completion. 7. Clarified the definition of the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). 8. Clarified male contraception requirements
Original Protocol	22-Apr-2020	[redacted]	Not applicable

Document	Date of Issue	Approver(s)	Summary of Changes
		[redacted]	

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 02:

Rationale:

The primary purpose of this protocol amendment is to remove the BMS-986165 6 mg twice daily (BID) treatment arm from the induction phase (first 12 weeks) as a BMS-986165 Phase 2 study in subjects with ulcerative colitis (UC) (Study IM011024) did not meet prespecified efficacy endpoints during induction (the first 12 weeks of treatment) at the BMS-986165 6 mg BID dose.

Key additions and clarifications include:

- Removed the BMS-986165 6 mg BID treatment arm, with subjects subsequently randomized in a 3:1 ratio to either 12 mg BID (~37 subjects) or placebo BID (~13 subjects) treatment.
- Clarified that subjects currently receiving treatment in the BMS-986165 6 mg BID arm under the Original Protocol or Protocol Amendment 01 will continue to receive BMS-986165 6 mg BID treatment throughout the double-blind period.
- Updated prior UC medication Inclusion Criterion 4)a) to Criterion 4)b) to require inadequate response, loss of response, or intolerance to a treatment course of 1 or more of the standard of care UC medications; added Inclusion Criterion 4)c) to require at least 1 prior treatment course of corticosteroids for UC; and added corticosteroids (must have had 2 exposures separated by a corticosteroid-free period) to the list of these standard of care UC medications.
- Added potential inclusion of subjects in the study who discontinue treatment with biologics due to inadequate funding (previously located in Appendix 5).
- Added an enrollment target number of subjects and included washout parameters for the medication class.
- Added study treatment interruption rule for skin AEs and dose interruption criteria for medical procedures in the open-label extension (OLE) period in Section 8.1.1.

- Moved study treatment interruption information from Section 7.4 to Section 8.1.1.
- Added definitions/exploratory efficacy endpoints for durable clinical response and durable endoscopic response at Week 52, and added a definition for corticosteroid-free remission (clinical remission in subjects using oral corticosteroids at baseline who have discontinued corticosteroids for UC in the OLE period for ≥ 12 weeks prior to Week 52).
- Added Exclusion Criterion 2)g) for subjects receiving cytomegalovirus colitis treatment within 12 weeks of randomization.
- Added Exclusion Criterion 7)k) for subjects with a positive diagnostic test for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) during screening and added instruction that the screening SARS-CoV-2 diagnostic test must be performed and confirmed negative prior to randomization.
- Added to the guidance for rescreening of subjects with a positive SARS-CoV-2 test who had Coronavirus Disease 2019 (COVID-19) symptoms.
- Clarified that AEs related to SARS-CoV-2 should be reported within 24 hours of site awareness.
- Removed exception to Exclusion Criterion 7)g)ix previously allowing subjects with Gilbert's syndrome to enroll in the study.
- Clarified potential acceptability of prophylactic use of antimicrobial agents during the study.
- Added calculation of modified Mayo score at Week 52 and symptomatic Mayo score for treatment response at Week 20.
- Clarified process for rescreening when qualifying endoscopy is completed, including determining stool frequency and rectal bleeding scores for eligibility. Additionally, for all rescreening, added a 45-day window after the original screening of select laboratory assessments during which these laboratory assessments do not need to be repeated if rescreening is required.
- Incorporated changes from Administrative Letter 01 (aligned the laboratory to be used for Clostridioides difficile testing in Table 11 with Section 9.4.3) and added guidance regarding the preference for usage of the central laboratory versus local laboratories for performing safety assessments.
- Added the potential to extend the 14-day window for randomization after the initial screening endoscopy by an additional 3 days with BMS Medical Monitor/designee approval (rescreening only).
- Removed details of potential exposure-response analyses and replaced them with reference to separate analysis plan as needed.
- Removed reference to "legally acceptable" representatives in relation to signing the informed consent form only.
- Clarified in Section 10.4.4 that an interim analysis of data would potentially be conducted in addition to the primary efficacy analysis to be conducted, and added corresponding required steps related to Statistical Analysis Plan finalization and interim analysis plan approval if an interim analysis is to be conducted.
- Updated Appendix 4 according to the 25-Nov-2020 Protocol Model Document Appendix template.

- Updated Appendix 13 according to current enterprise COVID-19 language.

This protocol amendment will be implemented after the investigator receives all appropriate agency and Investigational Review Board/Independent Ethics Committee approvals.

All changes applied to the body were applied to the synopsis, as necessary, and synopsis changes are not included in the list below.

Only major additions and deletions are provided in this summary document, and all minor grammatical, formatting, rephrasing, stylistic changes, or clarifications, as well as reorganizational changes are not included.

The rationales for changes to this protocol amendment are provided in the summary of key changes table, as shown below:

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1.2: Schema Section 2: Schedule of Activities, Table 2 Section 3.2: Benefit/Risk Assessment Section 5.1: Overall Design, Figure 1 Section 5.1.2: Double-blind Treatment Period Section 5.4: Scientific Rationale for Study Design [redacted] Section 7.1: Treatments Administered Section 7.2: Method of Treatment Assignment Section 10.1: Sample Size Determination Section 10.1.1: Clinical Response Rate Section 10.4.3.2: Exposure-response Modeling	Removed the BMS-986165 6 mg twice daily (BID) induction treatment arm from the study design, updated the randomization ratio to 3:1, and updated the subject numbers in each arm.	Removed the BMS-986165 6 mg BID treatment arm from the induction phase as the Phase 2 study (Study IM011024) did not meet prespecified efficacy endpoints during induction (the first 12 weeks) at the BMS-986165 6 mg BID dose. The randomization ratio was updated to accommodate the change in randomization scheme; this ratio change will allow for a more robust assessment of treatment effect.
Section 1.2: Schema Section 5.1: Overall Design, Figure 1 Section 5.1.2: Double-blind Treatment Period [redacted]	Clarified that subjects randomized to the BMS-986165 6 mg BID dose arm under the Original Protocol or Protocol Amendment 01 will continue to receive this dose throughout the double-blind period.	Clarified that subjects who previously received the 6 mg BID dose will continue to receive the same dose during the double-blind period.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7: Treatment, Table 4 Section 7.1: Treatments Administered Section 10.1: Sample Size Determination		
Section 1.2: Schema Section 5.1: Overall Design, Figure 1 Section 5.1.3: Open-label Extension Period [redacted]	[redacted]	[redacted] language added to allow more flexibility for the investigator.
Section 2: Schedule of Activities, Table 2 Section 9.6: Biomarkers, Table 13 and Table 14	[redacted]	Added [redacted] sample collections to allow for a more complete characterization of BMS-986165 pharmacology over time.
Section 2: Schedule of Activities, Table 2 Section 5.1.3: Open-label Extension Period (symptomatic Mayo score only)	Added calculation of modified Mayo score at Week 52 and symptomatic Mayo score for treatment response at Week 20.	Clarified the need for sites to perform these calculations at these time points.
Section 2: Schedule of Activities, Table 1 Section 6.2: Exclusion Criteria, 7) Physical and Laboratory Test Findings	Added Exclusion Criterion 7)k) for subjects with a positive molecular (polymerase chain reaction) or antigen diagnostic test for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) during screening (Section 6.2 only), and added instruction (Section 2 only) that the screening SARS-CoV-2 diagnostic test must be performed and confirmed negative prior to randomization.	Added for clarification.
Section 4: Objectives and Endpoints Section 5.1.3: Open-label Extension Period [redacted]	[redacted]	[redacted]

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 4: Objectives and Endpoints [redacted] Section 9.1.2: Disease Activity and Quality of Life Indices Used in this Study, Table 10	Added definitions/exploratory efficacy endpoints for durable clinical response and durable endoscopic response, and added definition of corticosteroid-free remission.	Added to assess the durability of efficacy with dose reduction in the open-label extension (OLE) period.
Section 5.1.1: Screening Period Section 5.2: Number of Subjects Section 5.4: Scientific Rationale for Study Design Section 6.1: Inclusion Criteria, 4) Prior UC Medication Inclusion Criteria	[redacted]	Revised to ensure that the study population reflects the range of patients with moderately to severely active UC.
Section 5.1.1: Screening Period Section 6.5.2: Rescreening	Added the potential to extend the 14-day window for randomization following the initial screening endoscopy by an additional 3 days with approval of the BMS Medical Monitor/designee (rescreening only).	Added to simplify study operations.
Section 5.1.5: Treatment Failure	[redacted]	Removed requirement [redacted]
Section 5.1.5: Treatment Failure	[redacted]	Expanded to include additional criteria that apply to the definition of treatment failure.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.2: Number of Subjects Section 6: Study Population Appendix 7: Examples of Washout Times Required Prior to Randomization	Added an enrollment target number of subjects previously exposed to biologics [redacted] and included washout parameters for the medication class.	Added to ensure that the study population reflects the range of patients with moderately to severely active UC [redacted].
Section 6.1: Inclusion Criteria, 4) Prior UC Medication Inclusion Criteria Appendix 5: Criteria To Define Inadequate Response (Primary), Loss Of Response (Secondary), And Intolerance To Previous Standard Of Care Medication(s)	Moved potential study inclusion of subjects who stop treatment with biologics due to loss of funding previously in Appendix 5 to Inclusion Criterion 4)b).	Moved for clarity/greater visibility.
Section 6.2: Exclusion Criteria, 2) UC Exclusion Criteria	Added Exclusion Criterion 2)g) for subjects receiving treatment for cytomegalovirus (CMV) colitis within 12 week of randomization.	Added treatment for CMV colitis as exclusionary avoid confounding efficacy and safety assessments.
Section 6.2: Exclusion Criteria, 5) Immune and Infectious Disease Exclusion Criteria - updated 5)b) → 5)f) Section 6.2: Exclusion Criteria, 6) Prior/Concomitant Therapy - updated 6)l) → 6)n) Section 7.7.1: Prohibited Treatments, Table 6	Added potential study eligibility of subjects being treated prophylactically with antimicrobial agents (including antibiotics) during the study.	Clarified inclusion/exclusion in the study by distinguishing antimicrobial therapy as either for direct treatment or strictly for prophylactic use.
Section 6.2: Exclusion Criteria, 7) Physical and Laboratory Test Findings - updated 7)g)ix) → 7)g)xi)	Removed Exclusion Criterion exception which previously allowed subjects with Gilbert's syndrome to participate in the study.	Removed Gilbert's exception to simplify interpretation of liver abnormalities if they occur.
Section 6.5.2: Rescreening	Clarified process for rescreening when qualifying endoscopy is completed, including determining stool frequency and rectal bleeding scores for eligibility. Additionally, for all rescreening, added a 45-day window after the original screening of select laboratory assessments during which these laboratory assessments do not need to be repeated if rescreening is required.	Added to simplify study operations.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.4: Dosage Modification Section 8.1.1: Temporary Interruption of Study Treatment	Moved study treatment interruption information from Section 7.4 to Section 8.1.1.	Moved for clarity/greater visibility.
Section 7.7.1: Prohibited Treatments, Table 6 Section 7.7.3: Dose Stabilization Rules for Permitted UC Treatments, Table 8	[redacted]	Expanded stabilization window for corticosteroids and 5-ASA to minimize impact on efficacy.
Section 8.1.1: Temporary Interruption of Study Treatment	Added a study treatment interruption rule for skin adverse events (AEs) and dose interruption criteria for medical procedures in the OLE period.	Aligned dose interruption criteria related to skin AEs with Revised Protocol 00a CA-specific (dated 29-Oct-2020) and to clarify conditions under which dose interruption related to medical procedures is permitted.
Section 9.2.1: Time Period and Frequency for Collecting AE and SAE Information Section 9.8: SARS-CoV-2 Testing	Clarified reporting time requirements for AEs related to SARS-CoV-2 (within 24 hours of site awareness).	Added to clarify safety reporting.
Section 9.4.3: Clinical Laboratory Assessments	Aligned the laboratory to be used for Clostridioides difficile testing in Table 11 with Section 9.4.3 (central or local laboratory acceptable) and added guidance regarding the preference for usage of the central laboratory versus local laboratories for performing safety assessments.	Added to incorporate changes from Administrative Letter 01 and to simplify study operations.
Section 9.8: SARS-CoV-2 Testing	Added to the guidance for rescreening of subjects with a positive SARS-CoV-2 test who had Coronavirus Disease 2019 (COVID-19) symptoms.	Clarified rescreening requirements related to resolution of COVID-19 symptoms.
Section 10.4.3.2: Exposure-response Modeling	Removed details of potential exposure-response analyses and replaced with reference to separate analysis plan as needed.	Streamlined this section.
Section 10.4.4: Interim Analyses	Clarified that an interim analysis of data would potentially be conducted in addition to the primary efficacy analysis, and added that the Statistical Analysis Plan will be finalized and an interim analysis plan will be approved	Clarified information related to an interim analysis.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	prior to interim analysis database lock if an interim analysis is to be conducted.	
Appendix 2: Study Governance Considerations	Removed reference to "legally acceptable" representatives in relation to signing the ICF only.	Removed because all subjects must sign the ICF themselves.
Appendix 4: Women of Child Bearing Potential	Removed vaginal suppositories, gels, and creams from highly effective user-dependent contraceptive methods.	Harmonized with the 25Nov2020 Protocol Model Document Appendix template.
Appendix 5: Criteria To Define Inadequate Response (Primary), Loss Of Response (Secondary), And Intolerance To Previous Standard Of Care Medication(s)	[redacted]	Aligned criteria with updates to Inclusion and Exclusion criteria.
Appendix 13: Vaccine Guidance Including SARS-CoV-2 Vaccines	Updated appendix language related to SARS-CoV-2 vaccine guidance.	Harmonized with current enterprise COVID-19 language.

Please provide a copy to your Investigational Review Board/Independent Ethics Committee, unless agreed otherwise with BMS.

TABLE OF CONTENTS

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Efficacy, and Biomarker Response of BMS-986165 in Subjects with Moderate to Severe Ulcerative Colitis

Short Title: Safety, Efficacy, and Biomarker Response of BMS-986165 in Subjects with Moderate to Severe Ulcerative Colitis

Study Phase: 2

Study Rationale: Study IM011127 is a Phase 2 randomized, double-blind, placebo-controlled, multicenter study designed to assess the safety and tolerability, efficacy, and biomarker response of BMS-986165 12 mg twice daily (BID) orally (PO) in subjects with moderate to severe ulcerative colitis (UC).

This study is being conducted in the context of a wider clinical development program of BMS-986165 in inflammatory bowel disease (IBD; Section 3.1.5). Study IM011023 (NCT03599622) assesses safety and efficacy of BMS-986165 6 mg BID and 3 mg BID PO regimens compared with placebo in subjects with moderately to severely active Crohn's disease (CD). Study IM011024 (NCT03934216) compares BMS-986165 6 mg BID PO with placebo in subjects with moderately to severely active UC.

BMS-986165 6 mg BID and placebo reference arms were originally included in this study to facilitate an integrated analysis of safety, efficacy, and biomarker data from the current study and Study IM011024. The 6 mg BID treatment arm is being removed from the induction phase in Protocol Amendment 02 due to Study IM011024 not meeting prespecified efficacy endpoints during induction (the first 12 weeks of treatment) at the 6 mg BID dose. The placebo reference arm has also been included to manage bias in the reporting of safety data and the reporting of patient-reported outcomes (PROs), including the PRO components of the modified Mayo score that contribute to the evaluation of disease activity-based Inclusion Criteria and the primary endpoint of this study.

BMS-986165 12 mg BID is being assessed in this study for the following reasons:

[redacted]

The safety and tolerability of BMS-986165 at single doses of up to 40 mg and at multiple doses of up to 12 mg BID was assessed in NHV studies. In addition, the safety, tolerability, and efficacy of BMS-986165 at doses of up to 6 mg BID and 12 mg QD have been explored in a Phase 2 clinical trial in psoriasis.

The safety and tolerability of BMS-986165 at 12 mg QD or 12 mg BID regimens in NHV studies is detailed in Section 3.1.3. [redacted]

[redacted]

[redacted]

The goals of this study are to:

1. Estimate the efficacy of BMS-986165 12 mg BID in subjects with UC

The efficacy of BMS-986165 12 mg BID PO will be estimated at Week 12, and over time, using both standard instruments (eg, modified Mayo score) and novel instruments specifically designed for use in exploratory studies (eg, UC-100; see Section 9.1.2).

2. Evaluate the safety and tolerability of BMS-986165 12 mg BID in subjects with UC

BMS-986165 12 mg QD and 12 mg BID have been explored in healthy volunteers for up to 14 days (Section 3.1.3 and IB[5]). [redacted] BMS-986165 6 mg BID is currently being explored in subjects with UC and CD (Section 3.1.5). However, this study is the first experience of BMS-986165 12 mg BID PO in subjects with UC. Consequently, this study will carefully assess the safety and tolerability of this regimen in this patient population. Additional safety assessments will be incorporated into this study, based on experience at relevant dose levels in preceding studies. Multiple levels of study oversight will be provided by the Sponsor through medical monitoring as well as periodic review of collected safety data by an external, independent Data Monitoring Committee (DMC) (Section 5.1.6).

[redacted]

[redacted]

Study Population:

Key Inclusion Criteria (Section 6.1) include:

- Males and females, ages 18 (or local age of majority) to 65 years, inclusive, at the time of screening
- Documented diagnosis of UC ≥ 3 months' duration prior to screening
- UC disease distribution extending proximal to the rectum (ie, left-sided colitis or pancolitis)
- Moderately to severely active UC, defined by a modified Mayo score of 5 to 9 points, inclusive (modified Mayo score range = 0 to 9 points), which includes all of the following:
  - A stool frequency (SF) subscore of ≥ 2, and
  - A rectal bleeding (RB) subscore ≥ 1, and

  - An endoscopic (ES) subscore of ≥ 2 (screening endoscopy)
- Inadequate response, loss of response, or intolerance to a treatment course of 1 or more of the following standard of care UC medications (APPENDIX 5):
  - Oral 5-aminosalicylic acids (5-ASAs) (eg, mesalamine, sulfasalazine, olsalazine, or balsalazide)
  - Corticosteroids (eg, prednisone or budesonide Multi-Matrix System [MMX]) (must have had 2 exposures separated by a corticosteroid-free period)
  - Immunomodulators (eg, azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX])
  - Anti-TNF agents or integrin inhibitors (eg, vedolizumab) approved for the treatment of UC
  - Subjects who stop treatment with biologics due to loss of funding (eg, loss of insurance coverage) may also be eligible for inclusion into the study. Subject eligibility should be discussed with the BMS Medical Monitor/designee.

Key Exclusion Criteria (Section 6.2) include:

- UC involving the rectum only (UC proctitis)
- Current diagnosis of CD, indeterminate colitis, ischemic colitis or microscopic colitis, a monogenic cause of UC-like intestinal inflammation, or a diagnosis of pseudomembranous colitis other than that associated with Clostridioides *difficile* (formerly *Clostridium difficile* [*C. difficile*])
- Current or recent (within 12 weeks prior to randomization) evidence of fulminant UC (also known as acute severe UC), toxic megacolon, evidence of bowel perforation, or intra-abdominal abscess
- Current colonic adenomas or mucosal dysplasia

- Prior treatment failure (inadequate response or loss of response) [redacted]

Objectives and Endpoints:

The key efficacy, safety, [redacted] objectives and endpoints are summarized below:

Objective	Endpoints
Primary - Efficacy	
• To estimate the efficacy of BMS-986165 at Week 12	• Proportion of subjects in clinical response at Week 12
Safety	
• To assess the **safety and tolerability** of BMS-986165	• Number and proportion of subjects experiencing AEs, SAEs, AEs leading to discontinuation from the study, and AEIs throughout the study
Exploratory [redacted]	
[redacted]	

AE = adverse event; AEI = adverse event of interest; SAE = serious adverse event

A complete list of objectives and endpoints is provided in Section 4.

Overall Design:

- **Study design:** Parallel, double-blind, placebo-controlled, multicenter clinical trial (12 weeks), with a 40-week open-label extension (OLE) period
- **Blinding:** Double-blind, matching placebo oral tablets
- **Treatment assignment method/stratification:**
  - Subjects who have completed screening procedures (up to 28 days duration) and met Inclusion/Exclusion criteria will be randomized on Day 1 of the treatment period.
  - **Not Applicable to Subjects Enrolled Under Protocol Amendment 02**. Subjects will be randomized in a 3:1:1 ratio using interactive response technology (IRT) to receive oral BMS-986165 12 mg BID, BMS-986165 6 mg BID, or placebo BID during the 12-week treatment period.
  - Subjects will be randomized in a 3:1 ratio using IRT to receive oral BMS-986165 12 mg BID or placebo BID during the 12-week treatment period.
  - Subjects randomized to the BMS-986165 6 mg BID arm under the Original Protocol or Protocol Amendment 01 will continue to receive BMS-986165 6 mg BID for the 12-week double-blind treatment period.
  - Randomization will not be stratified.

- **Study periods:**
  - Screening: up to 4 weeks (28 days)
  - Double-blind treatment: 12 weeks (84 days)
  - OLE: up to 40 weeks (280 days)
  - Follow-up: 4 weeks (28 days)

The total duration of study participation is approximately 60 weeks (420 days) in 4 periods.

- **Study assessments:** Include assessments of medical and UC disease history, prior medications, concomitant medications and UC medications, tobacco use, baseline SF; physical examinations; chest x-ray (CXR); 12-lead electrocardiogram (ECG); blood, stool, and urine sample collections; endoscopies with biopsies; additional efficacy assessments and the Physician's Global Assessment (PGA); and subject collection of PROs in daily electronic diaries as outlined in the Schedule of Activities (Section 2).

[redacted]

- **Discontinuation from the study:** Subjects who discontinue study treatment will remain in the study and are required to continue to be followed for protocol-specified post-treatment follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the subject to provide this information.

Safety monitoring will occur at study sites, by the Sponsor, and also by an external, independent DMC (Section 5.1.6).

Number of Subjects: Approximately 50 subjects

Treatment Arms and Duration:

Double-blind Treatment Period: On Day 1, subjects will be randomized to receive 1 of the following study treatments:

- BMS-986165 12 mg BID
- **Not Applicable to Subjects Enrolled Under Protocol Amendment 02**. BMS-986165 6 mg BID
- Placebo BID

OLE Period: Subjects who are likely to derive a clinical benefit from ongoing participation in the study following Week 12, as judged by the investigator, are eligible to enter the OLE period and receive the following study treatment:

- BMS-986165 6 mg BID

Study Treatment:

Study Treatments for IM011127

Product Description/ Class and Dosage Form	Potency	IP/ Non-IP	Blinded or Open-label	Packaging/ Appearance	Storage Conditions (per label)
BMS-986165 12 mg oral tablet	12 mg	IP	Blinded	Blister card containing 72 tablets	Store 15° to 25°C; Protected from light
BMS-986165 6 mg oral tablet *Applicable only to subjects enrolled under the Original Protocol or Protocol Amendment 01*	6 mg	IP	Blinded	Blister card containing 72 tablets	Store 15° to 25°C; Protected from light
Placebo matching BMS-986165 12 mg oral tablet	Not applicable	IP	Blinded	Blister card containing 72 tablets	Store 15° to 25°C; Protected from light
Placebo matching BMS-986165 6 mg oral tablet	Not applicable	IP	Blinded	Blister card containing 72 tablets	Store 15° to 25°C; Protected from light
BMS-986165 6 mg oral tablet	6 mg	IP	Open-label	Bottle containing 68 tablets	Store 15° to 25°C; Protected from light

IP = investigational product

Statistical Methods: Approximately 50 subjects will be randomized in a 3:1 ratio to BMS-986165 12 mg BID and placebo BID, respectively (ie, approximately 37 subjects receiving BMS-986165 12 mg BID and 13 subjects receiving placebo BID). Approximately 3 subjects (enrolled under the Original Protocol or Protocol Amendment 01) are expected to receive BMS-986165 6 mg BID and will also be included. The sample size for this study is not based on statistical power for comparisons among treatment groups. It has been selected to provide adequate precision for the estimation of efficacy (Section 10.1.1), safety (Section 10.1.2) [redacted] in subjects treated with BMS-986165 12 mg BID.

Categorical data will be summarized as frequency counts and percentages. Continuous data will be summarized using n, mean, standard deviation, median, minimum, and maximum, unless otherwise specified.

Efficacy data will be summarized using the full analysis set population, unless otherwise stated, and listed by treatment group.

The primary efficacy endpoint (proportion of subjects achieving clinical response at Week 12) and the associated 95% confidence interval (CI) for the BMS-986165 12 mg BID treatment arm will be estimated using the Clopper-Pearson exact method. Supportive analysis using logistic regression for the clinical response (binary endpoint) may be performed if the data are sufficient to do so.

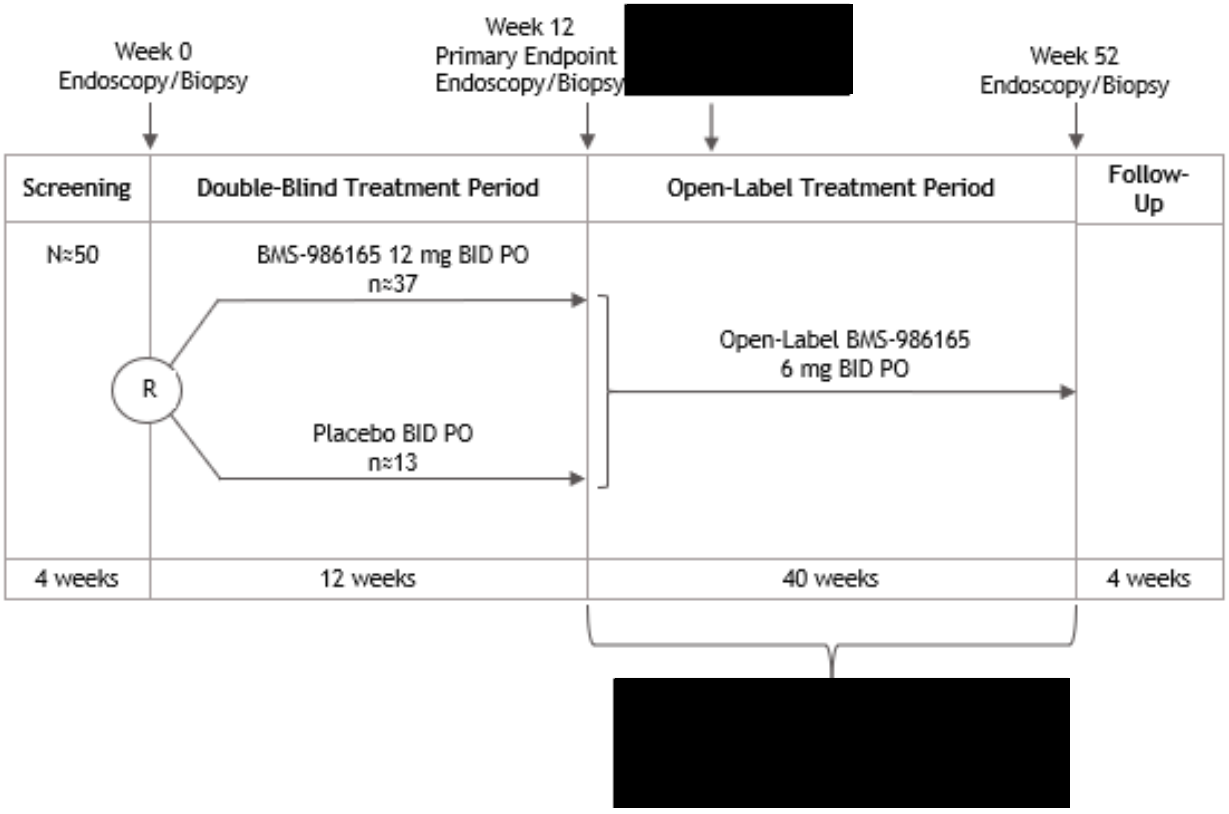
Safety endpoint analyses will be descriptive in nature.

[redacted]

[redacted]

1.2 Schema

The study design schematic for this study is presented below:



BID = twice daily; OLE = open-label extension; PO = orally; R = randomization

Note: Subjects randomized to the BMS-986165 6 mg BID induction treatment arm under the Original Protocol or Protocol Amendment 01 will continue to receive this dose throughout the double-blind period and will receive 6 mg BID in the OLE period.

2 SCHEDULE OF ACTIVITIES

The schedules of procedures for the screening and on-treatment study periods are described in Table 1. The schedules of procedures for the OLE and post-treatment follow-up periods are described in Table 2.

Table 1: Screening and Double-Blind Treatment Period Procedural Outline (IM011127)

Study Procedure	Screening Day -28 to -1	Day 1	Week 1 (Day 8)	Week 2 (Day 15)	Week 4 (Day 29)	Week 8 (Day 57)	Week 12 (Day 85)	Notes
Visit window (± n days)	N/A	0	2	3	3	3	3	
Eligibility and Disease Assessments								
Informed Consent	X							Section 5.1.1
Obtain subject number (IRT)	X							Section 7.2
Medical history and UC disease history	X							Section 5.1
Prior medications	X							Section 5.1.1
Concomitant medications and UC medications	X	X		X	X	X	X	Section 7.7 and APPENDIX 7
Tobacco/e-cigarette use	X	X		X	X	X	X	Section 6.4
Baseline SF	X							APPENDIX 9
Review Inclusion/Exclusion criteria, eligibility	X	X						Section 6
Physical Examination								Section 9.4.1
Physical examination	X	X					X	Section 9.4.1
Weight	X	X					X	Section 9.4.1
Height	X							Section 9.4.1
Vital signs (HR, BP, Temp)	X	X		X	X	X	X	Section 9.4.5
Electronic Diary (eCOA Device)								Section 9.1.1
Dispense and train subject on electronic daily diary	X							APPENDIX 9
Subject completes electronic daily diary	X →						X	APPENDIX 9
Review compliance with electronic daily diary		X		X	X	X	X	APPENDIX 9

Table 1: Screening and Double-Blind Treatment Period Procedural Outline (IM011127)

Study Procedure	Screening Day -28 to -1	Day 1	Week 1 (Day 8)	Week 2 (Day 15)	Week 4 (Day 29)	Week 8 (Day 57)	Week 12 (Day 85)	Notes
Visit window (± n days)	N/A	0	2	3	3	3	3	
CXR and ECG								
CXR	X[g]							Section 9.4.2
ECG	X						X	Section 9.4.6
Blood and Urine Tests								
Hematology, chemistry, coagulation	X	X	X[h]	X	X	X	X	Section 9.4.3 and Table 11
Fasting lipid panel and glucose		X					X	Section 9.4.3 and Table 11
[redacted]								
TSH	X							Section 9.4.3 and Table 11
FSH[b]	X							Section 9.4.3 and APPENDIX 4
[redacted]								
Serum hsCRP		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]								

Table 1: Screening and Double-Blind Treatment Period Procedural Outline (IM011127)

Study Procedure	Screening Day -28 to -1	Day 1	Week 1 (Day 8)	Week 2 (Day 15)	Week 4 (Day 29)	Week 8 (Day 57)	Week 12 (Day 85)	Notes
Visit window (± n days)	N/A	0	2	3	3	3	3	
Urinalysis and urine chemistry	X						X	Section 9.4.3 and Table 11
Additional Blood Tests [redacted]								
Whole blood for genotyping	X[l]							Section 9.6 and Table 13
[redacted]								
Whole blood for gene expression	X	X		X	X		X	Section 9.6 and Table 13
Whole blood for FACS		X			X		X	Section 9.6 and Table 13
Whole blood for PBMC		X			X		X	Section 9.6 and Table 13
[redacted]								
Diagnostic test for SARS-CoV-2[d]	X							Section 9.8
Stool Collection								Aliquots from single sample
Stool culture[e]	X							Section 9.4.3
Stool for C. difficile testing	X							Section 9.4.3
[redacted]								
Stool for fecal lactoferrin	X	X[m]		X	X	X	X	Section 9.6 and Table 13
[redacted]								

Table 1: Screening and Double-Blind Treatment Period Procedural Outline (IM011127)

Study Procedure	Screening Day -28 to -1	Day 1	Week 1 (Day 8)	Week 2 (Day 15)	Week 4 (Day 29)	Week 8 (Day 57)	Week 12 (Day 85)	Notes
Visit window (± n days)	N/A	0	2	3	3	3	3	
Endoscopy and Endoscopic Biopsies								
Endoscopy	X						X	Section 9.1.1
[redacted]								
Biopsies for gene expression	X						X	Section 9.6 and Table 14
[redacted]								
Biopsy from noninvolved area (if available) for gene expression	X						X	Section 9.6 and Table 14
Additional Efficacy Assessments								
Site calculates the modified Mayo score	X[n]						X	Section 9.1.2 and APPENDIX 9
PGA	X	X		X	X	X	X	Section 9.1.2 and APPENDIX 9
The partial Mayo score may be determined from data collected at these visits[f]	X	X		X	X	X	X	Section 9.1.2 and APPENDIX 9
The modified Mayo score, total Mayo score, and UC-100 may be determined from data collected at these visits[f]	X	X					X	Section 9.1.2 and APPENDIX 9
Health-related Quality of Life								Section 9.1.1
IBDQ		X			X		X	Section 9.1.2 and APPENDIX 11

Table 1: Screening and Double-Blind Treatment Period Procedural Outline (IM011127)

Study Procedure	Screening Day -28 to -1	Day 1	Week 1 (Day 8)	Week 2 (Day 15)	Week 4 (Day 29)	Week 8 (Day 57)	Week 12 (Day 85)	Notes
Visit window (± n days)	N/A	0	2	3	3	3	3	
UC-related hospitalization and surgery		X		X	X	X	X	Section 9.1.2 and APPENDIX 12
Safety Assessment (in addition to the above)								APPENDIX 3
Monitor AEs	X[p]	X	X	X	X	X	X	Section 0
Monitor SAEs	X	X	X	X	X	X	X	Section 0
IP Supply								
Dispense IP		X		X	X	X	X[o]	Section 5.1.2
Study treatment		X →	→	→	→	→	X	Section 7.1
Review subject compliance with IP				X	X	X	X	Section 7.6

AE = adverse event; [redacted] BP = blood pressure; COVID-19 = Coronavirus Disease 2019; CXR = chest x-ray; [redacted] ECG = electrocardiogram; eCOA = electronic clinical outcome assessments; FACS = fluorescence-activated cell sorting; [redacted] HBsAg = hepatitis B surface antigen; [redacted] HR = heart rate; hsCRP = high-sensitivity C-reactive protein; IBDQ = Inflammatory Bowel Disease Questionnaire; ICF = informed consent form; [redacted] IP = investigational product; IRT = interactive response technology; N/A = not applicable; OLE = open-label extension; PBMC = peripheral blood mononuclear cells; PCR = polymerase chain reaction; PGA = Physician's Global Assessment; [redacted] SAE = serious adverse event; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2; [redacted] SF = stool frequency; [redacted] Temp = temperature; TSH = thyroid-stimulating hormone; UC = ulcerative colitis; WOCBP = women of childbearing potential

[redacted]

b FSH may be performed in amenorrheic females < 55 years of age if indicated to confirm postmenopausal status (see APPENDIX 4). It will not be considered a protocol deviation if a site obtains an FSH level in error, ie, in male subjects.

[redacted]

[d] Diagnostic testing for SARS-CoV-2 infection should be performed as close as possible to randomization and must be confirmed as "negative" prior to randomization.

[e] A multipathogen molecular panel for enteric pathogens (eg, multipathogen PCR) may be considered as an alternative to stool culture, if this is routinely performed at a site and its use is consistent with local standard of care. Use of this test within the study should be discussed with the BMS Medical Monitor/designee.

[f] Efficacy instruments listed in italics are for site reference only. **These scores will not be calculated by the investigator**.

[g] A CXR performed less than 6 months prior to signing of the ICF may be used in place of the screening CXR, provided the subject has no symptoms or signs suggestive of pulmonary disease in the interim.

[h] Chemistry only (liver function test panel).

[redacted]

[l] To be collected only from those subjects who sign the appropriate consent form.

[m] It will not be considered a protocol deviation if a subject is unable to produce a stool sample at Day 1, provided that [redacted] fecal lactoferrin have been successfully collected at the screening visit.

[n] The modified Mayo score calculated to determine eligibility will be used for randomization on Day 1 as the baseline score.

[o] IP will be dispensed only to those subjects who continue in the study and enter the OLE period (Table 2).

[p] AEs related to COVID-19 should be collected from time of signing informed consent.

General procedural note: The protocol does not mandate specific investigations at unscheduled visits. Unscheduled visit study procedures should be based on the clinical judgment of the investigator.

Table 2: Open-label Extension Period Procedural Outline (IM011127)

Study Procedure	Week 16 (Day 113)	Week 20 (Day 141)	Week 24 (Day 169)	Week 32 (Day 225)	Week 40 (Day 281)	Week 52 (Day 365) EOT/ET[d]	Week 56 (Day 393) F/U	Notes
Visit window (± n days)	3	3	3	3	3	3	7	
Disease Assessments								
Concomitant medications and UC medications	X	X	X	X	X	X	X	Section 7.7 and APPENDIX 7
Tobacco/e-cigarette use	X	X	X	X	X	X	X	Section 6.4
Physical Examination								Section 9.4.1
Physical examination	X	X	X	X	X	X	X	Section 9.4.1
Weight						X	X	Section 9.4.1
Vital signs (HR, BP, Temp)	X	X	X	X	X	X	X	Section 9.4.5
Electronic Diary (eCOA Device)								**Section 9.1.1**
Subject completes electronic daily diary	X →					X		APPENDIX 9
Review compliance with electronic daily diary	X	X	X	X	X	X		APPENDIX 9
ECG								
ECG			X			X	X[e]	Section 9.4.6
Blood and Urine Tests								
Hematology, chemistry, coagulation	X	X	X	X	X	X	X	Section 9.4.3 and Table 11
Fasting lipid panel and glucose			X			X		Section 9.4.3 and Table 11
[redacted]								

Table 2: Open-label Extension Period Procedural Outline (IM011127)

Study Procedure	Week 16 (Day 113)	Week 20 (Day 141)	Week 24 (Day 169)	Week 32 (Day 225)	Week 40 (Day 281)	Week 52 (Day 365) EOT/ET[d]	Week 56 (Day 393) F/U	Notes
Visit window (± n days)	3	3	3	3	3	3	7	
[redacted]								
Serum hsCRP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]								
Urinalysis and urine chemistry						X		Section 9.4.3 and Table 11
Additional Blood Tests [redacted]								
[redacted]								
Whole blood for gene expression	X		X			X		Section 9.6 and Table 13
[redacted]								
Stool Collection								Aliquots from single sample
[redacted]								
Stool for fecal lactoferrin	X	X	X	X	X	X	X	Section 9.6 and Table 13
[redacted]								
Endoscopy and Endoscopic Biopsies								
Endoscopy						X		Section 9.1.1

Table 2: Open-label Extension Period Procedural Outline (IM011127)

Study Procedure	Week 16 (Day 113)	Week 20 (Day 141)	Week 24 (Day 169)	Week 32 (Day 225)	Week 40 (Day 281)	Week 52 (Day 365) EOT/ET[d]	Week 56 (Day 393) F/U	Notes
Visit window (± n days)	3	3	3	3	3	3	7	
[redacted]								
Biopsies for gene expression						X		Section 9.6 and Table 14
[redacted]								
Biopsies from noninvolved area (if available) for gene expression						X		Section 9.6 and Table 14
Additional Efficacy Assessments								
Site calculates the modified Mayo score						X		
Site calculates the symptomatic Mayo score for treatment response		X						
PGA	X	X	X	X	X	X		Section 9.1.2 and APPENDIX 9
The partial Mayo score may be determined from data collected at these visits[c]	X	X	X	X	X	X		Section 9.1.2 and APPENDIX 9
The modified Mayo score, total Mayo score, and UC-100 may be determined from data collected at this visit[c]						X		Section 9.1.2 and APPENDIX 9

Table 2: Open-label Extension Period Procedural Outline (IM011127)

Study Procedure	Week 16 (Day 113)	Week 20 (Day 141)	Week 24 (Day 169)	Week 32 (Day 225)	Week 40 (Day 281)	Week 52 (Day 365) EOT/ET[d]	Week 56 (Day 393) F/U	Notes
Visit window (± n days)	3	3	3	3	3	3	7	
Health-related Quality of Life								Section 9.1.1
IBDQ	X		X			X		Section 9.1.2 and APPENDIX 11
UC-related hospitalization and surgery	X	X	X	X	X	X		Section 9.1.2 and APPENDIX 12
Safety Assessment (in addition to the above)								APPENDIX 3
Monitor AEs	X	X	X	X	X	X	X	Section 0
Monitor SAEs	X	X	X	X	X	X	X	Section 0
IP Supply								
Dispense IP	X	X	X	X	X			Section 5.1.2
Study treatment	X →	→	→	→	→	X		Section 7.1
Review subject compliance with IP	X	X	X	X	X	X		Section 7.6

AE = adverse event; [redacted] BP = blood pressure; [redacted] ECG = electrocardiogram; eCOA = electronic clinical outcome assessments; EOT = end of treatment; ET = early termination; F/U = follow-up; [redacted] HR = heart rate; hsCRP = high-sensitivity C-reactive protein; IBDQ = Inflammatory Bowel Disease Questionnaire; IP = investigational product; PGA = Physician's Global Assessment; SAE = serious adverse event; [redacted] Temp = temperature; UC = ulcerative colitis; WOCBP = women of childbearing potential

[redacted]

[c] Efficacy instruments listed in italics are for site reference only. **These scores will not be calculated by the investigator.**

[d] ET visit should be scheduled at least 4 weeks after the last per protocol-required endoscopy.

[e] Required only if Week 52 ECG is abnormal.

[redacted]

General procedural note: The protocol does not mandate specific investigations at unscheduled visits. Unscheduled visit study procedures should be based on the clinical judgment of the investigator.

3 INTRODUCTION

3.1 Background

Ulcerative colitis (UC) is a chronic inflammatory disease of the gastrointestinal tract that causes significant morbidity, impact on quality of life, and healthcare expenditure. Outcomes for patients with UC have improved significantly over the last several years due to better treatment strategies and the emergence of highly targeted biological therapies. However, significant therapeutic challenges remain with this and other inflammatory bowel diseases (IBDs). Current treatment regimens often fail, induce only a partial response, or are poorly tolerated. For example, studies with tumor necrosis factor inhibitors (TNFi) report that 10% to 30% of subjects do not respond to their first treatment and 23% to 46% of subjects lose their response over time.[6] Therefore, there is still an unmet need for novel, safe, well-tolerated, and orally administered therapies with a different mechanism of action that can effectively treat UC and modify the disease course.

Tyrosine kinase 2 (TYK2) is an intracellular kinase involved in interleukin (IL)-12, IL-23, and Type I interferon (IFN) signaling.[7] TYK2 is a widely expressed, nonreceptor tyrosine kinase that catalyzes the phosphorylation of signal transducer and activator of transcription (STAT) proteins downstream of the receptors for the IL-12p40-containing cytokines IL-12 and IL-23 as well as the Type I IFN receptor. This results in the activation of STAT-dependent transcription and functional responses specific for these cytokines.[8, 9, 10] [redacted] TYK2-dependent pathways and the cytokine networks they modulate have been implicated in the pathophysiology of multiple immune-mediated diseases including UC, Crohn's disease (CD), psoriasis, psoriatic arthritis, systemic lupus erythematosus (SLE), and spondyloarthropathies.

BMS-986165 is an orally administered, selective TYK2 inhibitor. A comprehensive in vitro and in vivo characterization of BMS-986165 has been established and supports the development of this compound in humans.[11, 12] [redacted]

3.1.1 Nonclinical Toxicology

The projected systemic exposure multiples presented in this section are expressed relative to [redacted]. These multiples were calculated as animal sex-combined mean AUC ÷ human sex-combined mean AUC at the no-observed-adverse-effect level (NOAEL) or level associated with adverse findings in the pivotal toxicology studies.

In vitro screening against a panel of receptors, ion channels, transporters, and enzymes demonstrated that BMS-986165 did not significantly alter ligand binding or functional activity at clinically relevant concentrations and is considered to have low potential to produce effects in vivo related to secondary pharmacology. Transient decreases in blood pressure (BP) and increases in heart rate (HR) were seen in anesthetized rabbits, and conscious telemetrized dogs and monkeys, with monkey being the most sensitive species. However, the HR or BP changes were not identified in repeat-dose monkey toxicity studies at higher doses or in healthy subjects in a Phase 1 single ascending dose study at plasma concentrations comparable to plasma levels at the lowest-observed-effect-level in a Good Laboratory Practice study in telemetrized monkeys. In addition, [redacted] up to the highest evaluated dose of 12 mg BID or in the thorough QT (TQT) study in healthy subjects up to a single dose of 36 mg (Study IM011048). Overall, the totality of available data indicates that BMS-986165 has low potential for off-target effects at clinical doses and corresponding plasma concentrations.

[redacted]

[redacted]

3.1.2 Early Clinical Experience

BMS-986165 has a favorable pharmacokinetic (PK) profile characterized by consistent oral absorption, [redacted]

[redacted]

3.1.3 BMS-986165 12 mg QD or BID Dose Regimen Studies

Several studies of BMS-986165 have been conducted using single- or multiple-dose regimens of BMS-986165 12 mg BID PO or higher. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.1.5 BMS-986165 and Inflammatory Bowel Disease Studies: Overview

Study IM011024 is a multicenter, randomized, double-blind, placebo-controlled, parallel group, Phase 2 clinical trial designed to evaluate the safety and efficacy of BMS-986165 6 mg BID PO, compared with placebo, in subjects with moderate to severe UC. The primary endpoint is at Week 12. Following a 12-week induction period, eligible subjects enter a 40-week maintenance period. An additional 52-week open-label extension (OLE) period (to Week 104) is available for subjects who continue to derive clinical benefit. Topline results from Study IM011024 indicate that BMS-986165 6 mg BID compared to placebo BID did not meet primary efficacy endpoint of clinical remission at Week 12 or the predefined secondary efficacy endpoints. The safety profile of BMS-986165 was consistent with previously reported studies in psoriasis and psoriatic arthritis, and no new safety signals were observed. The study remains ongoing, and results from the Week 52 and Week 104 endpoints are not yet available.

Study IM011023 is a multicenter, randomized, double-blind, placebo-controlled, parallel group, Phase 2 clinical trial designed to evaluate the safety and efficacy of BMS-986165 6 mg BID PO and 3 mg BID PO, compared with placebo, in subjects with moderate to severe CD, following a 12-week induction period. After the induction period, eligible subjects enter a 40-week maintenance period. An additional 52-week OLE period (to Week 104) is available for subjects who continue to derive clinical benefit.

Study IM011077 is an open-label, long-term extension study to evaluate the long-term safety and efficacy of BMS-986165 6 mg BID in subjects who have previously been enrolled in a Phase 2 BMS-986165 study for moderate to severe CD (Study IM011023) or moderate to severe UC (Studies IM011024 and IM011127).

Study IM011127 (the current study) is a multicenter, randomized, double-blind, placebo-controlled, parallel group, Phase 2 clinical trial designed to assess the safety and tolerability, efficacy, and biomarker response of BMS-986165 12 mg BID PO following a 12-week treatment period. An additional 40-week OLE period (to Week 52) is available for eligible subjects.

Inclusion/Exclusion criteria, safety, and efficacy assessments for the current study are based on the design of Study IM011024. Data from this study will be analyzed alone and may be compared with the data collected in Study IM011024 (which is likely to recruit a similar patient population due to similarities in the eligibility criteria between studies).

[redacted]

[redacted]

3.2 Benefit/Risk Assessment

Multiple lines of evidence suggest that inhibition of TYK2 signaling by BMS-986165 may be beneficial in patients with active UC.

In a cohort of healthy humans, carriage of a naturally occurring protein variant in TYK2 (P1104A, rs34536443) that results in reduction of TYK2 kinase function is associated with a reduced risk of inflammatory diseases, [redacted] adoptive transfer model of murine colitis and the anti-CD40 agonist antibody murine model of colitis.[11]

[redacted]

therapeutic effect in subjects with active UC.[31] Taken together, these data support a hypothesis that BMS-986165 may be beneficial in the treatment of UC.

[redacted] BMS-986165 6 mg BID is currently being studied (compared to placebo in subjects with moderate to severe UC) in Study IM011024.

Briefly, BMS-986165 12 mg BID is being assessed in this study for the following reasons:

[redacted]

[redacted]

There is adequate safety information from the studies described above to understand expected TEAEs at BMS-986165 12 mg BID in the current study. The protocol includes design elements that may allow these events to be recognized and managed appropriately by investigators during the study, should they occur. Furthermore, assessment of the safety and tolerability of BMS-986165 12 mg BID in this study population, and comparison with safety and tolerability data from Study IM011024, may inform Phase 3 dose selection of BMS-986165.

BMS-986165 is a potential immunomodulator. The inclusion (Section 6.1) and exclusion (Section 6.2) criteria have been designed to minimize the risk for infections and malignancies, and additional data collection will be triggered if these AEIs are observed in this study.

Participants in UC clinical trials, particularly those receiving placebo, may experience an increase in disease activity (ie, a "flare") during their participation. This protocol contains detailed criteria for treatment failure (Section 5.1.5) and detailed discontinuation criteria (Section 8) to assist investigators in the recognition and management of treatment failure within the study. Standard of care rescue therapy can be initiated at any time, at the investigator's discretion (Section 5.1.5).

The risk for PK DDIs with BMS-986165 was assessed using Food and Drug Administration (FDA) and European Medicines Agency guidance documents for DDI assessments. [redacted]

The global coronavirus disease 2019 (COVID-19) pandemic has been identified as a potential risk to clinical trial subjects in general, and it may particularly affect individuals with underlying chronic diseases. The risk of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection in participants taking BMS-986165 is unknown. The individual benefit-risk considerations regarding COVID-19 infection remains the responsibility of the investigator.

BMS-986165 is an immunomodulatory IP. The inclusion (Section 6.1) and exclusion (Section 6.2) criteria have been designed to exclude people with active infections and people at higher risk of malignancies. In order to reduce the risk of asymptomatic SARS-CoV-2 at baseline, subjects will be tested for SARS-CoV-2 during the screening period, as close as possible prior to randomization and must be confirmed as "negative" prior to randomization (Section 9.8).

The study has been designed with study visits that allow for close monitoring of study subjects' safety throughout the study, and additional data collection will be triggered if AEIs are observed in this study. Each study visit will include a clinical assessment for signs and/or symptoms of intercurrent illness, including COVID-19 and other infections. Subjects will also be encouraged to contact the investigator if they develop an intercurrent illness between study visits.

The Sponsor has developed guidance for investigators on how to manage a subject with a clinical suspicion of, or a diagnosis of, COVID-19. This includes criteria for temporary interruption of IP in the context of clinical suspicion of COVID-19, or a positive diagnostic test for SARS-CoV-2 (Section 8.1.1). This also includes criteria for potentially recommencing IP upon complete resolution of a COVID-19 infection, confirmed by a negative diagnostic test (Section 9.8).

The study captures treatment-emergent AEs (occurring after randomization). In order to facilitate enhanced reporting of SARS-CoV-2 related AEs that occur during the study, these AEs (and SAEs) must be reported from the time of consent (Section 9.2.1). In addition, SARS-CoV-2 related AEs or SAEs will trigger additional data collection through specialized electronic case report form (eCRF) pages, which will enable additional evaluation of these events.

4 OBJECTIVES AND ENDPOINTS

Study objectives and specific endpoints are listed in Table 3. Additional endpoints and analyses will be described in the statistical analysis plan (SAP), the Endoscopy Image Review Charter [redacted]. Selected efficacy endpoints are further defined in Table 10.

Table 3: Study Objectives and Endpoints

Objective	Endpoints
Primary - Efficacy	
• To estimate the efficacy of BMS-986165 **at Week 12**	• Proportion of subjects in clinical response at Week 12
Safety	
• To assess the safety and tolerability of BMS-986165	• Number and proportion of subjects experiencing AEs, SAEs, AEs leading to discontinuation from the study, and AEIs throughout the study
Exploratory - Efficacy	
[redacted]	

Table 3: Study Objectives and Endpoints

Objective	Endpoints
• To explore the efficacy of BMS-986165 at Week 52	• Proportion of subjects in clinical remission at Week 52 • Proportion of subjects in clinical response at Week 52 • Proportion of subjects in endoscopic remission at Week 52 • Proportion of subjects with endoscopic improvement at Week 52 • Proportion of subjects with histologic improvement at Week 52 • Proportion of subjects with corticosteroid-free remission at Week 52 • Proportion of subjects in durable clinical response at Week 52 • Proportion of subjects in durable endoscopic response at Week 52 • Proportion of subjects in clinical response at Week 12 [redacted]
Exploratory [redacted]	
• To explore the effect of BMS-986165 on PB immune cells	• Change from baseline in PB immune cells over time
[redacted]	
• To explore the effect of BMS-986165 on the transcriptome in blood and colon biopsies	• Change from baseline in gene expression over time
[redacted]	
Exploratory [redacted]	
[redacted]	
Exploratory - Health-related Quality of Life and Medical Resource Utilization	
• To explore the effect of BMS-986165 on PROs and quality of life	• Change from baseline at various time points for the IBDQ

Table 3: Study Objectives and Endpoints

Objective	Endpoints
• To explore the effect of BMS-986165 on UC-related hospitalization and surgery	• Proportion of subjects with surgery and/or hospitalization due to UC at various time points

AE = adverse event; AEI = adverse event of interest; IBDQ = Inflammatory Bowel Disease Questionnaire; PB = peripheral blood; [redacted] PRO = patient-reported outcomes; RB = rectal bleeding; [redacted] SAE = serious adverse event; [redacted] SF = stool frequency; UC = ulcerative colitis; [redacted]

5 STUDY DESIGN

5.1 Overall Design

Study IM011127 is a Phase 2 randomized, double-blind, placebo-controlled, multicenter clinical study designed to assess the safety and tolerability, efficacy, [redacted] and biomarker response of BMS-986165 12 mg BID in subjects with moderate to severe UC. The primary objective is to estimate the effect of BMS-986165 on clinical response at Week 12 (Table 10).

The duration of study participation is approximately 60 weeks (420 days) in 4 periods, as follows:

- Screening period: up to 4 weeks (28 days; Section 5.1.1)
- Double-blind treatment period: 12 weeks (84 days; Section 5.1.2)
- OLE period: up to 40 weeks (280 days: Section 5.1.3)
- Posttreatment follow-up period: 4 weeks (28 days; Section 5.1.4)

Assessments of medical and UC disease history; prior medications, concomitant medications, and UC medications; tobacco use; baseline SF; physical examinations; chest x-ray (CXR); 12-lead ECG; and blood, stool, and urine sample collections; endoscopies with biopsies; additional efficacy assessments, PGA, PROs; and eligibility assessment will be performed as indicated in the Schedule of Activities (Section 2). Subjects will be closely monitored for AEs throughout the study.

The primary endpoint of this study is the proportion of subjects in clinical response at Week 12. This is assessed using the modified Mayo score. This instrument utilizes data from 2 sources: (1) PROs, ie, SF and RB captured by the subject in their electronic daily diary (modified Mayo score and total Mayo score); and (2) Centrally-read endoscopic assessments (modified Mayo score and total Mayo score). In addition, the physician-reported PGA, assessed by the investigator or designee at each study visit, will also be captured to facilitate the calculation of the total and partial Mayo scores. Efficacy will also be assessed using additional instruments, such as the UC-100 instrument (which uses the modified Mayo score SF and ES subscores [redacted]). Consequently, accurate and timely collection of each of these types of data (or samples that contribute to these data) is critical to the assessment of efficacy in this study. Additional detail on data capture for efficacy assessment and the efficacy instruments used in this study are given in Section 9.1.1.

Subjects will receive and be trained on the electronic daily diary at the screening visit. Subjects are expected to complete this diary on a daily basis throughout their participation in the study. In order to confirm that subjects are successfully recording data in the electronic daily diary, sites should review subject compliance with completion of the electronic daily diary, as indicated in the Schedule of Activities (Section 2), or more frequently if required. For the purpose of eligibility assessment and efficacy analysis, the **3 most recent (not necessarily consecutive), valid, electronic subject diary entries recorded from the 7 days prior to the day of a study visit (or up to the day before a subject starts bowel preparation for an endoscopy, if that visit includes an endoscopy)** will be used to calculate the SF and RB subscores (see APPENDIX 9). Electronic diary entries for SF and RB are considered valid when no medications for constipation, diarrhea, or bowel irregularity are reported (through E-diary) as taken that day. Review of electronic daily diary compliance during these previsit (or preendoscopy) periods is recommended. Subjects are not eligible to participate in this study if they are unable to complete study procedures, which includes daily completion of the electronic diary. The modified Mayo score calculated to determine eligibility will also be used as the baseline disease activity score.

Endoscopic evaluations and collection of colonic tissue biopsies will be performed during the screening period, at Weeks 12 and 52, at unscheduled visits (if clinically indicated), and at early termination (ET) visits that occur at least 4 weeks after the last per protocol-required endoscopy in the double-blind period and any time after Week 20 in the OLE period. Endoscopy is encouraged in subjects terminating in the OLE period between Week 12 and Week 20. Endoscopic procedures will be video recorded and scored for disease activity by a blinded central reader. Histologic scoring of gastrointestinal tissue specimens will also be performed by a blinded central reader.

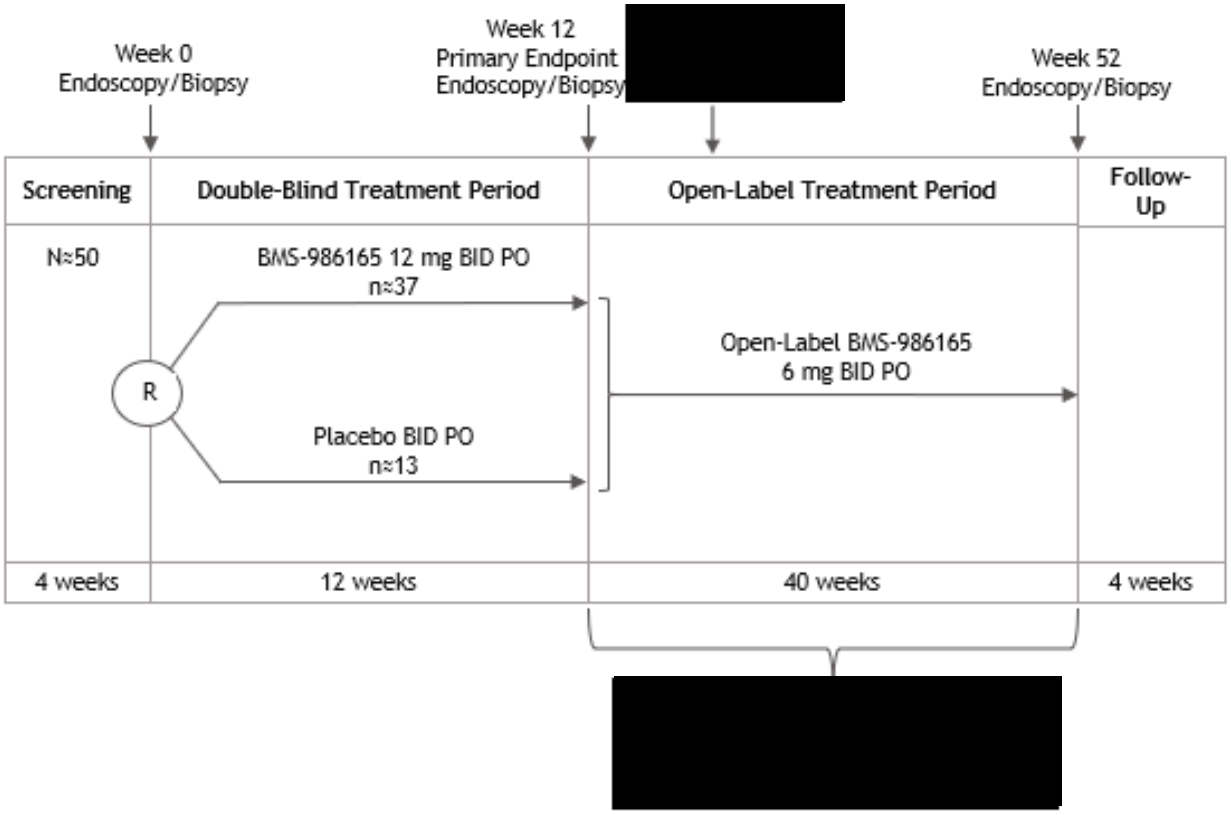
[redacted]

Subjects who meet the criteria for treatment failure will permanently discontinue IP and enter the posttreatment follow-up period (Section 5.1.3).

An independent Data Monitoring Committee (DMC) will be instituted to assess safety data (Section 5.1.6).

The study design schematic is presented in Figure 1.

Figure 1: Study Design Schematic



BID = twice daily; OLE = open-label extension; PO = orally; R = randomization

Note: Subjects randomized to the BMS-986165 6 mg BID induction treatment arm under the Original Protocol or Protocol Amendment 01 will continue to receive this dose throughout the double-blind period and will receive 6 mg BID in the OLE period.

5.1.1 Screening Period

Study procedures cannot be performed until subjects sign the informed consent form (ICF). Once subjects sign the ICF, they are considered "enrolled" in the study, and they enter the screening period. During the screening period, subjects will complete the study procedures and baseline assessments outlined in the Schedule of Activities (Section 2) to determine if they continue to meet eligibility criteria (Section 6). [redacted]

To be eligible for the study, **a subject must meet minimum disease activity criteria** outlined in Section 6.1, including a modified Mayo score of 5 to 9 points, inclusive.

[redacted]

[redacted]

An endoscopy (colonoscopy or flexible sigmoidoscopy) will be performed to determine if a subject has active intestinal inflammation (assessed by central reading) and to obtain biopsies for biomarker [redacted] assessment. To avoid unnecessary endoscopies, best practice is to complete other screening investigations first and check the results of those investigations to confirm ongoing eligibility before a subject begins bowel preparation for endoscopy. **Subjects must be randomized within 14 calendar days of the screening endoscopy**.

NOTE: *In the case of rescreening, the 14-day window to be randomized following endoscopy may be extended an additional 3 days with approval of the BMS Medical Monitor/designee.*

A **full colonoscopy will be required**: (1) in subjects with a history of UC > 8 years, if endoscopy was not performed in the prior 12 months; or (2) in subjects who require a colonoscopy to screen or surveille for dysplasia, based on local guidelines; or (3) in subjects who require a colonoscopy to screen for colorectal carcinoma, based on local guidelines.

A **full colonoscopy is encouraged** if disease extent is unknown in order to define the proximal extent of colitis.

To be eligible for randomization, subjects must meet the Inclusion Criteria outlined in Section 6.1 and must not meet any of the Exclusion Criteria outlined in Section 6.2. Subjects must have had an inadequate response, loss of response, or intolerance to a treatment course of 1 or more of the standard medications for UC and completed at least 1 treatment course of corticosteroids (Section 6.1). Detailed criteria defining inadequate response, loss of response, or intolerance to biologic therapy are described in APPENDIX 5. The prior medication failure or intolerance used to qualify a subject for inclusion must be recorded in source documents and the appropriate eCRF.

Prohibited treatments are listed in Section 7.7.1 (Table 6).

Restricted treatments are listed in Section 7.7.2 (Table 7).

Dose stabilization rules are outlined in Section 0 (Table 8). Briefly, 5-aminosalicylic acids (5-ASAs) and oral corticosteroids (prednisone ≤ 20 mg QD PO or equivalent or budesonide ≤ 9 mg QD PO Multi-Matrix System [MMX®] colonic-delivery technology; eg, Uceris® or equivalent) are allowed, subject to dose stabilization rules. Equivalent doses of common corticosteroids are listed in APPENDIX 6.

Washout periods for immunomodulators and biologic medications are outlined in the eligibility criteria (Section 6) and Table 6, and detailed in APPENDIX 7. Subjects must comply with these washout periods in order to be eligible to be randomized. [redacted] assays that test for drug levels of some biologic medications are commercially available in many countries for use in routine clinical practice. They are also available as an optional test during the screening period. The washout period for these biologics can be waived in subjects who have an undetectable drug level [redacted] that is performed either in routine clinical practice or during the screening period.

[redacted] used to waive the washout period as described above, the result [redacted] must be available in source documents, and the subject cannot receive another dose of that biologic prior to randomization.

Investigators are also encouraged to confirm if screening for noncolorectal malignancy is up to date prior to randomization, according to local guidelines (eg, screening for breast cancer or cervical carcinoma in situ).

5.1.2 Double-blind Treatment Period

At the Day 1 study visit, subjects who have completed the screening procedures and meet the eligibility criteria will be randomized in a 3:1 ratio to receive BMS-986165 12 mg BID or placebo BID PO, respectively for the 12-week double-blind treatment period. Randomization criteria are outlined in Section 6.3. Subjects randomized to the 6 mg BID arm under the Original Protocol or Protocol Amendment 01 will continue to receive 6 mg BID for the 12-week double-blind treatment period and will receive 6 mg BID in the OLE period.

Prior to each scheduled visit, the subject diary should be reviewed to ensure SF and RB data have been entered daily. Prior to each scheduled visit at which Mayo scores are to be calculated, study personnel should ascertain whether an adequate number of days of diary entries have been made (APPENDIX 9). If adequate entries have not been made, the site should contact the subject to reschedule the visit to allow time for a sufficient number of daily dairy entries for endpoint assessment, and the subject should be counseled about proper study procedures.

Endoscopy for the assessment of efficacy at Week 12 must occur in a window of 7 days prior to the Week 12 visit.

If a colonoscopy is performed during the screening visit, colonoscopy will be the preferred endoscopic procedure for subsequent endoscopies within the study. This approach will facilitate comparison between the individual colonic segments assessed at the screening visit and subsequent assessments.

Treatment discontinuation criteria are detailed in Section 8.1. Subjects who **temporarily interrupt study treatment** will remain in the study and continue to participate in study procedures (Section 8.1.1).

Subjects who **permanently discontinue study treatment** will complete an **ET visit**. For subjects who permanently discontinue study treatment between Weeks 4 and 12, the ET visit will include an endoscopy. For subjects who permanently discontinue study treatment prior to Week 4, endoscopy at the ET visit is optional but encouraged. Subjects who permanently discontinue study treatment will be followed for protocol-specified posttreatment follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or with persons previously authorized by the subject to provide this information (see Section 8.2).

5.1.3 Open-label Extension Period

Subjects who are likely to derive a clinical benefit from ongoing participation in the study following Week 12, as judged by the investigator, are eligible to enter the OLE period. The OLE

period will last up to 40 weeks, to Week 52. Subjects will receive BMS-986165 6 mg BID PO during the OLE. There is no provision for dose escalation of IP during the OLE.

[redacted]

The symptomatic Mayo score at the Week 20 visit will be calculated using the **3 most recent (not necessarily consecutive) valid electronic subject diary entries recorded from the 7 days prior to the day of the study visit**.

[redacted] Subjects who require any rescue therapy during the OLE period (Section 5.1.5) must permanently discontinue from study treatment (Section 8.1).

Endoscopy for the assessment of efficacy at Week 52 must occur in a window of 7 days prior to the Week 52 visit.

Endoscopy is required at the ET visit for subjects who permanently discontinue study treatment between Week 20 and prior to Week 52. Endoscopy is optional, but encouraged, for subjects who have an ET visit between Weeks 12 and 20.

5.1.4 Follow-up Period

Subjects who complete the Week 12 visit and decline to enter the OLE period, those who complete the Week 52 visit and do not roll-over into a long-term extension study, or those who permanently discontinue study drug at any time during the study (Section 8) will enter a 4-week posttreatment follow-up period.

5.1.5 Treatment Failure

For the purpose of this study, treatment failure will be defined as:

[redacted]

[redacted]

5.1.6 Safety Monitoring and Data Monitoring Committee

Study IM011127 is the first experience of subjects with moderate to severe UC to BMS-986165 at doses above 6 mg BID PO. Consequently, this study has been designed to closely monitor subjects' safety throughout the duration of the study. Safety monitoring will occur at study sites, by the Sponsor, and by an external, independent DMC.

Subject Safety Assessments at the Study Site

Subject safety will be closely assessed at study sites by the investigator and appropriately delegated members of the study team. The assessments outlined in the Schedule of Activities (see Section 2) have been designed to facilitate assessment of safety in addition to efficacy. Based on the timing of hepatic AEs observed [redacted], liver function testing during the treatment phase will commence at Week 1 (~Day 8) (Table 1). In addition, the Sponsor has implemented additional data collection for AEIs, including skin SOC TEAEs (see Section 9.2.8), in order to more completely characterize these TEAEs (were they to occur) and understand the tolerability of BMS-986165 in this study.

Additional clinical assessments or investigations can be performed during the study as indicated, based on the judgment of the investigator.

Medical Monitoring by the Sponsor

Subject safety will be monitored in a blinded manner by the Sponsor on a regular basis. The Sponsor will review blinded subject-level data entered in the clinical database as well as aggregated safety data across studies. This approach facilitates close monitoring of individual safety events as well as surveillance for potential safety signals.

Data Monitoring Committee

An external, independent DMC will provide oversight on the safety of trial subjects within this study, The DMC will regularly review accumulating data from this study and advise the Sponsor

regarding the continuing safety of trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial.

Data summaries and listings will be provided to the DMC to facilitate their safety assessment at regularly scheduled meetings and on an ad hoc basis if needed. Efficacy data will be made available on request by the DMC to assess ongoing acceptability of the benefit-risk profile. The DMC will also be provided with suspected, unexpected serious adverse reaction (SUSAR) reports relating to BMS-986165 and recommendations from other DMCs supporting the BMS-986165 clinical development program.

Regular DMC safety reviews will include all AEs, SAEs, and AEs of special interest. Based on their review of safety data, the DMC will make recommendations regarding the appropriateness of continuing the study, with or without study modifications, or stopping the study.

In addition to regularly scheduled DMC meetings, ad hoc DMC meetings will occur in the following circumstances:

- Two or more subjects experience an SAE of the same PT and that is considered related to the study treatment by the investigator (for example, not explained by intercurrent medical condition or concomitant medication)
- Two or more subjects are discontinued due to the same laboratory abnormality as defined by criteria in Section 8.1

Additional details on the DMC's processes and procedures will be outlined in the DMC Charter.

5.2 Number of Subjects

Approximately 50 subjects will be randomized in the main study protocol. The sample size justification is included in Section 10.1. [redacted]

5.3 End-of-Study Definition

The duration of study participation for individual subjects may be up to approximately 60 weeks (420 days).

The start of the study is defined as the first visit for the first subject screened. The end of the study is defined as the last scheduled procedure shown in the Schedule of Activities (Section 2) for the last subject. Study completion is defined as the final date on which data were or are expected to be collected. The end of study for analysis of [redacted] samples is outlined in Section 9.6.

5.4 Scientific Rationale for Study Design

This is a Phase 2 randomized, double-blind, placebo-controlled, multicenter study to assess the safety and tolerability, efficacy, [redacted] and biomarker response of BMS-986165 12 mg BID in subjects with moderate to severe UC.

[redacted]

This study will estimate the effect of BMS-986165 on clinical response at Week 12 using standard UC efficacy instruments to determine eligibility and assess efficacy (Section 9.1).[38, 39]

[redacted]

[redacted]

[redacted]

Study IM011127 also includes a placebo control arm. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6 STUDY POPULATION

Eligibility criteria for this study have been carefully considered to ensure both the safety of the study subjects and the validity of the study results. It is imperative that subjects fully meet all eligibility criteria.

[redacted]

[redacted]

All screening and randomization evaluations must be completed and reviewed by the responsible investigator to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to either confirm eligibility or to record the reason(s) for screening failure. Procedures conducted as part of the subject's routine clinical management (eg, blood count) and obtained before the ICF was signed may be used for prescreening purposes, unless otherwise specified in the protocol.

The duration of the screening period is up to 4 weeks. If eligibility parameters cannot be obtained within this time period, the screening period may be extended by up to 5 days, if approved by the BMS Medical Monitor/designee. Rules for retesting and rescreening are provided in Section 6.5.1.

To be eligible for the study, subjects must meet all Inclusion Criteria (Section 6.1) and must not meet any of the Exclusion criteria (Section 6.2). To be randomized into the study on Day 1, subjects must meet the criteria in Section 6.3.

In this section, Inclusion and Exclusion criteria are listed in standard text. Additional instructions to investigators, designed to further clarify selected eligibility criteria, are presented in *italics*.

6.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1) Signed Written Informed Consent

a) Willing to participate in the study and sign the ICF

b) Willing and able to complete all study specific procedures and visits

2) Type of Participant and Target Disease Characteristics

a) A diagnosis of UC ≥ 3 months' duration prior to screening

Subject must have a clinical diagnosis of UC ≥ 3 months' duration prior to screening, and source documents must include (i) an endoscopy report, which shows features consistent with UC, and (ii) a histopathology report showing features consistent with UC.

If an endoscopy report is not available prior to screening, the screening endoscopy can be used to confirm the diagnosis. If a histopathology report is not available prior to screening, endoscopic biopsies can be obtained at the screening endoscopy (with appropriate consent) and sent to a local histopathology laboratory for reporting, to meet the criteria described above prior to randomization.

b) UC disease distribution extending proximal to the rectum (ie, left-sided colitis or pancolitis)

c) Moderately to severely active UC, defined by a modified Mayo score of 5 to 9 points inclusive (see Section 9.1 and APPENDIX 9), which includes all of the following:

i) A stool frequency (SF) subscore of ≥ 2, **and**

ii) A rectal bleeding (RB) subscore ≥ 1, **and**

iii) An endoscopic (ES) subscore of ≥ 2

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

3) Age and Reproductive Status

Investigators shall counsel women of childbearing potential (WOCBP), and male subjects who are sexually active with WOCBP, 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 Subjects

i) Females, ages 18 (or local age of majority) to 65 years, inclusive, at the time of screening.

ii) Women who are not of childbearing potential are exempt from contraceptive requirements.

iii) Female subjects must have documented proof that they are not of childbearing potential.

iv) **Not applicable per Protocol Amendment 02** - WOCBP must have a negative highly sensitive [redacted] test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the start of study treatment.

If a urine test cannot be confirmed as negative (eg, an ambiguous result), a [redacted] *test is required. In such cases, the participant must be excluded from participation if the* [redacted] *result is positive.*

v) WOCBP must have a negative highly sensitive [redacted] test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the start of study treatment (applicable to Canada only, a negative highly sensitive [redacted] test with the same minimum sensitivity as indicated above is also required at the screening visit).

If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

vi) Additional requirements for pregnancy testing during and after study intervention are located in the Schedule of Activities (Section 2).

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

viii) **Not applicable per Protocol Amendment 02 -** WOCBP must agree to follow instructions for method(s) of contraception defined in APPENDIX 4 and as described below and included in the ICF.

ix) WOCBP must agree to use 1 of the highly effective or 1 of the less than highly effective methods of contraception defined in APPENDIX 4 (applicable to Germany only, 1 highly effective method of contraception is required; applicable to Canada only, 1 highly effective contraception method or 2 less than highly effective contraception methods are required).

x) WOCBP are permitted to use hormonal contraception methods as described in APPENDIX 4.

xi) A female subject 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(s) as described in APPENDIX 4 during the intervention period (at a minimum until after the last dose of study intervention)

b) Male Subjects

i) Males, ages 18 (or local age of majority) to 65 years, inclusive, at the time of screening.

ii) **Not applicable per Protocol Amendment 01 -** Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception defined in APPENDIX 4 and as described below.

iii) **Not applicable per Protocol Amendment 01 -** Azoospermic males are exempt from contraceptive requirements.

iv) **Not applicable per Protocol Amendment 01 -** No additional contraceptive measures are required to be used.

v) Male participants should maintain their usual practice with regards to contraception (if any); however no specific contraceptive measures are required.

4) Prior UC Medication Inclusion Criteria

a) **Not applicable per Protocol Amendment 02 -** Documentation of an inadequate response, loss of response, or intolerance to a treatment course of 1 or more of the following standard of care medications:

i) Oral 5-aminosalicylic acids (5-ASAs) (eg, mesalamine, sulfasalazine, olsalazine, or balsalazide).

ii) Corticosteroids (eg, prednisone or budesonide MMX).

iii) Immunomodulators (eg, azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]).

iv) Anti-TNF agents (eg, infliximab, adalimumab, or golimumab).

v) Integrin inhibitors (eg, vedolizumab).

[redacted]

b) Inadequate response, loss of response, or intolerance to a treatment course of 1 or more of the following standard of care UC medications:

i) Oral 5-aminosalicylic acids (5-ASAs) (eg, mesalamine, sulfasalazine, olsalazine, or balsalazide).

ii) Corticosteroids (eg, prednisone or budesonide MMX) (must have had 2 exposures separated by a corticosteroid-free period).

iii) Immunomodulators (eg, azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]).

iv) Anti-TNF agents (eg, infliximab, adalimumab, or golimumab).

v) Integrin inhibitors (eg, vedolizumab).

[redacted]

viii) Subjects who stop treatment with biologics due to loss of funding (eg, loss of insurance coverage) may be eligible for inclusion in the study. Subject eligibility should be discussed with the BMS Medical Monitor/designee.

Specific prior medication failure/intolerance criteria are listed in APPENDIX 5.

[redacted]

5) Washout and Dose Stabilization Inclusion Criteria

a) Must comply with washout periods for prohibited concomitant medications summarized in Table 6 (Section 7.7.1) and listed in APPENDIX 7

b) Must comply with dose stabilization rules for 5-ASAs, corticosteroids and probiotics (if applicable) prior to randomization, listed in Table 8 (Section 0)

6.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1) Medical Conditions

a) Women who are pregnant or breastfeeding

2) UC Exclusion Criteria

a) UC involving the rectum only (UC proctitis)

b) Current diagnosis of CD, indeterminate colitis, ischemic colitis or microscopic colitis, a monogenic cause of UC-like intestinal inflammation, or a diagnosis of pseudomembranous colitis other than that associated with *Clostridioides difficile* (formerly *Clostridium difficile* [*C. difficile*])

c) Current or recent (within 12 weeks prior to randomization) evidence of fulminant UC (also known as acute severe UC) or toxic megacolon

d) Current or recent (within 12 weeks prior to randomization) evidence of bowel perforation or intra-abdominal abscess

e) Current or recent colonic diverticulitis. Subject must be adequately treated and off antibiotics for diverticulitis for 60 days prior to randomization.

f) Current colonic adenomas or mucosal dysplasia

A subject with adenomatous polyps may be eligible if the polyps have been completely removed or eradicated (documented), and the subject is free of polyps at randomization.

A subject with mucosal dysplasia may be eligible if the dysplasia has been completely removed/resected/eradicated (as applicable, documented), and the subject is free of dysplasia at randomization. This should be discussed with the BMS Medical Monitor/designee prior to screening.

Subjects with a history of UC > 8 years' duration (who have not had a colonoscopy in the prior 12 months), subjects who require a colonoscopy to screen or surveille for dysplasia (based on local guidelines), and subjects who require a colonoscopy to screen for colorectal cancer (based on local guidelines) must have a full colonoscopy at screening.

g) Treatment for CMV colitis within 12 weeks of randomization

3) Gastrointestinal Surgery Exclusion Criteria

a) History or evidence of extensive colonic resection, subtotal or total colectomy, with or without a stoma or pouch

b) Current need for, or anticipated need for, surgical intervention for UC during the study

c) Gastrointestinal surgery within 3 months prior to randomization

Subject must have adequate wound healing prior to randomization.

4) Additional Gastrointestinal Exclusion Criteria

a) Current or recent (within 12 weeks prior to randomization) gastrointestinal disease that may confound efficacy assessment or be associated with poor absorption of IP, eg, untreated celiac sprue, bile salt-mediated diarrhea, or short bowel syndrome

b) Receiving enteral feeding, defined formula diets, or total parenteral alimentation

5) Immune and Infectious Disease Exclusion Criteria

a) History of congenital or acquired immunodeficiency

b) **Not applicable per Protocol Amendment 02 -** Known serious infection, defined as any infection requiring hospitalization or treatment with parenteral (intramuscular [IM] or IV) antimicrobial agents (eg, antibiotics, antiviral, antifungal, or antiparasitic agents) within 30 days of the first dose of study treatment, or completion of oral antimicrobial agents within 2 weeks of the first dose of study treatment. Antibiotics used to cover a procedure such as endoscopy would not exclude the subject.

c) **Not applicable per Protocol Amendment 01 -** Current or recent (within 12 weeks prior to randomization) herpes zoster, herpes simplex, or influenza infection

d) History of disseminated or complicated herpes zoster infection (including, but not limited to, multi-dermatomal involvement, ophthalmic zoster, central nervous system involvement, or post-herpetic neuralgia)

e) Current or recent (within 12 weeks prior to randomization) herpes zoster, herpes simplex, or influenza infection. In the case of prior SARS-CoV-2 infection, symptoms must have completely resolved **4 weeks prior to screening** and based on investigator assessment in consultation with the Medical Monitor, there are no sequelae that would place the participant at a higher risk when receiving BMS-986165. See Section 9.8 for additional information regarding retesting subjects who have prior SARS-CoV-2 infection.

f) Known serious infection, defined as any infection requiring hospitalization or treatment with parenteral (intramuscular [IM] or IV) antimicrobial agents (eg, antibiotics, antiviral, antifungal, or antiparasitic agents) within 30 days of the first dose of study treatment, or treatment with oral antimicrobial agent(s) within 2 weeks of the first dose of study treatment. Antibiotics used to cover a procedure such as endoscopy would not exclude the subject.

Study inclusion eligibility of subjects being treated with chronic prophylactic antimicrobial agents should be discussed with the BMS Medical Monitor/designee.

6) Prior/Concomitant Therapy

Prohibited concomitant medications and washout periods are further detailed in Table 6 *(Section 7.7.1) and* APPENDIX 7*). Subjects must also comply with the protocol requirements for restricted concomitant medications (*Table 7 *[Section 7.7.2]) and dose stabilization rules (*Table 8 *[Section 0]).*

[redacted]

Subjects who have been exposed to the medications listed above, but who have not had a treatment failure, may be eligible for inclusion. Similarly, subjects who have experienced intolerance to the medications listed above (eg, an infusion reaction) without a treatment failure may be eligible for inclusion.

c) Prior treatment failure (inadequate response or loss of response) [redacted]

e) **Not applicable per Protocol Amendment 02 -** Use of topical rectal treatment with 5-ASA or corticosteroid within 2 weeks prior to randomization

f) Use of intravenous (IV) corticosteroids within 2 weeks prior to the screening period (signing the ICF)

g) Use of immunomodulators (AZA, 6-MP, or MTX) within 4 weeks prior to randomization

h) Use of other investigational agents within 4 weeks or 5 half-lives (whichever is longer) prior to randomization

Fecal transplant is considered an investigational agent for the purpose of this protocol and is subject to a 4-week washout period prior to randomization.

[redacted]

k) Administration of a live vaccine within 90 days prior to randomization

Live vaccines should not be used during the study or within the 2 months following last dose.

Heat-killed, or otherwise inactivated vaccines, or protein or subunit vaccines (eg, influenza and pneumococcal vaccines) may be received at any time on study. The efficacy of vaccination in subjects who are receiving BMS-986165 is unknown.

l) **Not applicable per Protocol Amendment 02 -** Currently on any therapy for chronic infection (eg, pneumocystis, cytomegalovirus, herpes simplex, herpes zoster, invasive bacterial or fungal infections, or atypical mycobacteria).

m) Use of topical rectal treatment with 5-ASA or corticosteroid within 2 weeks prior to screening (signing of ICF).

n) Currently on any therapy for chronic infection (eg, pneumocystis, CMV, herpes simplex, herpes zoster, invasive bacterial or fungal infections, or atypical mycobacteria).

Study inclusion eligibility of subjects being treated with antimicrobial agents strictly for prophylaxis should be discussed with the BMS Medical Monitor/designee.

7) Physical and Laboratory Test Findings

a) Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECG, CXR, or clinical laboratory determinations beyond what is consistent with the target population

b) Clinically significant abnormalities on CXR or ECG

c) Evidence of active or latent tuberculosis (TB), as follows:

i) History of active TB prior to the screening visit, regardless of completion of adequate treatment

OR

ii) Has signs or symptoms of active TB as judged by the investigator

OR

iii) CXR obtained during the screening period or anytime within 6 months before screening, with documentation, with evidence of current active or old active pulmonary TB

OR

iv) **Not applicable per Protocol Amendment 02 -** Latent TB infection (LTBI) defined as positive [redacted]

[redacted] at screening, or other diagnostic test in the absence of clinical manifestations

v) LTBI defined as positive [redacted] at screening

OR

vi) An indeterminate [redacted] result at screening with no signs or symptoms of active TB

Subjects diagnosed with LTBI during screening may be eligible if (1) there are no current signs or symptoms of active TB and (2) the subject has received adequate documented treatment for LTBI within 5 years of screening OR has initiated prophylactic treatment for LTBI per local guidelines and is now rescreened after 1 month of treatment. The subject must agree to complete a locally recommended course of treatment for LTBI to continue in the study.

A subject with an indeterminate [redacted] test result may be retested within the same screening period. If the second result is also indeterminate, the subject will be excluded from the study. If the second result is positive, the subject should be treated as having LTBI. If the second result is negative, the subject may be eligible provided no other Exclusion Criterion for TB is met.

[redacted]

g) Clinically significant abnormalities in laboratory testing including (but not limited to):

***Hematology**:*

i) Hemoglobin level < 8.5 g/dL

ii) White blood cell count < 3.0×10^9/L (< 3000/mm^3)

iii) Lymphocyte count < 0.75×10^9/L (< 750/mm^3)

iv) Neutrophil count < 1.0×10^9/L (< 1000/mm^3)

v) Platelet count < 100×10^9/L (< 100,000/mm^3)

Renal function:

vi) Serum creatinine > 2 × ULN or renal impairment based on an estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m^2 (calculated using the Modification of Diet in Renal Disease [MDRD] equation)

Liver-related blood tests and liver function:

vii) Serum ALT > 2 × ULN

viii) Serum AST > 2 × ULN

ix) **Not applicable per Protocol Amendment 02 -** Serum total bilirubin > 1.5 × ULN (Subjects with total bilirubin > 1.5 × ULN who have a confirmed diagnosis of Gilbert's

syndrome are not excluded from this study but must be discussed with the BMS Medical Monitor/designee.)

x) Alkaline phosphatase (ALP) > 1.5 × ULN

xi) Serum total bilirubin > 1.5 × ULN

h) Positive stool culture for enteric pathogens (not including flora that are considered commensal within a study region)

Subject may rescreen 30 days after completion of a standard treatment course with antimicrobial agents, with a subsequent "negative" stool culture.

A multipathogen molecular panel for enteric pathogens (eg, multipathogen PCR) may be considered as an alternative to stool culture, if this is routinely performed at a site and its use is consistent with local standard of care. Use of this test within the study should be discussed with the BMS Medical Monitor/designee.

i) A diagnosis of *C. difficile* infection

C. difficile *toxin A and B, and* C. difficile *glutamate dehydrogenase (GDH) antigen, with reflex to a confirmatory* C. difficile *nucleic acid amplification test (NAAT) are provided within the study. Subjects should not be randomized if there is a clinical suspicion of* C. difficile *infection.*

Subjects may be rescreened 30 days after completion of an adequate course of treatment for C. difficile *(ie, standard of care antibiotics, fecal transplantation, etc.) and subsequent negative testing for* C. difficile *stool toxin and a* C. difficile *NAAT. Test results should be discussed with the BMS Medical Monitor/designee prior to rescreening.*

j) Any other findings on physical examination, vital signs, or clinical laboratory testing that, in the opinion of the investigator, may place the subject at an unacceptable risk for participation in this study

k) A positive [redacted] test for SARS-CoV-2 during screening

See Section 9.8 for additional information regarding retesting subjects who have a positive diagnostic test for SARS-CoV-2 infection during the screening period.

8) Allergies and Adverse Drug Reaction

a) History of any significant drug allergy (eg, anaphylaxis) or significant adverse drug reaction (eg, hepatotoxicity)

9) Other Exclusion Criteria

a) Any major illness or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, cardiac, immunologic, psychiatric), or local active infection/infectious illness that, in the investigator's judgment, will substantially increase the risk to the subject if he or she participates in the study

b) Any major surgery (requiring general anesthesia) within the last 30 days prior to randomization, or any other major surgery planned during the course of the study

Such subjects should be discussed with the BMS Medical Monitor/designee. Subject must have adequate wound healing prior to randomization. This criterion does not include endoscopy performed using sedation or general anesthesia (eg, propofol).

c) History of bleeding disorders or recent use of anti-platelet or anti-thrombotic agents that in the investigator's judgment preclude safely performing endoscopic procedures and biopsy within the timeframe outlined in the study protocol

d) Cancer or history of cancer or lymphoproliferative disease within the previous 5 years (other than adequately treated cutaneous basal cell or squamous cell carcinoma or resected cervix carcinoma in situ with no evidence of recurrence)

e) Subjects with cancer screening or surveillance that is suspicious for malignancy, or where the possibility of malignancy cannot be reasonably excluded after additional clinical, laboratory, or other diagnostic evaluations

f) Class III or IV congestive heart failure, as classified by the New York Heart Association (NYHA) Functional Classification or any recent onset of heart failure resulting in NYHA Class III/IV symptoms

g) Acute coronary syndrome (eg, myocardial infarction, unstable angina pectoris) and/or any history of significant cerebrovascular disease (eg, stroke, cerebral hemorrhage, transient ischemic attack) within 24 weeks before screening

h) Known history of hereditary galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption

i) Significant blood loss (> 500 mL) or blood transfusion within 4 weeks prior to the randomization visit

j) **Not applicable per Protocol Amendment 01 -** Drug or alcohol abuse, as determined by the investigator, within 6 months prior to Day 1 (Note: medical marijuana is not allowed.)

k) Any other sound medical, psychiatric, and/or social reason as determined by the investigator

l) Prisoners or subjects who are involuntarily incarcerated

m) Unable to comply with study procedures and visits

n) Unable to tolerate oral medication

o) Unable to undergo venipuncture and/or tolerate venous access

p) Drug or alcohol abuse, as determined by the investigator, within 6 months prior to Day 1

6.3 Randomization Criteria

Subjects must meet the following criteria at the randomization visit on Day 1 in order to be eligible to be randomized and to receive the first dose of study treatment:

1. The subject continues to meet the Inclusion Criteria, listed in Section 6.1.
2. The subject continues to not meet any of the **Exclusion Criteria**, listed in Section 6.2.
3. The subject has discontinued any **prohibited treatments** (Table 6, Section 7.7.1).
4. The subject meets the **dose stabilization rules** for permitted UC medications, outlined in Section 7.7.3 (Table 8).
5. The subject meets the **washout periods** for prior concomitant medications, outlined in APPENDIX 7.

6.4 Lifestyle Restrictions

Subjects are required to fast for a minimum of 10 hours before the randomization visit (Day 1) and the Week 12 (Day 85) visit, as fasting lipid and glucose samples will be obtained at those times.

WOCBP must agree to follow instructions for methods of contraception for the duration of treatment with IP (APPENDIX 4).

Otherwise, no lifestyle restrictions are required.

Smoking can have an influence on the severity of UC disease symptoms. Consequently, use of tobacco products will be assessed at each study visit. Use of a nicotine patch should be recorded as a concomitant medication.

Study treatment may be taken without regard to meals.

6.5 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but who are not subsequently randomized in the study/included in the analysis population. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, as applicable, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any SAEs. Additional screening data, such as SF, RB, and ES subscores; PGAs; fecal calprotectin; and other clinically relevant data may also be required.

6.5.1 Retesting During the Screening Period

For laboratory parameters and/or assessments (Section 2) that initially do not meet eligibility requirements, a single retest within the screening period may be permitted after consultation with the BMS Medical Monitor/designee. The investigator should have a reasonable expectation that the retested laboratory parameter and/or assessment is likely to meet eligibility requirements.

Confirmatory testing of parameters that require confirmation per protocol (eg, indeterminate or borderline [redacted] result) and repeat testing of laboratory parameters that are unable to be reported (eg, due to an inadequate sample) can be performed without consultation with the BMS Medical Monitor/designee.

6.5.2 Rescreening

This study permits the rescreening of a subject who has been deemed as ineligible (a screen failure) during the screening period (ie, the subject has not been randomized/has not been treated). Subjects who wish to be rescreened should be discussed with the BMS Medical Monitor/designee prior to rescreening. The subject must be re-consented and will be assigned a new identification number, and a full screening visit must be performed again (unless individual screening investigations can be waived, as discussed below). The most current result prior to randomization is the value by which study eligibility will be assessed.

A subject can only be rescreened 1 time. If the subject fails 1 rescreening attempt, no additional rescreening is allowed.

For subjects requiring rescreening, the initial screening endoscopy result may be used, provided that randomization occurs within 14 days of the initial screening endoscopy. In that circumstance, the screening endoscopy does not have to be repeated. Subjects who are likely to benefit from this approach should be discussed with the BMS Medical Monitor/designee prior to rescreening.

- *In the case of rescreening after an initial eligible screening endoscopy, the SF and RB scores for eligibility will be based on the Day 1 visit date rather than the bowel preparation date.*
- *The window between the initial screening endoscopy and randomization may be extended up to an additional 3 days with approval of the BMS Medical Monitor/designee.*

Duration of existing treatments and required discontinuation periods shall be considered relative to the successful screening visit and/or randomization.

Subjects who are diagnosed with *C. difficile* infection during screening may be rescreened 30 days after completion of an adequate course of treatment for *C. difficile* (ie, standard of care antibiotics, fecal transplantation, etc.) and subsequent negative testing for *C. difficile* stool toxin and a *C. difficile* NAAT. Test results should be discussed with the BMS Medical Monitor/designee prior to rescreening.

Subjects who are diagnosed with LTBI during screening may be eligible to be rescreened for this study provided they have completed at least 4 weeks of treatment for LTBI and they comply with treatment for LTBI (both according to local standard of care) during study participation. For these subjects, a repeat CXR is required during rescreening, but [redacted] should not be repeated. LTBI screening is further discussed in Section 9.4.2.

The following laboratory assessments are not required to be repeated during rescreening if the subject is randomized within 45 days of the original screening results: [redacted] thyroid-stimulating hormone (TSH).

7 TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo or medical device intended to be administered to a study subject according to the study randomization or treatment allocation.

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

IM011127 consists of IP study treatments BMS-986165 and placebo (see Table 4). Information about the pharmacology and previous experience with BMS-986165 is provided in Section 3.1.1 and Section 3.1.2.

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

Table 4: Study Treatments for IM011127

Product Description/ Class and Dosage Form	Potency	IP/ Non-IP	Blinded or Open-label	Packaging/ Appearance	Storage Conditions (per label)
BMS-986165 12 mg oral tablet	12 mg	IP	Blinded	Blister card containing 72 tablets	Store 15° to 25°C; Protected from light
BMS-986165 6 mg oral tablet *Applicable only to subjects enrolled under the Original Protocol or Protocol Amendment 01*	6 mg	IP	Blinded	Blister card containing 72 tablets	Store 15° to 25°C; Protected from light
Placebo matching BMS-986165 12 mg oral tablet	Not applicable	IP	Blinded	Blister card containing 72 tablets	Store 15° to 25°C; Protected from light
Placebo matching BMS-986165 6 mg oral tablet	Not applicable	IP	Blinded	Blister card containing 72 tablets	Store 15° to 25°C; Protected from light
BMS-986165 6 mg oral tablet	6 mg	IP	Open-label	Bottle containing 68 tablets	Store 15° to 25°C; Protected from light

IP = investigational product

7.1 Treatments Administered

During the double-blind treatment period (induction), subjects will receive BMS-986165 12 mg BID or placebo BID PO over 12 weeks (Section 5.1.2), once in the morning and once in the evening. Subjects randomized to the 6 mg BID dose arm under the Original Protocol or Protocol Amendment 01 will continue to receive 6 mg BID during the double-blind treatment period. Dose information for each treatment group is provided in [redacted] The morning dose should be taken [redacted] Study treatment will be supplied in blister cards, each containing 72 active or placebo tablets. Blister cards are to be stored at 15°C to 25°C and protected from light.

During the OLE period, subjects will take BMS-986165 6 mg BID PO over 40 weeks (Section 5.1.3), once in the morning and once in the evening. Dose information is provided in [redacted] Study treatment will be supplied in bottles containing 68 (6 mg) active tablets. Bottles are to be stored at 15°C to 25°C and protected from light.

If a subject forgets a dose, but remembers within 4 hours of the expected dose, the dose should be taken. If it is past 4 hours (or if the dose is vomited), that dose should be missed, and the next expected dose should be taken at the usual time.

7.2 Method of Treatment Assignment

At the time of the screening visit, immediately after informed consent is obtained and before any study-related procedures are performed, the investigative site will access the interactive response technology (IRT) system for assignment of the subject number. This number will be unique across all sites. All subjects who sign the ICF will be assigned sequential subject numbers. The subject number may not be used for any other subject. If a potential subject is rescreened, they will be given a new subject number.

Eligible subjects will be centrally randomized using IRT at a 3:1 randomization ratio to receive oral treatment during the treatment period with either BMS-986165 12 mg BID or placebo BID, according to a computer-generated block randomization scheme. Randomization numbers will be assigned prior to dosing.

Before the study is initiated, each user (at investigative sites) will receive log-in information and directions on how to access the IRT. Study treatment will be dispensed at study visits as shown in the Schedule of Activities (Section 2).

7.3 Blinding

7.3.1 Maintaining the Blind

Blinded treatment assignments will be managed using IRT.

Each BMS-986165 tablet (12 mg and 6 mg) has an identical matching placebo tablet in order to maintain the blind. Tablets will be supplied in blister cards (see Section 7.1). Investigative site staff, Sponsor and designee personnel, and subjects and their families will remain blinded to treatment assignments.

The Sponsor may perform an unblinded interim analysis of study data prior to final data analysis. A SAP, which will include a section on interim analysis, will be created to fully detail the activities around the interim analysis.

The DMC may review unblinded data summaries and listings, at their request (see Section 5.1.6). DMC processes and procedures will be outlined in the DMC Charter.

Designated staff of BMS may be unblinded (obtain the randomization codes) prior to database lock to facilitate the bioanalytical analysis of [redacted] samples and immunogenicity. A bioanalytical scientist in the Bioanalytical Sciences department of BMS (or a designee in the external central bioanalytical laboratory) may be unblinded to the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples.

7.3.2 Circumstances for Unblinding

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

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

In case of an emergency, the investigator has unrestricted access to randomization information via IRT and is capable of breaking the blind through the IRT system without prior approval from the Sponsor. After the unblinding via IRT, the investigator shall notify the BMS Medical Monitor/designee and/or study director. The method of unblinding for emergency purposes is described in the IRT manual. Subject and unblinded treatment information and the reason for the blind being broken, must be recorded on the appropriate study status page of the eCRF.

In cases of accidental unblinding, contact the BMS Medical Monitor/designee and ensure every attempt is made to preserve the blind. Any request to unblind a subject for nonemergency purposes must be discussed with the BMS Medical Monitor/designee.

7.4 Dosage Modification

There is no provision for dose modification of study treatment.

Dose stabilization criteria for permitted UC treatments are detailed in Section 0 (Table 8). Modification of permitted UC treatments or dose regimens is allowed for safety reasons, or if a

subject experiences an AE attributable to that treatment. Subjects should continue to take their assigned treatment even if their clinical condition worsens (ie, they experience a "flare"), unless any of the criteria in Section 8.1 are met. If a subject's clinical condition worsens before Week 12 of the treatment period to the extent that rescue therapy is required, based on the investigator's judgment, the subject must discontinue study treatment (IP or placebo) in favor of appropriate alternative available treatment.

See Section 8.1.1 for information regarding temporary interruption of study treatment.

7.5 Preparation/Handling/Storage/Accountability

The IP should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that IP is only dispensed to study subjects. 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 treatment is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study treatment arise, the study treatment should not be dispensed and BMS should be contacted immediately.

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

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

Further guidance and information for final disposition of unused study treatment are provided in APPENDIX 2 and the Study Reference Manual.

7.5.1 Retained Samples for Bioavailability/Bioequivalence/Biocomparability

Not applicable.

7.6 Treatment Compliance

Study treatment compliance will be monitored as indicated in the Schedule of Activities (Section 2) using standard drug accountability procedures (comparing the number of tablets returned to number dispensed, considering the expected regimen and any reported missed doses). Drug accountability will be reviewed by the investigative site staff at each visit to confirm treatment compliance. Site staff will discuss any discrepancies with the subject and remind the subject of the importance of compliance with the assigned regimen.

7.7 Concomitant Therapy

All medications taken from within 4 weeks before the first dose of study treatment until 30 days after the last dose of IP or last visit (whichever comes later) must be recorded on the appropriate eCRF.

Other than existing treatment for UC (with restrictions as described in the eligibility criteria [Section 6]), concomitant medications (prescription, over-the-counter [OTC], or herbal) should be

administered during the study only if they are prescribed for treatment of specific medical reasons separate from UC.

7.7.1 Prohibited Treatments

Prohibited prior and current concomitant medications are summarized in Table 6. Additional details on washout periods are listed in APPENDIX 7.

Table 6: Summary of Prohibited Concomitant Medications

Prohibited Treatments	
Medication/Formulation	**Notes**
BMS-986165 or other TYK2 inhibitors	Prior exposure is prohibited
[redacted]	
Immunomodulatory drugs	Prohibited within required washout periods (APPENDIX 7) and during the study
Biologic drugs	Prohibited within required washout periods (APPENDIX 7) and during the study
Live vaccines	Prohibited 90 days prior to the randomization visit, during the treatment period, or within the 2 months after the last dose[a]. Vaccine guidance for the study is outlined in APPENDIX 13
Apheresis	Receipt of either lymphocyte apheresis or selective monocyte, granulocyte apheresis (eg, Cellsorba™) is prohibited within 12 months prior to the randomization visit and during the study
Investigational agents	Prohibited within 4 weeks or 5 half-lives (whichever is longer) before the randomization visit and during the study
Traditional Chinese medicines, herbal medicines, or herbal supplements	Prohibited within 1 week prior to the randomization visit; any exceptions to this must be cleared by the BMS Medical Monitor/designee
Fluvoxamine	Prohibited within 1 week of the randomization visit and during study
Therapy for chronic infections	Subjects who require treatment for chronic infections are excluded NOTE: *Eligibility of subjects receiving prophylactic antibiotic therapy for study inclusion should be discussed with the BMS Medical Monitor/designee.*

[redacted]

TYK2 = tyrosine kinase 2; [redacted]

[a] Heat-killed (or otherwise inactivated) or protein or subunit vaccines such as influenza and pneumococcal vaccines, nucleic acid vaccines that do not encode potentially infectious virus, and replication-incompetent recombinant vector vaccines may be received at any time during the study. The efficacy of vaccination in subjects who are receiving BMS-986165 is unknown (see APPENDIX 13 for vaccine guidance).

7.7.2 Restricted Treatments

Restricted concomitant medications are summarized in Table 7.

Table 7: Summary of Restricted Concomitant Medications

Restricted Treatments	
Medication/Formulation	**Notes**
[redacted]	
NSAIDs	May be used on an as needed basis during the study, but use is not recommended, as NSAIDs may be associated with gastrointestinal toxicity, including mucosal injury

NSAID = nonsteroidal anti-inflammatory drug; [redacted]

7.7.3 Dose Stabilization Rules for Permitted UC Treatments

Use of concomitant oral 5-ASAs or oral corticosteroids [redacted] is permitted, subject to the dose stabilization rules outlined in Table 8. Probiotics are allowed with no restrictions on use. Subjects will continue their existing UC treatment(s) during the study, provided the treatment complies with the eligibility criteria (see Section 6.1, Section 6.2, and Table 6).

Dose reduction or discontinuation of 5-ASAs or corticosteroids is allowed during the study if this is required for subject safety reasons, such as if a subject experiences an AE attributable to those medications. The rationale for dose reduction or discontinuation must be documented in source documents. The AE or SAE eCRF must be completed, if applicable.

Table 8: Dose Stabilization Rules for Allowed Concomitant Medications

Medication/Formulation	Notes
5-ASAs (oral):	• The oral 5-ASA regimen must be at a stable dose for at least 2 weeks prior to the initial screening visit (signing of ICF). Dose reduction (or discontinuation) is only allowed within this period for safety reasons, or if a subject experiences an AE attributable to the 5-ASA regimen.

Table 8: Dose Stabilization Rules for Allowed Concomitant Medications

Medication/Formulation	Notes
	• Stable doses are encouraged after randomization for the duration of the 12-week double-blind treatment period.
[redacted]	• [redacted] must be at a stable dose for at least 2 weeks prior to the initial screening visit (signing of ICF). Dose reduction (or discontinuation) is only allowed within this period for safety reasons or if the subject experiences an AE attributable to the [redacted]. This must be discussed with the BMS Medical Monitor/designee. • After randomization, a stable dose is required for the duration of the 12-week treatment period. Dose reduction (or discontinuation) is only allowed within the treatment period for safety reasons, or if the subject experiences an AE attributable to the [redacted]. This must be discussed with the BMS Medical Monitor/designee. • Throughout the study, an increase in [redacted] dose above the baseline dose is not permitted.
Probiotics:	• Probiotics are allowed. Dose stabilization is not required.

5-ASA = 5-aminosalicyclic acid; AE = adverse event; ICF = informed consent form; [redacted]

[redacted]

7.8 Treatment After the End of the Study

At the end of the study (Section 5.3), the investigator should ensure that subjects continue to receive appropriate standard of care to treat the condition under study.

In addition, for subjects who continue to demonstrate clinical benefit, BMS may continue to provide study treatment via an extension of the current study (ie, Study IM011077) or through another mechanism at the discretion of BMS.

BMS reserves the right to terminate access to BMS supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of BMS-986165 is terminated for any reason, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the subject can obtain medication from a government sponsored or private health program. In all cases BMS will follow local regulations.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

Subjects MUST discontinue IP (and non-IP at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment. Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified posttreatment follow-up procedures (Section 5.1.4). The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information.
- Any clinical AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject

- 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).
- Subject meets 1 of the following criteria for laboratory abnormalities in 2 sequential laboratory measurements taken 3 to 5 days apart:

[redacted]

- Subject meets any of the following criteria for liver-related laboratory abnormalities. If these abnormalities are identified, repeat testing should occur within 48-72 hours and these results should be discussed with the BMS Medical Monitor/designee. Additional recommendations on the recognition and investigation of potential 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%)

[redacted]

- Unblinding of a subject's treatment assignment for any reason (emergency or nonemergency)
- Inability or failure to comply with protocol requirements
- Pregnancy, positive pregnancy test, or subject no longer wishes to comply with study requirements relating to prevention of pregnancy (Refer to Section 9.2.5)

[redacted]

All subjects who discontinue study treatment should comply with protocol-specified ET and follow-up procedures as outlined in the Schedule of Activities (Section 2). The only exception to this requirement is when a subject withdraws consent for all study procedures including posttreatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study treatment is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate eCRF page.

8.1.1 Temporary Interruption of Study Treatment

The following criteria for temporary interruption of study treatment apply at any time during the 52-week treatment period:

- For those subjects who present with signs and/or symptoms of COVID-19 during the study, the study treatment should be temporarily interrupted while the subject undergoes diagnostic testing for SARS-CoV-2 (see Section 9.8 [SARS-CoV-2 Testing]).
- Study treatment must be temporarily interrupted for subjects who test positive for SARS-CoV-2 until complete recovery (if symptomatic) and a negative molecular test result is obtained. Study treatment may be restarted at investigator discretion following consultation with the BMS Medical Monitor/designee provided that the subject meets the criteria outlined in Section 9.8 (SARS-CoV-2 Testing).
- Study treatment should be temporarily withheld if a subject develops a skin-related AE that is either severe in intensity, or meets the criteria for an SAE (see APPENDIX 3 for definitions), or is sufficient to require temporary discontinuation in the judgment of the investigator. Study treatment should be temporarily withheld until the intensity of the AE decreases or the AE resolves, and may be restarted only after discussion of the case with the BMS Medical Monitor/designee.

Additional criteria for temporary interruption applicable to the **OLE period only** are as follows:

- Study treatment may be interrupted by the investigator for medical procedures not related to UC or for AEs that do not meet criteria for study discontinuation and are assessed by the investigator as not related to the study drug under the following conditions:
  - Documented prior approval from the BMS Medical Monitor/designee
  - Agreement between the investigator and the BMS Medical Monitor/designee that the subject has benefited from study treatment and that temporary interruption (rather than discontinuation) of study drug will result in the greatest benefit to the subject
  - Dose interruption is expected to be 4 weeks or less

Study treatment may be restarted at investigator discretion following consultation with the BMS Medical Monitor/designee provided that there has been adequate resolution of AE or post-procedure condition.

8.1.2 Poststudy Treatment Study Follow-Up

Subjects who discontinue study treatment will continue to be followed for 28 days post last dose of study drug, or longer, as required, and in line with Section 9.2.3 (Follow-up of AEs and SAEs). The posttreatment follow-up visit (Week 56) is not required for subjects who transition to a BMS-sponsored roll-over/follow-on study (eg, Study IM011077).

8.2 Discontinuation from the Study

Subjects who request to discontinue study treatment (Section 8.1) will remain in the study and continue to be followed for protocol-specified posttreatment follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information.

- Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the investigator and entered on the appropriate eCRF page.
- In the event that vital status (whether the subject 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 subject 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

- All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject.
- Lost to follow-up is defined by the inability to reach the subject after a minimum of **3** documented phone calls, faxes, or emails as well as lack of response by subject to 1 registered mail letter. All attempts should be documented in the subject's medical records.
- If it is determined that the subject has died, the site will use permissible local methods to obtain date and cause of death.
- If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's ICF, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining subject'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, to obtain updated contact information.
- If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

8.4 Replacement of Subjects

Subject replacement is not permitted.

8.5 Study Discontinuation

A DMC will provide oversight of the safety of trial subjects as outlined in Section 5.1.6 of the protocol and in the DMC Charter.

The DMC will periodically review safety data and make recommendations regarding the appropriateness of continuing the study, with or without study modifications, or stopping the study.

BMS reserves the right to terminate access to BMS supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of BMS-986165 is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government sponsored or private health program. In all cases BMS will follow local regulations.

9 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and timing are summarized in the Schedule of Activities (Section 2). Waivers or exemptions from protocol-required evaluations are not allowed.

All immediate safety concerns must be discussed with the BMS Medical Monitor/designee immediately upon occurrence or awareness to determine if the subject should continue or discontinue treatment.

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

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management (eg, complete blood count) and obtained before signing of the ICF may be utilized for screening purposes provided the procedure meets the protocol-defined criteria and this approach has been discussed and agreed with the BMS Medical Monitor/designee (Section 2). A CXR performed less than 6 months prior to signing of the ICF may be used in place of the screening CXR, provided the subject has no symptoms or signs suggestive of pulmonary disease in the interim.

Assessments at the randomization visit (Day 1) must be performed per protocol. Standard of care assessments may not be used to establish pretreatment baseline parameters (ie, at the randomization visit). Procedures not specified in the protocol that are part of standard care may be performed if they do not interfere with study procedures. Any data arising from such procedures are not to be reported in the eCRF.

The study data includes all the information that is collected as a result of the study, including participant demographics, disease characteristics, clinical information, blood tests, biomarker tests, endoscopic videos, intestinal biopsies obtained during endoscopy, and other tests listed in

Table 1. Study data collected during this study will be used to help us understand how BMS-986165 works in people with UC, and related health conditions. The study data may also be used to help us understand the biology of UC and related health conditions, how study tests perform in people with UC, and for other relevant health research relating to BMS-986165 or these health conditions.

9.1 Efficacy Assessments

Every effort must be made to ensure that the same evaluator(s) complete the assessment for each subject. If the evaluator(s) is unable to complete the evaluation, then a qualified individual with overlapping experience may perform the evaluation. Documentation of who performed the evaluation is to be recorded in source documents. Assessments are to be performed at approximately the same time of day throughout the duration of the study.

9.1.1 Capturing Data to Assess Disease Activity and Determine Efficacy

- **Subject's Electronic Daily Diary**: An electronic diary will be provided to each subject for daily recording of **SF** and **RB** data. **Baseline SF** (either reference remission SF or pre-UC SF; see Mayo score, below) and **health-related quality of life** (Inflammatory Bowel Disease Questionnaire [IBDQ]) will also be captured in the electronic diary at the timepoints indicated in the Schedule of Activities (Section 2).

  Data derived from the electronic daily diary are used for assessment of Inclusion Criteria and outcome measures. Subjects will be trained on the use of the electronic diary at the screening visit. Sites should periodically assess subject compliance with the electronic daily diary. Should the subject miss daily entries prior to a study visit, the investigator should assess if the visit should be rescheduled to ensure that an adequate number of daily entries for efficacy assessment are recorded.

- **Medidata Rave Electronic Data Capture (EDC)**: The **PGA** (see Mayo score, below) and **UC-related medical resource utilization** (see Section 9.7) will be evaluated by the investigator or designee and recorded in the Medidata Rave EDC system at the timepoints indicated in the Schedule of Activities (Section 2).

- **Endoscopy**: Endoscopy (colonoscopy or flexible sigmoidoscopy) will be performed at the timepoints indicated in the Schedule of Activities [redacted]

[redacted]

- **Endoscopic biopsies**: [redacted]
- **Serum high-sensitivity C-reactive protein (hsCRP)**: [redacted]
- [redacted] **fecal lactoferrin**: [redacted]

9.1.2 Disease Activity and Quality of Life Indices Used in this Study

The following instruments will be used to assess UC disease activity and health-related quality of life during the study as indicated in the Schedule of Activities (Section 2). Selected endpoints that use these indices are defined in Table 10:

- **Total Mayo score**: The **total Mayo score** is a composite disease activity index that is comprised of 4 subscores: SF, RB, and ES subscores, and a PGA subscore.[47] Consistent with regulatory draft guidance, the ES subscore scale has been modified so that friability is no longer included in the definition of an ES subscore = 1.[38, 48] Each subscore is scored on a 4-point scale, ranging from 0-3, leading to a maximum total score of 12. Higher scores indicate more severe disease. The total Mayo score may be determined at screening and/or Day 1 and at Weeks 12 and 52, and ET visit (if applicable). It will be used in endpoint assessment.
- **Modified Mayo score**: The **modified Mayo score** is a composite of the following total Mayo score subscores: SF, RB, and ES.[38] Friability is not included in the definition of an ES subscore = 1, and the PGA is not included in the calculation of the modified Mayo score.[38, 39, 48] The maximum total score of the modified Mayo score is 9. The modified Mayo score calculated to determine eligibility will be used as the baseline score for randomization on Day 1. The modified Mayo score will also be determined at Weeks 12 and 52, and ET visit (if applicable). It will be used in endpoint assessment.
- Details regarding the recording of the individual Mayo score components and the calculation of the total Mayo score and modified Mayo score are provided in APPENDIX 9, while timing of assessments are detailed in the Schedule of Activities (Section 2). Briefly, the investigator records the baseline SF at the screening visit, and the PGA at each study visit, while the subject

records daily SF and RB scores in the study diary. The ES subscore will be determined by a central reader who is blinded to subject details, including visit number and treatment assignment. The investigator will also record an ES subscore (local read) which will be used for post hoc analyses.

- **Partial Mayo score**: The **partial Mayo score** is a composite of the following Mayo score subscores: SF, RB, and PGA.[49] The partial Mayo score may be determined at the timepoints indicated in the Schedule of Activities (Section 2).
- **Symptomatic Mayo score**: The **symptomatic Mayo score** is a composite and defined as the sum of the Mayo SF and RB subscores. It may be calculated at various timepoints and will be used in endpoint assessment.
- **UCEIS**:[50, 51] The UCEIS is a composite index that evaluates the endoscopic appearance of the mucosa. Three descriptors are scored as follows: vascular pattern (0 to 2), bleeding (0 to 3), and erosions and ulcers (0 to 3), to give a score ranging from 0-8, where higher scores indicate more severe disease (APPENDIX 10). [redacted]

  Additional details on endoscopy image acquisition, image quality control and central reading for the assessment of Mayo ES subscore and UCEIS will be provided in the Endoscopy Image Review Charter.

- [redacted]

- **UC-100**[40]: The UC-100 is a composite index that uses the weighted Mayo SF subscore, Mayo ES subscore, [redacted] to derive a score that ranges from 1 to 100, where higher scores indicate a greater degree of disease activity. [40]

  Additional details regarding calculation of UC-100 scores will be provided in the SAP.

- **Patient-reported Outcomes (PROs)**: The following instruments will be used for the assessment of additional PROs, health-related quality of life, and healthcare utilization. All instruments are to be completed by subjects:
  - IBDQ[54]: The IBDQ is a well-established assessment to measure disease-specific health-related quality of life. It is composed of 32 items and 4 domains including gastrointestinal symptoms, systemic symptoms, emotional dysfunction, and social dysfunction. Questionnaire items have a 2-week recall period and are scored on a 7-point Likert scale from worst health (1) to best health (7) (APPENDIX 11).

- **UC-related Hospitalization and Surgeries**: This instrument provides questions/prompts representative of the data to be collected through eCRF regarding subjects' UC-related hospitalizations and surgical procedures (APPENDIX 12).

Table 10: Selected Endpoint Definitions

Endpoint	Definition
Clinical response	Achieving the following changes in the modified Mayo score: • A decrease from baseline in the modified Mayo score of ≥ 2 points, **and** • A decrease from baseline in the modified Mayo score ≥ 30%, **and** • A decrease in RB subscore of ≥ 1 point or absolute RB subscore ≤ 1
Clinical remission (modified Mayo score)	A modified Mayo score[a] with the following: • SF subscore ≤ 1, with ≥ 1 point decrease from baseline, **and** • RB subscore = 0, **and** • Modified ES[b] subscore ≤ 1
Clinical remission (total Mayo score)	• A total Mayo score[a] ≤ 2, with no individual subscore > 1
Symptomatic remission	A symptomatic Mayo score[a] with the following: • SF subscore ≤ 1, with ≥ 1 point decrease from baseline, **and** • RB subscore = 0
Corticosteroid-free remission	Clinical remission in subjects using oral corticosteroids at baseline who have discontinued corticosteroids for UC in the OLE period for ≥ 12 weeks prior to Week 52
Durable clinical response	Clinical response at Week 12, which is maintained at Week 52
Endoscopic remission	Mayo ES subscore = 0
Endoscopic improvement	Mayo ES subscore ≤ 1[b]
Endoscopic response	A decrease from baseline of ≥ 1 point in Mayo ES subscore

Table 10: Selected Endpoint Definitions

Endpoint	Definition
Durable endoscopic response	Endoscopic response at Week 12 which is maintained at Week 52
[redacted]	

ES = endoscopic; OLE = open-label extension; RB = rectal bleed; SF = stool frequency; UC = ulcerative colitis

a See Section 9.1.2 and APPENDIX 9 for a description of the total, modified, and symptomatic Mayo scores.

b Obtained from centrally-read endoscopy (Section 9.1.1). Friability is not included in the modified definition of ES = 1.

9.2 Adverse Events

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

AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

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

Contacts for SAE reporting are specified in APPENDIX 3**.**

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment and continue until the follow-up visit at Week 56 or the last visit, at the time points specified in the Schedule of Activities (Section 2). Nonserious AE information should also be collected from the start of the treatment period at Day1. The Reference Safety Information [redacted] should be used to determine the expectedness of SAEs for expedited reporting.

All AEs related to SARS-CoV-2 infection, and all SAEs, must be collected from the time of signing the consent to the end of the safety follow-up period (within 30 days of treatment discontinuation) or roll-over into a follow-on study.

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

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

- All SAEs and AEs related to SARS-CoV-2 infection (including a positive diagnostic SARS-CoV-2 test) will be recorded and reported immediately to the Sponsor or designee but no later than 24 hours after awareness of the event, as indicated in APPENDIX 3.
- The investigator will submit any updated SAE data to the Sponsor or designee immediately but no later than 24 hours of updated information being available.

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

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

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 subject. To prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.

9.2.3 Follow-up of AEs and SAEs

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

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and nonserious AEs of special interest (as defined in Section 9.2.8) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 8.3).

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

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor or designee of SAEs is essential so that legal obligations and ethical responsibilities toward the safety of subjects 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 or designee will file it along with the IB and will notify the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), if appropriate according to local requirements.

Sponsor or designee will be reporting AEs to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR is a subset of SAEs and will 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 treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during and at least for 30 days after study product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in APPENDIX 3.

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

Any pregnancy that occurs in a female partner of a male study subject should be reported to Sponsor or designee. In order for the Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an ICF for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

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

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

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

9.2.7 Potential Drug-Induced Liver Injury (DILI)

Clinical chemistry and coagulation tests will be assessed as indicated in the Schedule of Activities (Section 2). Subjects with abnormal liver blood tests should be further assessed to determine if these meet the criteria for discontinuation of the study drug (see Section 8.1) or the criteria for potential DILI.

Potential DILI is defined as:

1) ALT or AST elevation > 3 × ULN,

AND

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

AND

3) No other immediately apparent possible causes of ALT or AST elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, preexisting chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Identification of a clinically significant elevation(s) in liver-related chemistry or coagulation tests (including those defined in Section 8.1, or meeting the definition for potential DILI) should be followed by repeat testing of ALT, AST, total bilirubin, ALP, and INR within 48-72 hours to: (1) confirm the abnormalities, and (2) determine if they are increasing or decreasing.

Investigators should consult with the BMS Medical Monitor/designee immediately if a subject meets the laboratory criteria for potential DILI.

Investigators should consider gathering additional clinical information and laboratory and imaging tests to seek other possible causes of the observed liver blood test abnormalities, including (but not limited to) acute viral hepatitis, alcoholic and autoimmune hepatitis, biliary obstruction (small and large duct), cardiovascular causes (eg, ischemic hepatitis), nonalcoholic steatohepatitis (NASH), and the effect of concomitant treatments.

A review of all concomitant medications should include herbal medicines, dietary supplements, nonprescription OTC medications, including acetaminophen/paracetamol, and occupational exposure to chemical agents.

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 3 for reporting details). All subjects with clinically significant abnormalities in liver-related blood tests, or potential DILI, must be followed until all abnormalities return to normal or to the baseline state.

9.2.8 Adverse Events of Interest (Clinical Safety Program)

All AEs and SAEs that arise in the study will be reported and investigated. However, because of the characteristics of the disease under study, and BMS-986165 in particular, some AEs are considered adverse events of interest (AEIs). AEIs may be serious or nonserious. Such events may require further investigation to better characterize and understand them.

[redacted]

In addition, given that immunosuppression is consistent with the mechanism of action of BMS-986165, malignancies are considered to be an important potential risk of therapy with BMS-986165 and will be monitored as AEIs. Malignancies were not identified as adverse findings in nonclinical studies and no serious adverse reactions of malignancy have been reported to date in clinical studies of BMS-986165.

Additional information on AEIs will be collected in this study. Reporting of an AE or SAE that includes a PT that is linked to an AEI will trigger specialized eCRF pages to collect additional information related to characterization, social/family history, risk factors, signs/symptoms, diagnostics, and treatments. Additional information may also be requested to aid in the evaluation of these AEs.

9.2.9 Other Safety Considerations

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

9.3 Overdose

[redacted]

In the event of an overdose the investigator should do the following:

1) Contact the BMS Medical Monitor/designee immediately
2) Closely monitor the subject for AEs/SAEs and laboratory abnormalities until BMS-986165 can no longer be detected systemically (at least 3 days)
3) 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 BMS Medical Monitor/designee based on the clinical evaluation of the subject.

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities (Section 2). All urgent safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue treatment.

Safety evaluations that will be performed in addition to AE monitoring are physical examination (Section 9.4.1), TB screening (Section 9.4.2), vital signs (Section 9.4.5), ECGs (Section 9.4.6), concomitant medication use (Section 7.7), and laboratory tests (Section 9.4.3).

9.4.1 Physical Examinations

Schedules for physical examinations are provided in the Schedule of Activities (Section 2). Complete physical examinations must be performed by someone who is authorized to perform the examinations by training and has been delegated this task by the principal investigator. Key aspects of the examination should evaluate important body systems, including skin, as clinically indicated.

Every effort should be made to ensure the same evaluator will complete the examination for each subject at all visits throughout the study. Documentation of who performed the examination is to be recorded in source notes.

9.4.2 Tuberculosis Screening and Chest X-ray

Screening for active TB and LTBI includes medical history, physical examination, [redacted] and CXR. A tuberculin skin test (eg, Mantoux test) may also be performed, at the investigator's discretion, but this does not replace the requirement for [redacted]. A CXR at the screening visit is required if not already performed and documented within 6 months of obtaining written informed consent.

In order to be eligible for the study, a subject must not have symptoms or signs of active TB, as judged by the investigator.

[redacted] is provided as part of the screening investigation kit. This will be collected and sent to a central laboratory. An [redacted] test sent to a local laboratory may be an acceptable alternative, provided that this approach is agreed with the BMS Medical Monitor/designee.

A subject with a "negative" [redacted] test may be eligible to participate in the study, provided they do not have any clinical or radiologic (CXR) evidence supporting a diagnosis of active TB or LTBI.

A subject with an "indeterminate" QuantiFERON test or a "borderline" T-Spot test must have a retest before they are eligible to participate in the study. If the second result is again "indeterminate" or "borderline," the subject will be excluded from the study. If the second result is negative, the subject may be eligible provided there is no clinical or radiologic suspicion of active TB or LTBI.

A subject with a positive [redacted] result should be further assessed in order to determine if active TB or LTBI is present.

Subjects who are diagnosed with LTBI during screening may be eligible to be rescreened for this study provided they have completed at least 4 weeks of treatment for LTBI and they comply with treatment for LTBI (both according to local standard of care) during study participation. For these subjects, a medical history, physical examination, and a repeat CXR are required during rescreening, but [redacted] should not be repeated.

9.4.3 Clinical Safety Laboratory Assessments

- A central or local laboratory will perform safety laboratory assessments (as indicated in operational documents; except [redacted] tests and diagnostic SARS-CoV-2 tests [where applicable], which may be performed in clinic [if that is local standard of care]) and provide reference ranges and laboratory reports. The central laboratory is preferred (over the local laboratory) for safety assessments.
- Investigators must document their review of each laboratory safety report.

- Any laboratory test result that the investigator considers clinically relevant for safety is to be recorded on the appropriate AE page of the eCRF (Section 9.2.6).
- Results of clinical laboratory tests performed during the screening period must be available prior to randomization.
- The timing of laboratory assessments is indicated in the Schedule of Activities (Section 2).

The laboratory parameters to be assessed for clinical safety throughout the study are listed in Table 11.

Table 11: Summary of Laboratory Parameters used to Assess Clinical Safety

Hematology	
• Hemoglobin • MCV • MCH • Hematocrit • WBC (Total leukocyte count)	• Platelet count • RBC count CBC Differential (including absolute neutrophil count and absolute lymphocyte count)
Chemistry	
AST ALT GGT Total bilirubin Direct bilirubin ALP LDH Creatinine BUN Uric acid Total protein Albumin Sodium Potassium	Chloride Calcium Phosphorus Magnesium Creatine kinase Creatinine clearance (screening only) with eGFR calculated using the MDRD equation (screening only) TSH (with reflex T3/T4 testing for abnormal TSH results) (screening only) **Performed after ≥ 10 hour fast at Day 1 and Week 12 (Day 85):** Lipid panel (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides) Glucose
Coagulation	
PT INR	Either partial thromboplastin time or aPTT
Urinalysis	
Protein Glucose Blood Leukocyte esterase Specific gravity pH	Microscopic examination of the sediment if blood, protein, or leukocyte esterase are positive on the dipstick Spot urine for protein and creatinine

Table 11: Summary of Laboratory Parameters used to Assess Clinical Safety

Additional Analyses
[redacted]
Stool Tests
• Stool culture: culture for potentially pathogenic enteric bacteria, including (but not limited to) Salmonella, Shigella, Campylobacter, and EHEC (tested at screening visit and when deemed medically appropriate by the investigator) Testing for additional enteric pathogens including bacteria, protozoa, ova, and parasites may be performed based on the investigator's clinical judgment. • Stool for Clostridioides (formerly Clostridium) difficile testing: stool for C. difficile Toxin A and B test (EIA) and GDH antigen test (EIA), with reflex to NAAT (C. difficile PCR) if either positive (screening only, performed at central laboratory, or local laboratory). A direct NAAT test approach may be used if discussed with, and approved by, the BMS Medical Monitor/designee.

ALP = Alkaline phosphatase; ALT = alanine aminotransferase; [redacted] aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; [redacted] eGFR = estimated glomerular filtration rate; EHEC = enterohemorrhagic Escherichia coli; EIA = enzyme-linked immunosorbent assay; [redacted] GDH = glutamate dehydrogenase; GGT = gamma glutamyltransferase; [redacted] INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; MDRD = modification of diet in renal disease; NAAT = nucleic acid amplification test; PCR = polymerase chain reaction; PT = prothrombin time; RBC = red blood cell; [redacted] TSH = thyroid-stimulating hormone; WBC = white blood cell; [redacted]

9.4.4 Imaging Safety Assessment

Not applicable.

9.4.5 Vital Signs

Vital signs will be obtained as indicated in the Schedule of Activities (Section 2) and recorded in the relevant eCRF.

9.4.6 Electrocardiograms

ECGs will be performed as indicated in the Schedule of Activities (Section 2). ECGs will be read locally. Clinically significant ECG findings will be recorded in the relevant eCRF and should be discussed with the BMS Medical Monitor/designee.

[redacted]

[redacted]

9.6 Biomarkers

The [redacted] effects of BMS-986165 will be explored based on biomarker analyses of [redacted] biopsy sample collection are in Table 13 and Table 14, respectively.

Further details of blood, biopsy, and stool collection and processing will be provided to the site in the laboratory manual.

[redacted]

Table 13: Blood and Stool Sample Collection

Study Day of Sample Collection	[redacted]								
Screening	X		X			X	X	X	X
Double-blind On-treatment									
Day 1		X	X	X	X	X	X		
Week 2 (Day 15)			X			X	X		
Week 4 (Day 29)		X	X	X	X	X	X	X	X
Week 8 (Day 57)						X	X		
Week 12 (Day 85)		X	X	X	X	X	X	X	X
Open-label Extension									
Week 16 (Day 113)			X			X	X		
Week 20 (Day 141)						X	X		
Week 24 (Day 169)			X			X	X		
Week 32 (Day 225)						X	X		
Week 40 (Day 281)						X	X		
Week 52 (Day 365) EOT/ET		X	X			X	X	X	X
Follow-up									
Week 56 (Day 393) F/U						X	X		

[redacted] EOT = end of treatment; ET = early termination; [redacted] F/U = follow-up;

[redacted]

[redacted]

Table 14: Colon Biopsy Sample Collection [redacted]

Study Day of Sample Collection	[redacted]	Biopsies/ Gene Expression	[redacted]	Biopsy Noninvolved Area[b]
Screening		X		X
Double-blind On-treatment				
Week 12 (Day 85)	[redacted]	X	[redacted]	X
Open-label Extension				
Week 52 (Day 365) EOT/ET	[redacted]	X	[redacted]	X

[redacted] EOT = end of treatment; ET = early termination; [redacted]

[redacted]

[b] Biopsy samples will be collected from noninvolved areas, if available, for gene expression.

[redacted]

9.6.1 Additional Research Collection

This protocol will include residual sample storage for additional research (see Table 15).

For All sites:

Additional research is required for all study participants, except where prohibited by IRBs/ethics committees, prohibited by local laws or regulations, or academic/institutional requirements. Where one or more of these exceptions occurs, participation in the additional research will not be a condition of overall study participation.

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

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

Sample Collection and Storage

All requests for access to samples or data for additional research will be vetted through a diverse committee of the study Sponsor's senior leaders in Research and Development (or designee) to ensure the research supports appropriate and well-defined scientific research activities.

- Residual blood, stool, biopsies, DNA, and RNA samples from [redacted] collections (see Table 1 and Table 2) will be retained for additional research purposes where local laws/regulations allow.
- Residual blood samples from [redacted] will also be retained for additional research purposes where local laws/regulations allow.

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

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

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

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

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

Table 15: Residual Sample Retention for Additional Research Schedule

Sample Type	Time points for which residual samples will be retained
[redacted]	
DNA and RNA	All
Blood samples (blood, serum, plasma)	All
Stool samples	All

DNA = deoxyribonucleic acid; [redacted] RNA = ribonucleic acid

9.7 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data associated with medical encounters will be collected in the relevant eCRF by the investigator and study site personnel for all subjects during the treatment period of the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and may include the number and duration of the following:

- UC-related emergency room visits and hospitalizations
- All-cause emergency room visits and hospitalizations

An example of the data collection form to be used is in APPENDIX 12.

9.8 SARS-CoV-2 Testing

Diagnostic testing for SARS-CoV-2 infection refers to [redacted] test for SARS-CoV-2 infection, performed according to local standard of care. [redacted] testing is preferred. [redacted] testing is not acceptable as a diagnostic test for SARS-CoV-2 infection.

Diagnostic testing for SARS-CoV-2 infection should be performed as close as possible to randomization and must be confirmed as "negative" prior to randomization.

Subjects will be screened for AEs (including signs and symptoms of COVID-19) at each study visit. Subjects will be instructed to contact the investigator at any time if they develop an intercurrent illness, including a diagnosis, or signs and symptoms of COVID-19, which will enable close monitoring and additional screening for the infection between study visits.

The investigator should obtain a diagnostic test for SARS-CoV-2 infection if COVID-19 is clinically suspected. If a subject reports having recent direct contact with someone known to have COVID-19, the subject should undergo diagnostic testing for SARS-CoV-2.

IP should be temporarily interrupted in subjects who present with signs and/or symptoms suggestive of COVID-19 while the subject undergoes diagnostic testing for SARS-CoV-2 infection. This testing should be performed as soon as feasible.

Study subjects with a positive diagnostic test for SARS-CoV-2 must be reported to BMS within 24 hours by entering the AE into the EDC.

IP must be temporarily interrupted in subjects who test positive for SARS-CoV-2 infection. Such subjects should continue to be followed by the investigator. Such subjects must meet all the criteria outlined below prior to restarting IP. The final decision to restart IP must be made in consultation with the BMS Medical Monitor/designee.

Subjects with a positive diagnostic test for SARS-CoV-2 infection during the screening period may be considered eligible for the study once they meet all eligibility criteria related to active infection, and after meeting the criteria outlined below.

Criteria to rescreen or recommence IP after a positive SARS-CoV-2 test:

- At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result, and
- At least 24 hours have passed since last fever without the use of fever-reducing medications, and
- Acute symptoms (eg, cough, shortness of breath) have resolved, and
- In the opinion of the investigator, there are no COVID-19 sequelae that may place the subject at a higher risk from receiving investigational treatment, and
- There are no COVID-19 sequelae that may confound the assessment of safety or efficacy within the study, and
- Negative follow-up molecular or antigen test for SARS-CoV-2 based on institutional, local, or regional guidelines, and

- For rescreening only, symptoms must have completely resolved **4 weeks prior to rescreening**, and based on investigator assessment in consultation with the BMS Medical Monitor/designee, there are no sequelae that would place the subject at a higher risk when receiving BMS-986165
- The above must be discussed with the BMS Medical Monitor prior to rescreening or recommencing IP (as applicable).

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

Approximately 50 subjects will be randomized in a 3:1 ratio to BMS-986165 12 mg BID or placebo BID, respectively (ie, approximately 37 subjects receiving BMS-986165 12 mg BID and approximately 13 subjects receiving placebo BID). Subjects randomized to BMS-986165 6 mg BID under the Original Protocol or Protocol Amendment 01 will continue receiving BMS-986165 6 mg BID in the double-blind treatment period. Approximately 3 subjects are expected to be randomized to the BMS-986165 6 mg BID dose arm.

[redacted]

10.1.1 Clinical Response Rate

The assumed rate of clinical response at Week 12 is based on the observed rates of clinical response in recent clinical trials of mirikizumab (an anti–IL-23p19 antibody; Week 12 endpoint, NCT02589665)[31] and ustekinumab (an anti–IL-12p40 antibody; Week 8 endpoint, NCT02407236).[1]

Assuming BMS-986165 12 mg BID will provide a similar clinical response rate as was observed in these UC trials, the expected clinical response rate is assumed to be approximately 60%. If the observed clinical response rate in this study is the same as the assumed rate reported above, the estimated 95% CI of clinical response rate is expected to be (42%, 75%) for the BMS-986165 12 mg BID arm at Week 12 using the Clopper-Pearson exact method.

With the sample size selected for this study, the expected 95% CI of clinical response rate for the BMS-986165 12 mg BID arm will exclude a placebo rate of 33% (95% CI: 29%, 37%) reported in a recent meta-analysis of clinical trials in UC.[56]

10.1.2 Adverse Event Incidence

Administration of BMS-986165 12 mg BID to 37 subjects provides a 98% probability of observing at least 1 occurrence of any AE that occurs with 10% incidence in the population from which the sample is drawn. However, if the incidence rate is 6%, the probability of observing at least 1 occurrence of that AE with a sample size of 37 subjects is 90%.

[redacted]

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined in Table 16.

Table 16: Analysis Populations

Population	Description
Enrolled Set	All subjects who sign the ICF.
Full Analysis Set (FAS)	All subjects who are randomized to study treatment; subjects will be grouped according to the treatment to which they are randomized within the IRT. The FAS population is the primary efficacy analysis population.
Safety Analysis Set	All randomized subjects who receive at least 1 dose of double-blind study treatment. Subjects will be analyzed according to treatment received.
[redacted]	

ICF = informed consent form; IRT = interactive response technology; [redacted]

10.3 Endpoints

Study endpoints are defined in Section 4.

10.4 Statistical Analyses

The SAP will be developed and finalized before the database lock for the primary analysis or interim analysis (if applicable) and will describe the selection of subjects to be included in the analyses, and procedures for accounting for missing, unused, and spurious data.

Categorical data will be summarized as frequency counts and percentages. Continuous data will be summarized using n, mean, SD, median, minimum, and maximum unless otherwise specified.

During the treatment period, data will be presented for the following treatments:

- BMS-986165 12 mg BID
- BMS-986165 6 mg BID
- Placebo

10.4.1 Efficacy Analyses

Efficacy data will be summarized using the FAS population unless otherwise stated. Variables will be summarized for all visits in which the variable is assessed. Efficacy data will be listed by treatment group. Baseline values are defined as the last nonmissing value prior to the first dose of study drug unless otherwise indicated.

10.4.1.1 Primary Endpoint

Analysis Method:

The proportion of subjects achieving clinical response at Week 12 and the associated 95% CI for the BMS-986165 12 mg BID treatment arm will be estimated using the Clopper-Pearson exact method. Supportive analysis using logistic regression for the clinical response (binary endpoint) may be performed, and the odds ratio between treatment groups and the corresponding 95% CI may be provided if the data are sufficient to do so.

Imputation Method:

Occurrence of intercurrent events may have an impact on the estimand of interest for the following types of subjects: (1) subjects who discontinue treatment or study early (ie, prior to Week 12); (2) subjects who start a protocol prohibited medication/therapy; or (3) subjects who are lost to follow-up or have otherwise missing endpoint data at or prior to the Week 12 assessment. In these cases, the primary endpoint will be determined using the "Composite Strategy" as defined in the International Council for Harmonisation (ICH) E9 (R1) addendum and will be considered a measure of nonresponse to treatment.[58] Subjects with the identified intercurrent event(s) will have their clinical response endpoint imputed as being a "nonresponder." This is commonly known as nonresponder imputation.

Sensitivity analyses using different imputation methods may be performed and will be defined in the SAP.

10.4.1.2 Exploratory Endpoints

Statistical analyses of exploratory endpoints will be described in the SAP and finalized before database lock.

10.4.2 Safety Analyses

Safety endpoint analyses will be descriptive in nature. Safety data for each period will be summarized separately and combined. All safety data will be listed by treatment group.

10.4.2.1 Adverse Events

Treatment-emergent AEs (TEAEs) are defined as AEs that occur after the subject received first dose of study treatment or if a preexisting condition worsens in severity or becomes serious after receiving the first dose of study treatment up to 30 days after the last dose of study treatment. All reported TEAEs, SAEs, deaths, AEs leading to study treatment discontinuation, and target AEIs will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) SOC and PT.

10.4.2.2 Vital Signs and ECGs

Vital signs and ECGs will be summarized as raw, change from baseline, including the maximum postbaseline value. Baseline values are defined as the last nonmissing value prior to the first dose of study drug. The number and proportion of subjects with vital signs and ECG abnormalities will be summarized at each scheduled visit.

10.4.2.3 Clinical Laboratory Tests

Laboratory analytes will be summarized as raw, change from baseline, including the maximum postbaseline value. Incidence of abnormal, high, or low values will be summarized. Shift tables will also be provided. Baseline values are defined as the last nonmissing value prior to the first dose of study drug. The number and proportion of subjects with clinical laboratory abnormalities will be summarized at each scheduled visit.

10.4.3 Other Analyses

Statistical analyses of exploratory endpoints will be described in the SAP and finalized before database lock.

[redacted]

[redacted]

[redacted]

10.4.3.2 Exposure-response Modeling

A detailed [redacted] efficacy exploratory analyses plan will be described in the SAP, which will be finalized before database lock. Exposure-response analysis may be performed for key efficacy and safety endpoints. The detailed plan for this analysis will be described in a separate document as needed.

Data from this study may be combined with data from other BMS-986165 studies to conduct [redacted] analyses. [redacted]

10.4.3.3 Quality of Life and Medical Resource Analyses

Quality of life data analyses will be described in the SAP, which will be finalized before database lock and included in the CSR.

Medical resource utilization exploratory analyses will be described in the SAP, which will be finalized before database lock. These results will be presented separately from the main CSR.

10.4.4 Interim Analyses

In addition to the primary efficacy analysis conducted when subjects have either completed Week 12 efficacy assessments or have discontinued prior to Week 12 (as outlined above), the Sponsor may perform an unblinded interim analysis of study data prior to final data analysis to make a timely decision. In such circumstances, the SAP will be finalized and an interim analysis plan will be approved prior to the database lock for the interim analysis. The interim analysis report will be prepared by a separate unblinded statistical team who will provide the report to the Sponsor, who will be unblinded at the treatment group level. A select group of Sponsor personnel, who will have no contact with the study site, will be unblinded to data at the participant level. Summary level unblinded data may be communicated externally. A SAP, which will include a section on interim analysis, will be created prior to any unblinding to fully detail the activities around the interim analysis.

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[redacted]

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AEI	adverse event of interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
[redacted]	
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
[redacted]	
AZA	azathioprine
[redacted]	
BID	twice daily
BMS	Bristol Myers Squibb
BP	blood pressure
C. difficile	*Clostridioides (*formerly *Clostridium) difficile*
[redacted]	
CD	Crohn's disease
[redacted]	
CFR	Code of Federal Regulations
CI	confidence interval
[redacted]	
CMV	cytomegalovirus
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019

Term	Definition
CRF	case report form
CSR	clinical study report
[redacted]	
CXR	chest x-ray
[redacted]	
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
[redacted]	
ECG	electrocardiogram
eCRF	electronic case report form
eCOA	electronic clinical outcome assessment(s)
[redacted]	
eGFR	estimated glomerular filtration rate
EOT/ET	end of treatment/early termination
ES	endoscopic (Mayo score component)
FACS	fluorescence-activated cell sorting
FAS	full analysis set
FDA	Food and Drug Administration
[redacted]	
FSH	follicle-stimulating hormone
GDH	glutamate dehydrogenase
[redacted]	
HR	heart rate

Term	Definition
hsCRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
[redacted]	
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
[redacted]	
IL	interleukin
IM	intramuscular
IMP	investigational medicinal product
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
IV	intravenous
[redacted]	
LTBI	latent tuberculosis infection

Term	Definition
[redacted]	
MAR	missing at random
MDRD	Modification of Diet in Renal Disease
Min	minute(s)
MMRM	mixed model repeated measure
MMX	Multi-Matrix System
MTX	methotrexate
N/A	not applicable
NAAT	nucleic acid amplification test
[redacted]	
NHV	normal healthy volunteer
NOAEL	no-observed-adverse-effect level
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
[redacted]	
OLE	open-label extension
OTC	over-the-counter
[redacted]	
PB	peripheral blood
PCR	polymerase chain reaction
PBMC	peripheral blood mononuclear cells
[redacted]	
PGA	Physician's Global Assessment
PK	pharmacokinetic(s)
PO	oral(ly)
PRO	patient-reported outcome
PT	preferred term
QD	every day

Term	Definition
[redacted]	
RB	rectal bleeding (Mayo score component)
RBC	red blood cell
[redacted]	
RNA	ribonucleic acid
RNA-seq	RNA sequencing technology
[redacted]	
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
[redacted]	
SD	standard deviation
SF	stool frequency (Mayo score component)
SLE	systemic lupus erythematosus
SOC	system organ class
STAT	signal transducer and activator of transcription
SUSAR	suspected, unexpected serious adverse reaction
TB	tuberculosis
[redacted]	
TDAR	T cell-dependent antibody response
[redacted]	
TEAE	treatment-emergent AE
[redacted]	
TNF	tumor necrosis factor
TNFi	tumor necrosis factor inhibitor(s)
TSH	thyroid-stimulating hormone
TQT	thorough QT
TYK2	tyrosine kinase 2

Term	Definition
UC	ulcerative colitis
UCEIS	Ulcerative Colitis Endoscopic Index of Severity
[redacted]	
ULN	upper limit of normal
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The term 'Subject' is used in the protocol and eCRF to refer to a person who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Good Clinical Practice (GCP)
- As defined by the International Council for Harmonisation (ICH)
- In accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- Applicable local requirements.

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

All potential serious breaches must be reported to Sponsor or designee immediately. A potential serious breach is defined as a Quality Issue (eg, protocol deviation, etc) that is likely to affect, to a significant degree, one or more of the following: (1) the physical, safety or mental integrity of one or more subjects/participants; (2) the scientific value of the 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, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator's Brochure (IB) or product labeling information to be provided to subjects and any updates.

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form 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 subjects 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 subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
- Obtain an ICF signed and personally dated by the subject and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written ICF and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

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

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed Health Insurance Portability and Accountability Act Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

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

SOURCE DOCUMENTS

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original, and attributable, whether the data are hand-written 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/health records (EMRs/EHRs), adverse event (AE) tracking/reporting, protocol-required assessments, and/or drug accountability records).

When paper records from such systems are used in place of 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 TREATMENT RECORDS

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

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

If	Then
	• amount dispensed to and returned by each subject, including unique subject identifiers • dates and initials of person responsible for IP dispensing/accountability, as per the Delegation of Authority Form.

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

CASE REPORT FORMS

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

For sites using the Sponsor or designee electronic data capture (EDC) tool, electronic CRFs 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 paper Pregnancy Surveillance Form, respectively. If electronic SAE form is not available, a paper SAE form can be used.

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

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

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task. For electronic CRFs, review and approval/signature is completed electronically through the EDC tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

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

MONITORING

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality, such as risk management and

mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site, they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents:

In addition, the study may be evaluated by 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 Sponsor or designee.

RECORDS RETENTION

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

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

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

RETURN OF STUDY TREATMENT

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

If...	Then
Study treatments supplied by BMS (including its vendors)	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

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

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, 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 Monitor to review throughout the clinical trial period.

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

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

DISSEMINATION OF CLINICAL STUDY DATA

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

CLINICAL STUDY REPORT

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

SCIENTIFIC PUBLICATIONS

The data collected during this study are confidential and proprietary to Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing [Study site or investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

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

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

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable subjects with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights, and conclusion); AND

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

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

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

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

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

ADVERSE EVENTS

Adverse Event Definition:
An AE is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis. • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term.
Events NOT Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Definition of SAE

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

SERIOUS ADVERSE EVENTS

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

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

Any component of a study endpoint that is considered related to study therapy should be reported as SAE (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

EVALUATING AES AND SAES

Assessment of Intensity

The intensity of AEs is determined by a physician and will use the following levels:

- Mild: An event that is easily tolerated by the subject, 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.

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, evidences, 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 IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to 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 Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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

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

All SAEs and nonserious AEs that cause interruption or discontinuation of study treatment must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to BMS (or designee) immediately but no later than 24 hours after 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 only intended as a back-up option when the EDC system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile (fax) transmission
    - When paper forms are used, the original paper forms are to remain on site
- Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

Appendix 4 provides general information and definitions related to Woman of Childbearing Potential (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 and male participants, refer to Section 6.1 of the protocol. Only the contraception methods as described in Section 6.1 are acceptable for this study.

DEFINITIONS

WOCBP

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

Women in the following categories are not considered WOCBP

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

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

[redacted]

Note: Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed [redacted] levels and may require a washout period to obtain a physiologic [redacted] level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum [redacted] 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 [redacted] level is > 40 mIU/mL at any time during the washout period, the woman can be considered [redacted].

End of Relevant Systemic Exposure

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

METHODS OF CONTRACEPTION

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

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

- Vasectomized partner

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

- Sexual abstinence

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

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

NOTES:

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

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

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

Less Than Highly Effective Contraceptive Methods That Are User-Dependent

Failure rate of > 1% per year when used consistently and correctly.

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously
- Diaphragm with spermicide
- Cervical cap with spermicide

• Vaginal sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited.)
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, postovulation methods) • Withdrawal (coitus interruptus) • Spermicide only • LAM

COLLECTION OF PREGNANCY INFORMATION

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

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

Inadequate response, loss of response, and/or intolerance to each standard of care UC treatment is defined as follows:

- Oral 5-aminosalicylic acids (5-ASAs) (eg, mesalamine, sulfasalazine, olsalazine, or balsalazide):
  - Signs and symptoms of persistently active disease despite a history of at least one 4-week regimen at highest dose (institutional practice)
  - Documented history of intolerance
- Corticosteroids (eg, prednisone [or equivalent] or budesonide [or equivalent]):
  - Signs and symptoms of persistently active disease despite a history of at least one 4-week induction regimen that included a dose equivalent to [redacted] OR
  - At least 2 failed attempts to [redacted] corticosteroids below a dose that is equivalent to oral prednisone 10 mg/day (or equivalent) or budesonide 3 mg/day (or equivalent) on 2 separate occasions (ie, steroid-dependent disease); OR
  - Documented history of intolerance of corticosteroids where subject developed adverse reactions including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, cataracts, refractory steroid acne, or infection.
- Immunomodulators (eg, azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]):
  - Signs and symptoms of persistently active disease despite a history of at least one 8-week regimen of oral AZA, oral 6-MP, or oral or injectable MTX (per country's approved label); OR
  - History of intolerance of at least 1 immunomodulator (eg, nausea/vomiting, abdominal pain, pancreatitis, liver function test abnormalities, lymphopenia).
- Anti-tumor necrosis factor (TNF) agents (eg, infliximab, adalimumab, or golimumab):
  - Signs and symptoms of persistently active disease despite an adequate trial of induction treatment with an anti-TNF agent (per country's approved label); OR
  - Recurrence of symptoms during maintenance dosing following prior clinical benefit; OR
  - History of intolerance (including, but not limited to, infusion-related reaction, demyelination, congestive heart failure, development of TNF inhibitor (TNFi) antibodies, or infection).
- Integrin inhibitors (eg, vedolizumab):
  - Signs and symptoms of persistently active disease despite an adequate trial of induction treatment with an integrin inhibitor (per country's approved label); OR
  - Recurrence of symptoms during maintenance dosing following prior clinical benefit; OR
  - History of intolerance (including, but not limited to, infusion-related reaction, arthralgia, liver test abnormalities, or infection).

[redacted]

APPENDIX 6 COMMONLY USED CORTICOSTEROID EQUIVALENTS

Medication	Dose Equivalence
[redacted]	
Cortisone	100 mg
Hydrocortisone	80 mg
Prednisolone	20 mg
Methylprednisolone	16 mg
Triamcinolone	16 mg
Dexamethasone	3 mg
Betamethasone	2 to 4 mg

APPENDIX 7 EXAMPLES OF WASHOUT TIMES REQUIRED PRIOR TO RANDOMIZATION

Medication/treatments	Discontinuation Prior to Randomization	Notes
5-azathioprine (AZA)	≥ 4 weeks	
6-mercaptopurine (6-MP)	≥ 4 weeks	
Abatacept (CTLA4Ig)	≥ 12 weeks	
Adalimumab[a]	≥ 8 weeks	Washout period waived if undetectable levels [redacted].
Alefacept	≥ 8 weeks	
Alemtuzumab	≥ 12 months	
AMG 623	≥ 12 weeks	
Apheresis	≥ 12 months	Lymphocyte apheresis or selective monocyte or granulocyte apheresis (eg, Cellsorba™).
Atacicept (TACI-Ig)	≥ 48 weeks	
Belimumab	≥ 14 weeks	
Certolizumab pegol	≥ 8 weeks	
Cyclophosphamide	≥ 4 weeks	
Cyclosporine	≥ 4 weeks	
Danazol	≥ 4 weeks	
Dapsone	≥ 4 weeks	
Darvadstrocel	≥ 24 weeks	
Eculizumab	≥ 12 weeks	
Efalizumab	≥ 8 weeks	
Epratuzumab[b]	≥ 18 weeks	
Fecal transplant	≥ 4 weeks	This treatment is considered an investigational agent for the purposes of this study.
Golimumab[a]	≥ 8 weeks	Washout period waived if undetectable levels [redacted].
Infliximab[a]	≥ 8 weeks	Washout period waived if undetectable levels [redacted].
Interferon	≥ 12 weeks (or more than 5 half-lives, whichever is longer)	
Intravenous globulin	≥ 4 weeks	

Medication/treatments	Discontinuation Prior to Randomization	Notes
Investigational therapies	≥ 4 weeks (or 5 half-lives, whichever is longer)	Subjects treated with investigational agents 4-12 weeks prior to first dose of study treatment must be discussed with the BMS Medical Monitor/designee.
IPP-201101	≥ 12 weeks	
[redacted]	≥ 8 weeks	Subjects treated [redacted] 8-12 weeks prior to first dose of study treatment must be discussed with the BMS Medical Monitor/designee.
Leflunomide	≥ 12 weeks (or more than 5 half-lives, whichever is longer)	
Lenalidomide with cholestyramine	≥ 24 weeks	
Memantine	≥ 4 weeks	
Methotrexate	≥ 4 weeks	
Mycophenolate mofetil	≥ 4 weeks	Washout period may be waived after discussion with the BMS Medical Monitor/designee if undetectable mycophenolic acid (MMA) level on a relevant assay; test not provided within the study.
Natalizumab	≥ 8 weeks	
Ocrelizumab[b]	≥ 24 weeks	
Pimecrolimus	≥ 4 weeks	
Plasmapheresis	24 weeks	
Retinoids	≥ 4 weeks	
Rituximab	≥ 12 months	
Sphingosine 1-phosphate receptor modulators (eg, ozanimod)	≥ 8 weeks	
Sirolimus (rapamycin)	≥ 4 weeks	Washout period may be waived after discussion with the BMS Medical Monitor/designee if undetectable sirolimus level on a relevant assay; test not provided within the study.
Tabalumab	≥ 14 weeks	
Tacrolimus	≥ 4 weeks	Washout period may be waived after discussion with the BMS Medical Monitor/designee if undetectable tacrolimus level on a relevant assay; test not provided within the study.
Thalidomide	≥ 4 weeks	
Other TNF inhibitors	≥ 8 weeks	Washout period waived if undetectable levels [redacted].

Medication/treatments	Discontinuation Prior to Randomization	Notes
Tocilizumab	≥ 12 weeks	
Ustekinumab[a, d]	≥ 8 weeks	For subjects who have received > 12 weeks of ustekinumab treatment, the washout period may be waived if undetectable levels [redacted].
Vedolizumab[a]	≥ 4 weeks	Subjects who have received > 14 weeks vedolizumab treatment; or washout period waived if undetectable levels [redacted].
	≥ 8 weeks	Subjects who have received ≤ 14 weeks of vedolizumab treatment.

[redacted] TNF = tumor necrosis factor

[a] The washout period for this biologic can be waived for subjects who have an undetectable drug level [redacted], performed either in routine clinical practice or during the screening period. [redacted] used to waive the washout period for this biologic, the result [redacted] must be available in source documents, and the subject cannot receive another dose of that biologic [redacted] is obtained (Section 5.1.1).

[b] For epratuzumab, ocrelizumab, and any other B-cell-depleting agent, follow the required washout or document recovery of B cells (CD19+) after discontinuation of these therapies before a subject can be randomized.

[redacted]

[d] Failure or loss of response to previous treatment with ustekinumab (as well as other [redacted] antibodies or [redacted] antibodies) is exclusionary.

Note: Investigators should consult with the BMS Medical Monitor/designee for information about compounds not included in this list.

Some subjects will require adequate washout of biologics to be eligible for randomization. [redacted] assays that test for drug levels of these biologic medications can be commercially available in routine clinical practice and also available as an optional test during the screening period. The washout period for the following biologics can be waived in subjects who have an undetectable drug level [redacted], performed either in routine clinical practice or during the screening period: (1) infliximab, (2) adalimumab, (3) golimumab, (4) other TNF inhibitors, (5) vedolizumab (> 14 weeks of vedolizumab therapy), or (6) ustekinumab (> 12 weeks of ustekinumab therapy).

[redacted] used to waive the washout period for any of the biologics listed in the table above, the result [redacted] must be available in source documents, and the subject cannot receive another dose of that biologic prior to randomization.

[redacted]

[redacted]

[redacted]

APPENDIX 9 MAYO SCORE: COMPONENT SUBSCORES AND ELECTRONIC SUBJECT DIARY ENTRY INSTRUCTIONS

The Mayo score is a composite instrument designed to assess ulcerative colitis (UC) disease activity. It includes patient-reported outcomes (PROs), an objective assessment of disease activity by endoscopy, and a Physician's Global Assessment (PGA). The Mayo score was first proposed by Schroeder et al.[47] Scherl et al[48] proposed that the Mayo score should be modified by removing "mild friability" from the definition of an endoscopic (ES) subscore = 1. This was supported by draft guidance from the US Food and Drug Administration (FDA) that states the presence of friability is not consistent with the concept of "clinical remission" (Lines 249-251).[38] As the PGA is neither a PRO nor an objective assessment of disease activity, and the concept that it purports to measure is not distinct from the other components of the modified Mayo score, use of the PGA as a component of the modified Mayo score is no longer recommended by US[38] or European regulatory authorities.[39]

Consequently, disease activity assessments for inclusion and efficacy assessment will use the 9-point modified Mayo score (ie, excluding PGA). The PGA will continue to be captured as part of this study to facilitate the calculation of the total Mayo score, which will allow these data to be compared with previous clinical trials.

Table 1 outlines the components and scoring used to calculate the modified and total Mayo scores.

Table 1: Components of the Modified and Total Mayo Scores

Stool Frequency (SF)[a]	
0	Normal number of stools for this patient
1	1 to 2 stools/day more than normal
2	3 to 4 stools/day more than normal
3	> 4 stools/day more than normal
Rectal Bleeding (RB)[b]	
0	No blood seen
1	Streaks of blood with stool less than half the time
2	Obvious blood (more than just streaks) or streaks of blood with stool most of the time
3	Blood alone passed
Findings of flexible proctosigmoidoscopy (endoscopy used to determine ES subscore)	
0	Normal or inactive disease
1	Mild disease (erythema, decreased vascular pattern)[c]
2	Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3	Severe disease (spontaneous bleeding ulceration)
PGA (not included in the 9-point modified Mayo score)[d]	
0	Normal

Table 1: Components of the Modified and Total Mayo Scores

1	Mild disease
2	Moderate disease
3	Severe disease

Sources: after 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;317:1625–29; Draft Guidance for Industry, Ulcerative Colitis: Clinical Trial Endpoints US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Draft August 2016. Publication UCM515143.

PGA = Physician's Global Assessment

[a] Each subject serves as his or her own control to establish the degree of abnormality of the SF.

[b] The daily bleeding score represents the most severe bleeding of the day.

[c] The original description of the Mayo score included "mild friability" in an ES subscore = 1. The modified Mayo score removed friability from an ES subscore = 0.

[d] The PGA acknowledges the patient's SF, RB, and endoscopy reports; the patient's daily record of abdominal discomfort and general sense of well-being; and other observations, such as physical findings and the patient's performance status.

MAYO SCORES: DEFINITIONS

Two different versions of the Mayo score will be used as efficacy endpoints:

Modified Mayo Score: The modified Mayo score is a **9-point scale**; a score of 5 to 9 points (inclusive), which is required for randomization, denotes moderate to severe disease (by protocol definition). The modified Mayo score is an adaptation of the total Mayo score (defined below) that excludes the PGA subscore.

The modified Mayo score incorporates the following 3 components:

- Stool frequency (SF) subscore (0 to 3)
- Rectal bleeding (RB) subscore (0 to 3)
- ES subscore (0 to 3)

Total Mayo Score: The original total Mayo score incorporates all 4 components of UC severity listed in Table 1; each component subscore ranges from 0 to 3. The total Mayo score is a **12-point scale** in which a higher score equals more severe disease.

The modified and total Mayo scores will be calculated using component subscores entered into the electronic case report form (eCRF).

MAYO SCORES: SF AND RB COMPONENT SUBSCORES

SF and RB data will be recorded and calculated using an electronic subject diary.

Stool Frequency and Rectal Bleeding Subscores

Subjects will enter SF and RB data into the electronic subject diaries on a daily basis throughout their participation in the study. Instructions for recording the number of stools and worst rectal bleeding and definitions of SF and RB are provided in Table 2.

NOTE: The subject daily diary information should be reviewed prior to each scheduled visit at which Mayo scores are to be calculated and during each study visit to ensure that subjects are successfully entering and uploading diary data. If adequate entries have not been made, the subject should be counseled about proper study procedures.

For eligibility and efficacy analysis purposes, the **3 most recent (not necessarily consecutive), valid, electronic subject diary entries recorded from the 7 days prior to a study visit** will be used to calculate the SF and RB subscores. For study visits that include an endoscopy (eg, screening, Weeks 12, 52 and ET or unscheduled visit [if applicable]), the **3 most recent (not necessarily consecutive), valid, electronic subject diary entries recorded from the 7 days prior to the day a subject starts bowel preparation for the endoscopy** will be used to calculate the SF and RB subscores. If fewer than 3 days of daily SF and RB data have been recorded in the 7 day window described above, the modified Mayo score cannot be calculated for that timepoint. The SF and RB values used to establish eligibility will also be used for calculation of the baseline modified Mayo score.

The following will be considered invalid data and excluded from SF and RB subscore calculations:

- A day that medication(s) for constipation, diarrhea, or bowel irregularity are taken

Formal calculation of SF and RB subscores will be performed using the electronic subject diaries.

For the preendoscopy screening visit (ie, prior to the availability of electronic subject diary data):

The **baseline SF** will be determined based on the number of stools a subject has in a 24-hour period when in remission from UC symptoms; **or** if a subject has **not** been in remission, they should be asked to identify the number of stools they had in a 24-hour period before initial onset of signs and symptoms of UC (Table 2).

This **baseline SF** is used as the reference for subsequent SF subscores.

For the endoscopy screening visit:

Best practice is to complete the other screening investigations first and check results to ensure that a subject continues to be potentially eligible for the study prior to commencing bowel preparation for the endoscopy. When the endoscopy is scheduled, SF and RB data in the electronic subject diary from the 7 days **prior to the bowel preparation day** for the endoscopy will be evaluated to ensure eligibility is maintained.

Following endoscopy, the ES subscore will be received via email from the central reader [redacted]. This centrally-read screening ES subscore will be entered into the eCRF, in

addition to the SF and RB subscores, and the modified Mayo score will be calculated to determine subject eligibility.

For subsequent study visits at which Mayo scores are calculated:

For the Week 12 study visit, endoscopy timing should be reviewed prior to the visit to ensure adequate diary entries are available for SF and RB subscore determination. The averages of the 3 most recent (not necessarily consecutive), valid, electronic diary entries for SF and RB data from the 7 days **prior to the bowel preparation day** for the endoscopy will be used. If adequate entries have not been made, the site should contact the subject to reschedule the visit, and the subject should be counseled about proper study procedures. Following endoscopy, ES subscores will be emailed from the central vendor as noted above and entered into the eCRF together with the SF and RB subscores to calculate the modified Mayo score for a given visit.

Missing Data:

Assessments with fewer than 3 valid, daily diary entries for SF and RB from the 7 days **prior to the bowel preparation day** for endoscopy are considered missing data and will not count toward assessment of disease activity during the screening period or for endpoint assessment at Week 12.

MAYO SCORES: ELECTRONIC SUBJECT DIARY ENTRY INSTRUCTIONS

Standardized instructions for recording SF and RB data (based on draft FDA Guidance for UC clinical endpoints)[38] are in Table 2.

Table 2: Standardized Instructions for Recording Number of Stools and Worst Rectal Bleeding (for the Mayo Scores) (Each Over a 24-hour Period)

Completion of electronic subject diary	**Subjects will be trained on the completion of the electronic subject diary.**
SF	
Definition of stool	A stool is defined as a trip to the toilet when the subject has either a bowel movement or passes blood alone, blood and mucus, or mucus only.
Determine baseline SF (over 24 hours)	At the screening visit, the number of stools the subject has in a 24-hour period when in remission from UC symptoms or prior to diagnosis of UC should be asked by the site and entered in the electronic patient diary. If the subject has not been in remission, then the subject should be asked to identify the number of stools he/she had in a 24-hour period before initial onset of signs and symptoms of UC. Record whether the baseline SF is based on the reported SF when the subject was **in remission** OR the reported SF **before initial onset of signs and symptoms** of UC.
Recording of SF assessments	Subjects are to record the **total** number of stools for the previous 24-hour period in the electronic subject diary on a daily basis. Subjects should make diary entries at the same time each day.

Table 2: Standardized Instructions for Recording Number of Stools and Worst Rectal Bleeding (for the Mayo Scores) (Each Over a 24-hour Period)

Completion of electronic subject diary	**Subjects will be trained on the completion of the electronic subject diary.**
	NOTE: For eligibility and efficacy analysis purposes, the established baseline SF (defined above) will be used to calculate the number of stools above normal and subsequently assign a Mayo SF component score. This will be done automatically by the electronic diary and will not need to be calculated by the subject or study team.
RB	
Most severe category of RB (in a given 24-hour period)	Subjects should enter into the electronic subject diary the most severe category that describes the amount of blood they had in their stools for that given day. Categories (subscore) of RB are defined as follows: • No blood seen (0) • Streaks of blood with stool less than half the time (1) • Obvious blood (more than just streaks) or streaks of blood with stool most of the time (2) • Blood alone passed (3) Subjects should enter "No Blood Seen" in the RB section if they do not have stool during a given day.
Recording of RB assessments	Subjects are to record their RB assessments in the electronic subject diary on a daily basis. Subjects should make diary entries at the same time each day.

RB = rectal bleeding; SF = stool frequency; UC = ulcerative colitis

Adapted from: Draft Guidance for Industry, Ulcerative Colitis: Clinical Trial Endpoints US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Draft August 2016. Publication UCM515143.

ES Subscore

ES subscores will be provided via email by the independent central endoscopy vendor [redacted] for all eligibility and efficacy assessments, at all time points. The endoscopy procedure from screening (central read) will be used to determine the **baseline** ES subscore component of the Mayo score. The ES subscores of the Mayo score will be modified so that the value 1 does not include friability.

PGA

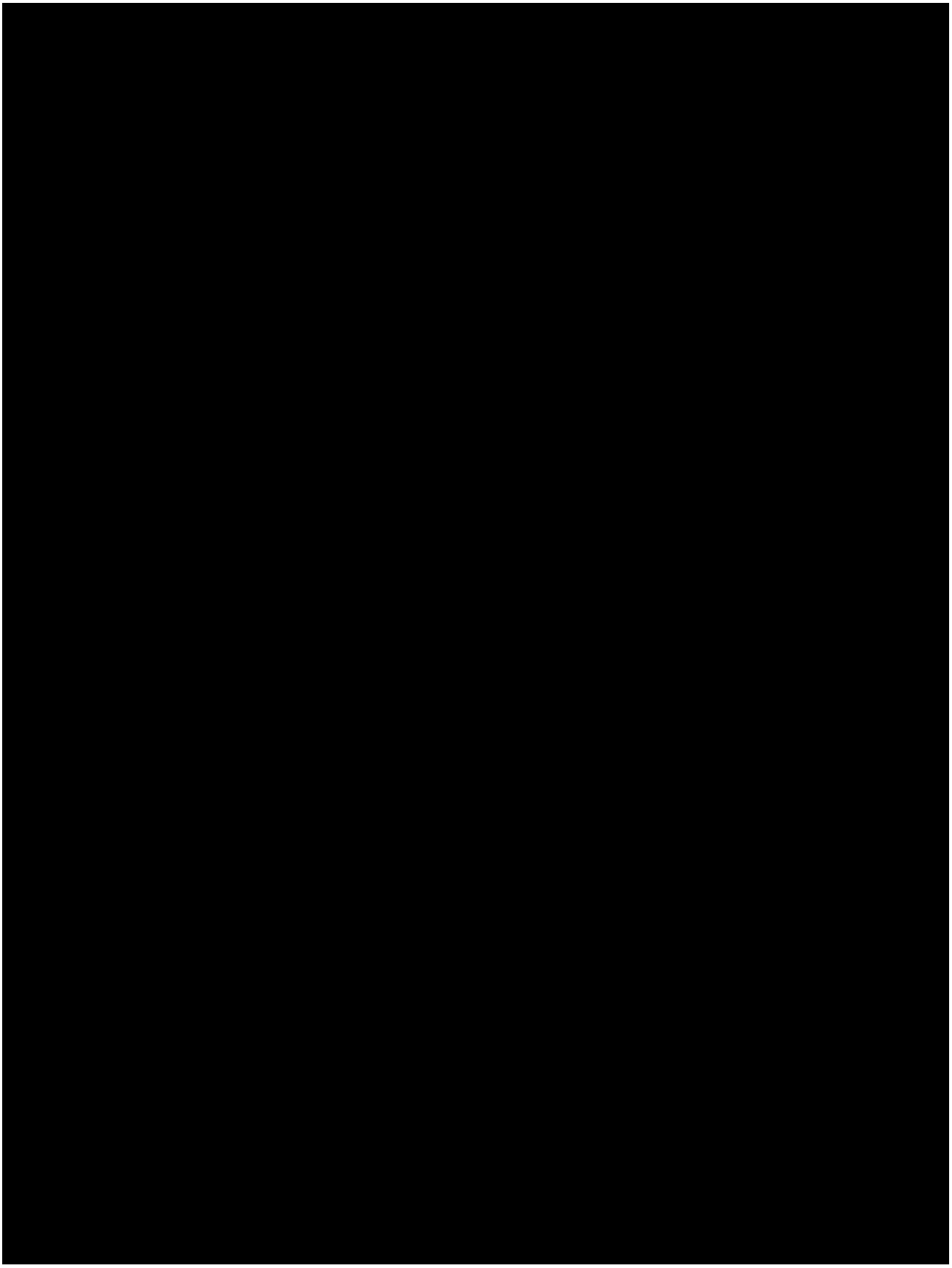
The investigator will provide the PGA at every required visit. Categories of the PGA are listed in Table 1, above.

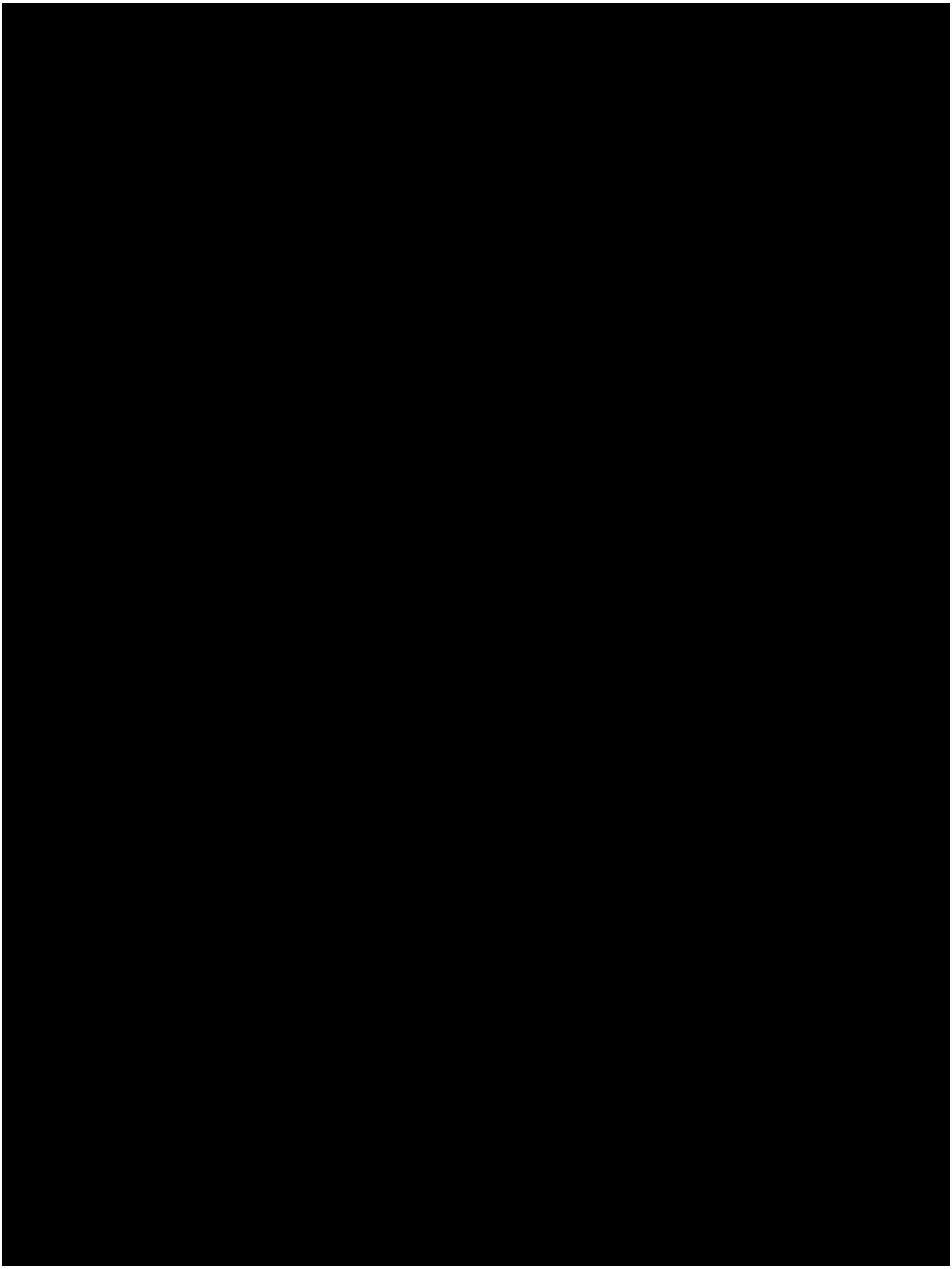
APPENDIX 10 ULCERATIVE COLITIS ENDOSCOPIC INDEX OF SEVERITY (UCEIS): SCORES AND DEFINITIONS

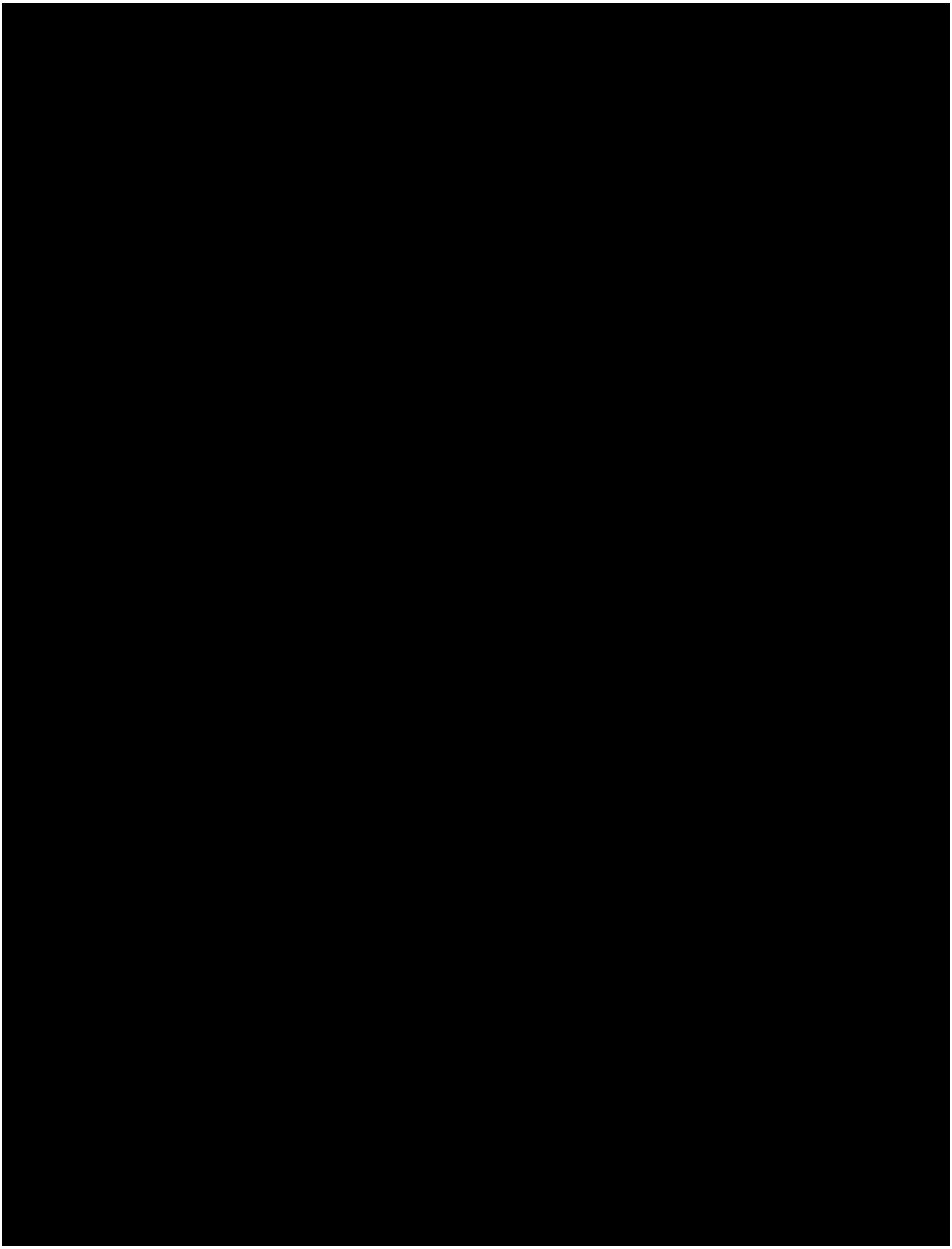
Descriptor	Likert scale anchor points	Definition
Vascular pattern	Normal (0)	Normal vascular patterns with arborization of capillaries clearly
	Patchy obliteration (1)	Patchy obliteration of vascular pattern
	Obliterated (2)	Complete obliteration of vascular pattern
Bleeding	None (0)	No visible blood
	Mucosal (1)	Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope that can be washed away
	Luminal mild (2)	Some free liquid blood in the lumen
	Luminal moderate or severe (3)	Frank blood in the lumen ahead of the endoscope or visibly oozing from the mucosa after washing intraluminal blood, or visibly oozing from a hemorrhagic mucosa
Erosions and ulcers	None (0)	Normal mucosa, no visible erosions, or ulcers
	Erosions (1)	Tiny (≤ 5 mm) defects in the mucosa of a white or yellow color with a flat edge
	Superficial ulcer (2)	Larger (> 5 mm) defects in the mucosa, which are discrete fibrin-covered ulcers when compared with erosions but remain superficial
	Deep ulcer (3)	Deeper excavated defects in the mucosa with slightly raised edge

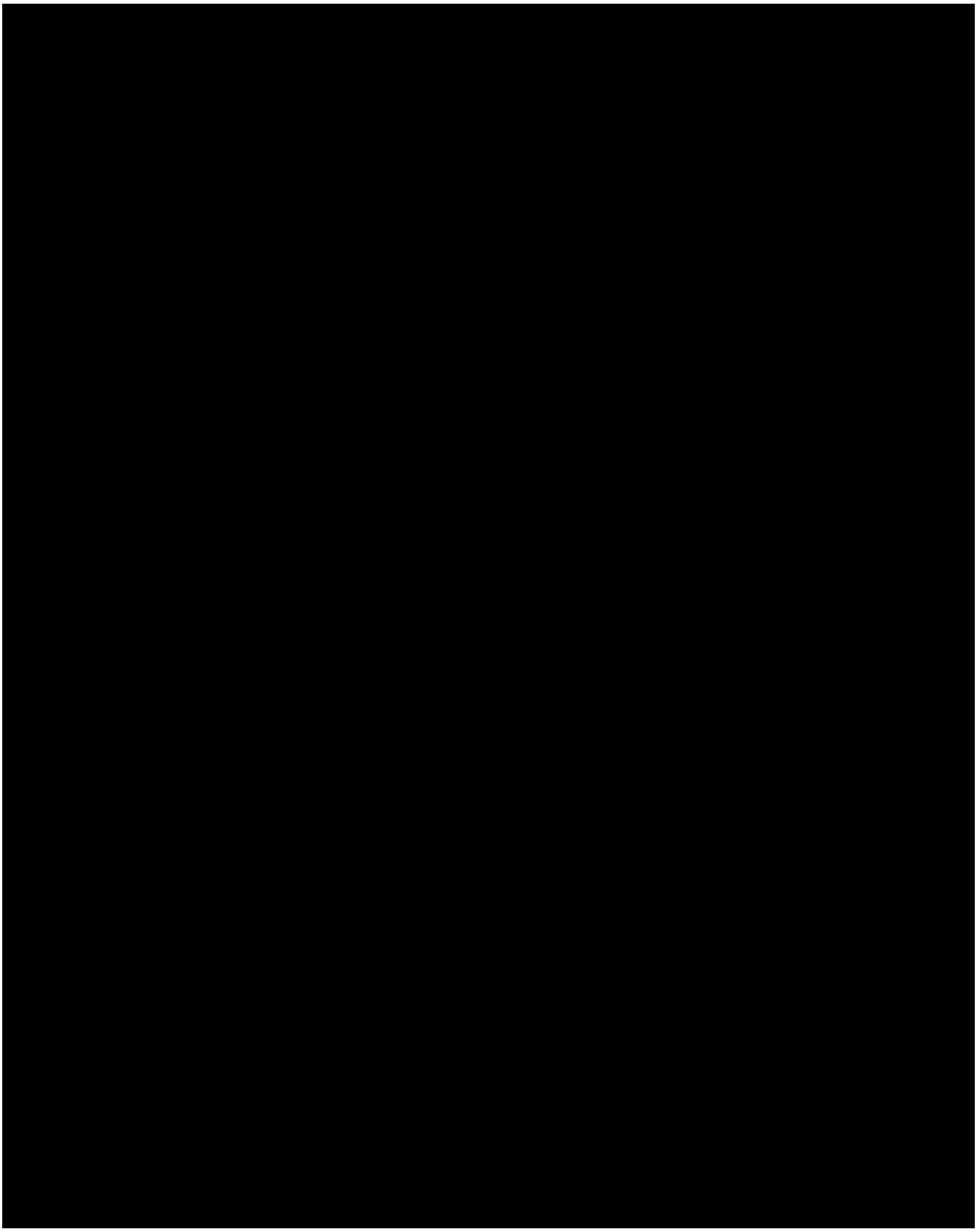
Source: Travis SP, Schnell D, Krzeski P, et al. Reliability and initial validation of the ulcerative colitis endoscopic index of severity. Gastroenterology 2013;145(5):987-95.

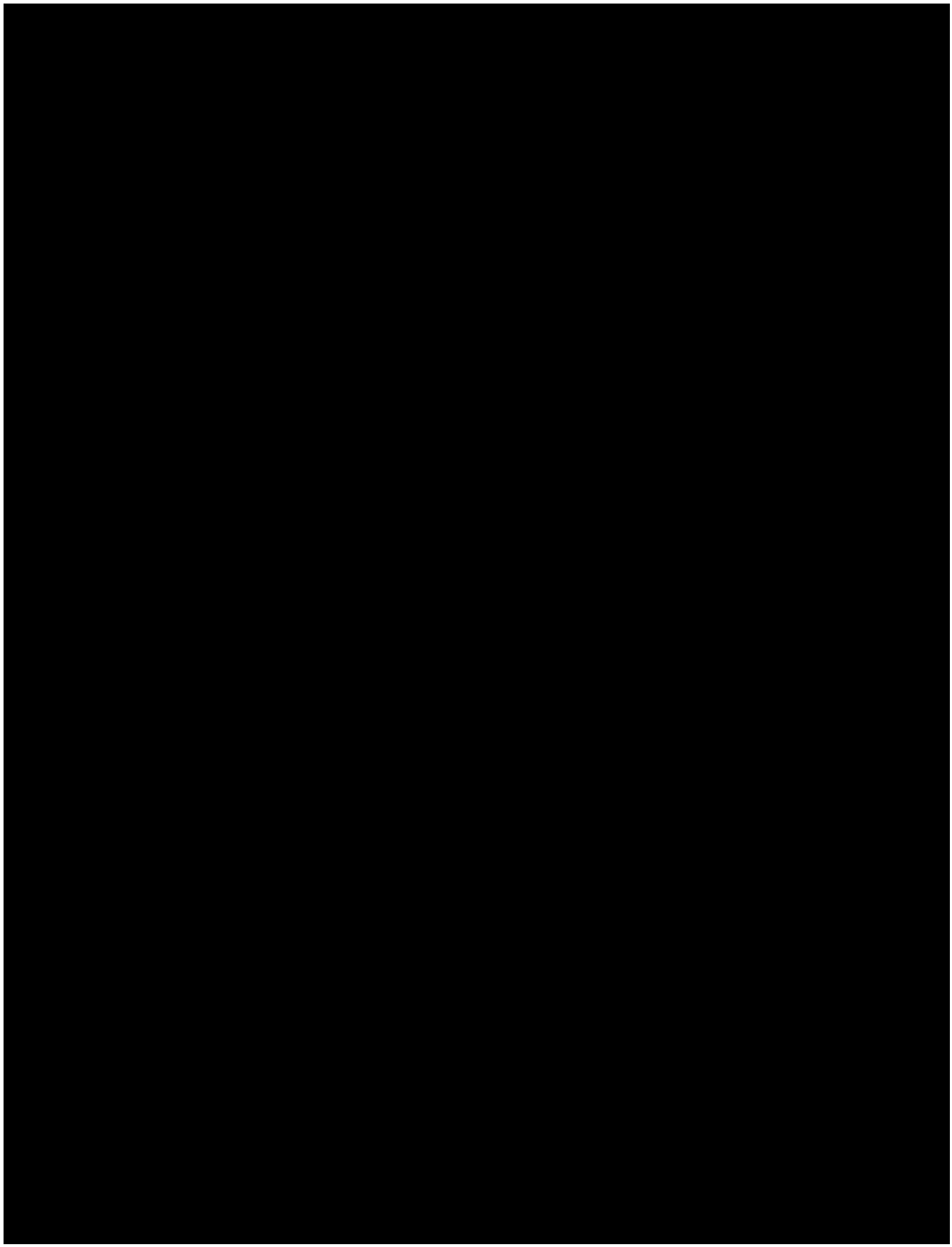
APPENDIX 11 INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

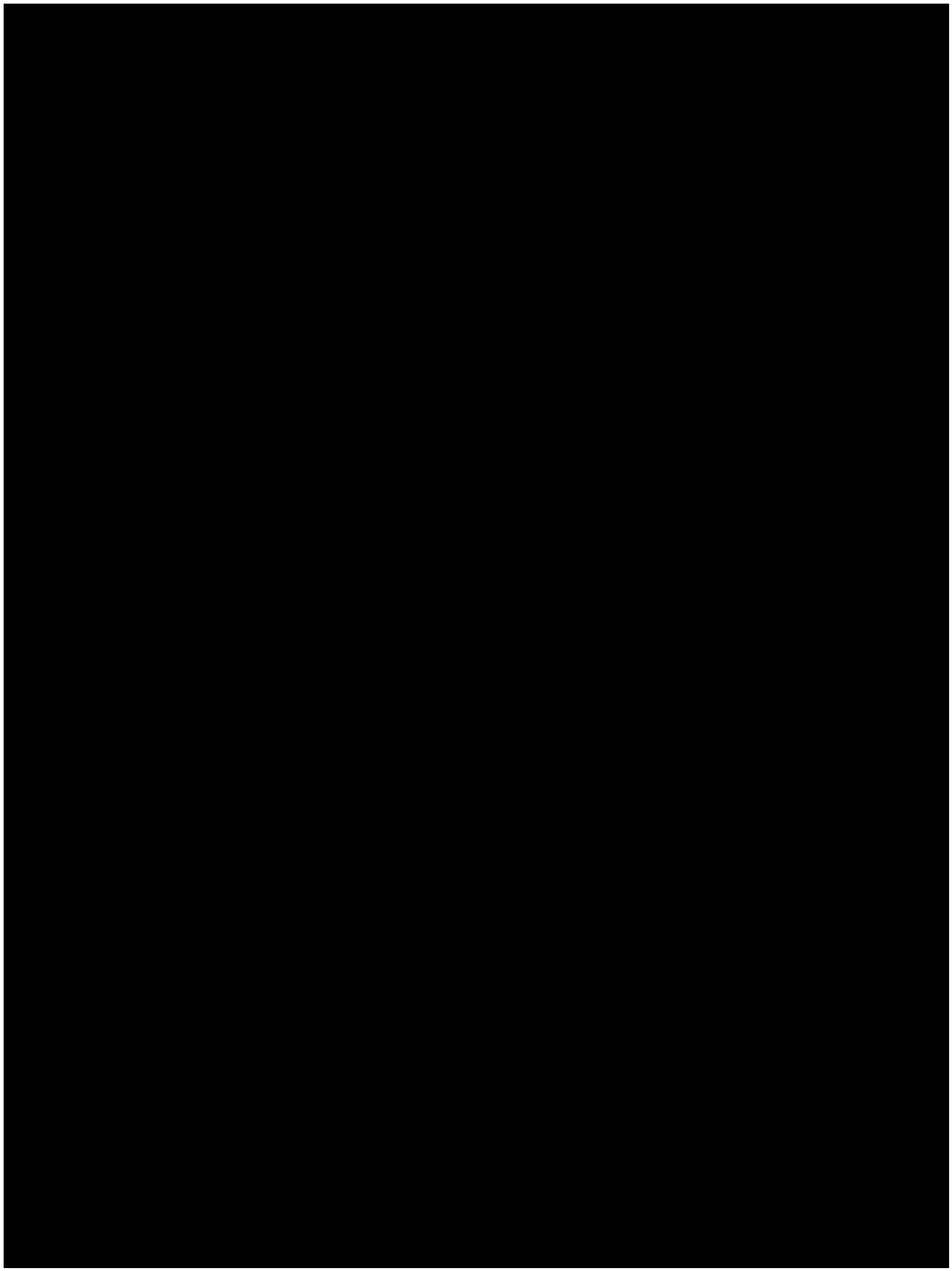


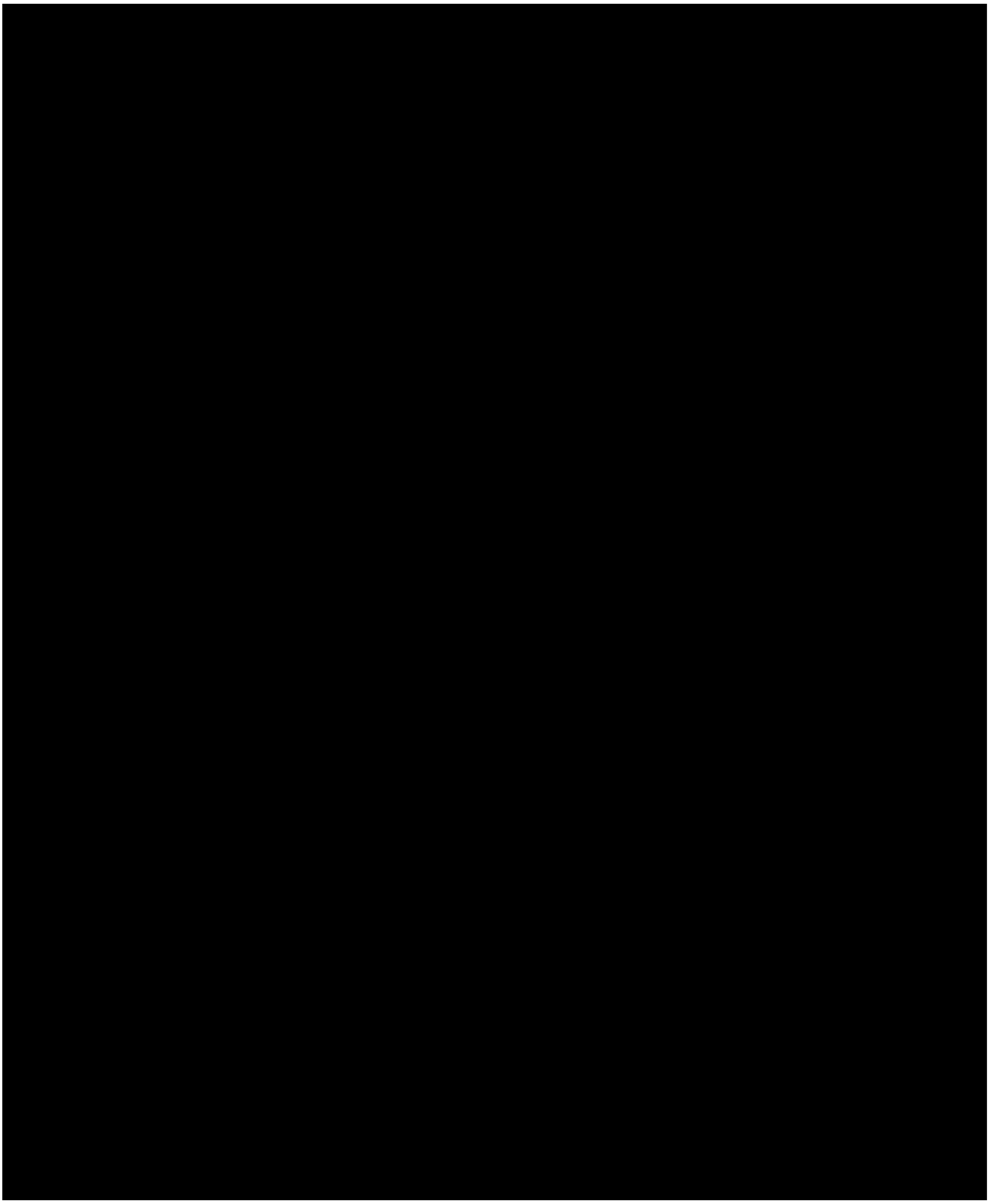


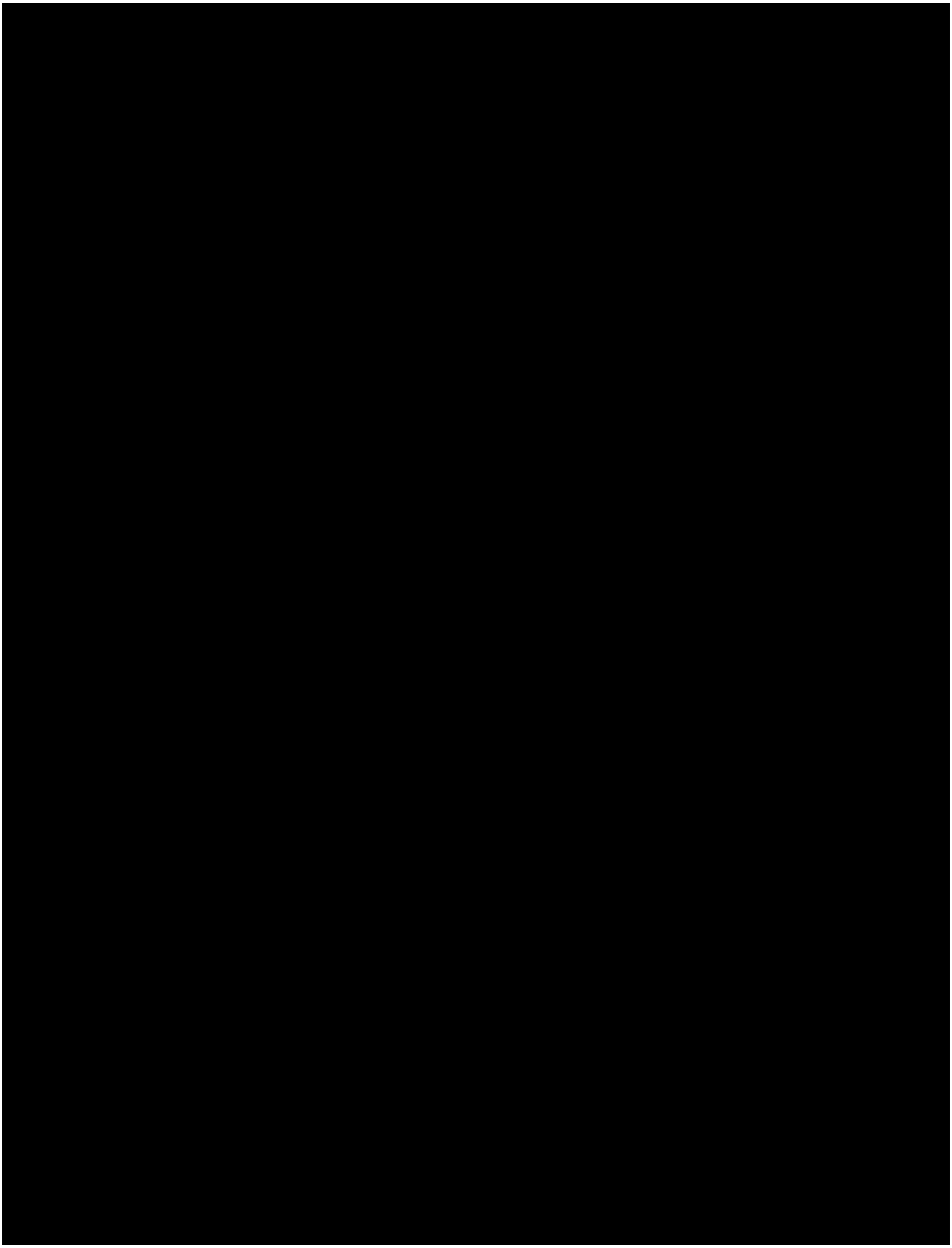


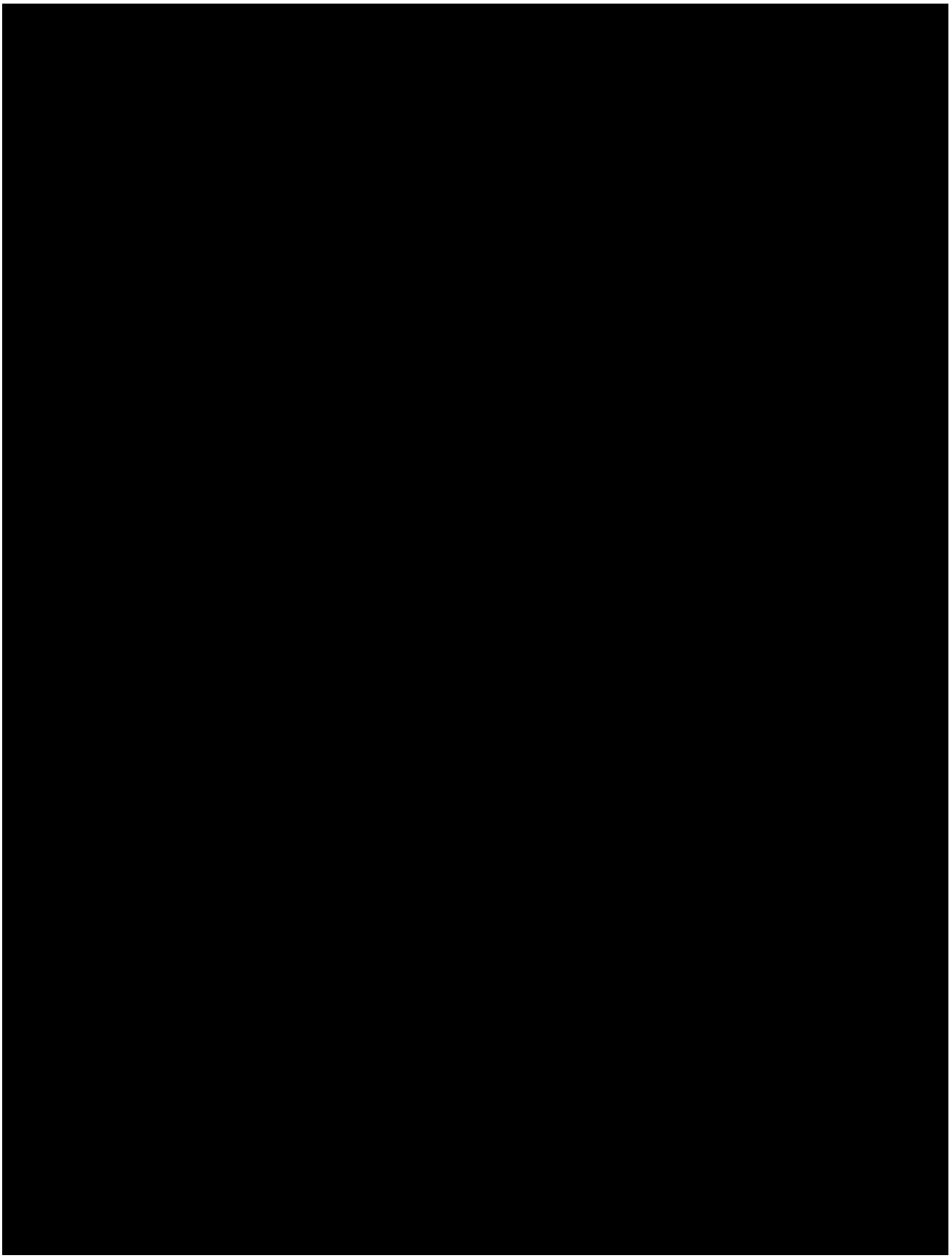












APPENDIX 12 ULCERATIVE COLITIS-RELATED HEALTHCARE UTILIZATION

APPENDIX 13 VACCINE GUIDANCE INCLUDING SARS-COV-2 VACCINES

The following outlines general vaccine guidance for the study:

- Administration of a live vaccine is prohibited 90 days prior to the randomization visit, during the induction period or maintenance period, or within 2 months after the last dose of IP.
- Administration of a nonlive vaccine is allowed during the study. However, the efficacy and safety of nonlive vaccines (including nonlive SARS-CoV-2 vaccines) in subjects receiving BMS-986165 is unknown.
- The following are NOT live vaccines: inactivated vaccines (eg, heat-killed and formalin-killed vaccines), subunit vaccines (eg, influenza and pneumococcal vaccines), toxoid vaccines, nucleic acid vaccines that do not encode potentially infectious virus (eg, Pfizer/BioNTech and Moderna COVID-19 vaccines) and replication-incompetent recombinant vector vaccines (eg, AstraZeneca/University of Oxford SARS-CoV-2 vaccine).

The following outlines specific SARS-CoV-2 vaccine guidance for the study:

- For SARS-CoV-2 vaccines requiring more than 1 dose, the full series (eg, both doses of a 2-dose series) should be completed prior to enrollment when feasible, and when a delay in enrollment would not put the study subject at risk.
- SARS-CoV-2 vaccination during the study should be considered for subjects who were not vaccinated or who have not completed eligible booster vaccinations prior to study entry.
- If a subject has received a specific SARS-CoV-2 vaccination, the COVID-19 vaccination information, including type of vaccine and date(s) received, will be recorded in the COVID-19 vaccination form.

Please contact the Medical Monitor with any questions related to SARS-CoV-2 vaccines.

APPENDIX 14 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for the Protocol Amendment 01, 06-May-2021

The primary purposes of this protocol amendment are to apply revisions relating to SARS-CoV-2 infection and add clarification regarding additional research collection.

Key additions and clarifications include:

- Adding information, instructions, and measures to be taken in relation to SARS-CoV-2 infection
- Adding clarification regarding additional research sample collection and use
- Removing prohibition of medical marijuana
- Adding assessments of mean corpuscular volume and mean corpuscular hemoglobin to the list of hematology laboratory tests to be conducted.
- Removing the endoscopic global severity score. This was included in error, and is not being collected in the study.
- Clarifying the definitions of steroid-dependent and steroid-resistant UC, to aid eCRF completion.
- Clarifying the definition of the Ulcerative Colitis Endoscopic Index of Severity (UCEIS).
- Clarifying male contraception requirements

This protocol amendment will be implemented after the investigator receives all appropriate agency and Investigational Review Board/Independent Ethics Committee approvals.

All changes applied to the body were applied to the synopsis, as necessary, and synopsis changes are not included in the list below.

Only major additions and deletions are provided in this summary document, and all minor grammatical, formatting, rephrasing, stylistic changes, or clarifications, as well as reorganizational changes are not included.

The rationales for changes to this protocol amendment are provided in the summary of key changes table, as shown below:

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
2 Schedule of Activities, Table 1 3.2 Benefit/Risk Assessment 4 Objectives and Endpoints 6.1 Inclusion Criteria 6.2 Exclusion Criteria 7.7.1 Prohibited Treatments	Added information, instructions, and measures to be taken related to SARS-CoV-2 infection/COVID-19, including the following: Replaced the following Exclusion Criteria: 5)c) → 5)e)	Provide guidance to investigators related to SARS-CoV-2.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
8.1.1 Temporary Discontinuation (new section) 9.1.2 Disease Activity and Quality of Life Indices Used in this Study 9.2.1 Time Period and Frequency for Collecting AE and SAE Information 9.4.3 Clinical Safety Laboratory Assessments 9.6 Biomarkers 9.6.1 Additional Research Collection 9.8 SARS-CoV-2 Testing (new section) Appendix 1 Abbreviations and Trademarks Appendix 5 Criteria to Define Inadequate Response (Primary), Loss of Response (Secondary), and Intolerance To Previous Standard Of Care Medication(s) Appendix 10 Ulcerative Colitis Endoscopic Index of Severity (UCEIS): Scores and Definitions Appendix 13 COVID-19 Vaccines (new appendix)	Removed exclusion of medical marijuana, including the following: Replaced the following Exclusion Criteria: 9)j) → 9)p)	Facilitate study feasibility.
	Removed inclusion criteria 5b ii and iii, added clarifying language to 5b iv (now ii) to clarify male contraception requirement	Clarify male contraception requirements.
	Added text regarding additional research sample collection and use.	Clarify additional research sample collection and use.
	Added assessments of mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) to the list of hematology laboratory tests to be conducted.	Estimation of MCV and MCH will assist in the characterization of red blood cell morphology.
	Removed the endoscopic global severity score.	This score was included in error, and is not being collected in the study.
	Clarification of the definitions of "steroid-refractory" and "steroid-dependent" disease for the purpose of eCRF completion	Additionally clarify the corticosteroids criteria.
	Clarified the definition of the Ulcerative Colitis Endoscopic Index of Severity (UCEIS).	Additionally clarify the classification of erosions and ulcers.