Protocol for

Official Title of Study

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

NCT03934216

April 14, 2021

CLINICAL PROTOCOL IM011024

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

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

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DOCUMENT HISTORY

Document	Date of Issue	Approver(s)	Summary of Changes
Protocol Amendment 03 (Global Revised Protocol 12_v4.0) im011024-protamend03	14-Apr-2021	[redacted]	• Added information, instructions, and measures to be taken related to SARS-CoV-2 infection/ COVID-19, including the following: o Amended exclusion criterion 5)l o Added diagnostic test at screening [redacted] • Removed fasting requirement for blood tests at screening • Amended wording of note from Administrative Letter 1 regarding consistent endoscopy procedures • Updated study endpoints and endpoint definitions • Clarified that study data may be used for additional analyses related to UC and other inflammatory diseases • Updated text in multiple sections of the protocol due to changes in BMS protocol standards
Revised Protocol 02a France-specific (Revised Protocol 11[a]) im011024-revprot02a-fr-specific	22-Jun-2020		This country-specific revised protocol applies to all subjects enrolled in France. It encompasses the removal of the first bullet point of inclusion criterion 2)h) and modification of APPENDIX 5, which allowed subjects with only an inadequate response, loss of response, or intolerance to a standard course of oral 5-aminosalicylates (5-ASAs) to be included in the trial.
Administrative Letter 1	16-Jan-2020		Includes clarifications and minor typographical error corrections.
Amendment 10 v3.0 (Japan)	08-Jan-2020		This country-specific amendment applies to all subjects enrolled in Japan. Modifications include: • Changes made in Global Revised Protocol v3.0 • Revisions based on the updated Japan hepatitis guideline

Document	Date of Issue	Approver(s)	Summary of Changes
Revised Protocol 09 v3.0 (Germany)	19-Dec-2019	[redacted]	This country-specific revised protocol applies to all subjects enrolled in Germany. The purpose of this revised protocol is to incorporate the changes from Revised Protocol 06 (global version 3.0) into the Germany-specific Revised Protocol 05 (global version 2.0). Additionally, a new exclusion criterion was added to Section 5.2 to exclude subjects with hereditary galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption.
Revised Protocol 08 v3.0 (Czech Republic)	19-Dec-2019		This country-specific revised protocol applies to all subjects enrolled in the Czech Republic. The purpose of this revised protocol is to incorporate the changes from Revised Protocol 06 (global version 3.0) into the Czech Republic–specific Revised Protocol 04 (global version 2.0).
Revised Protocol 07 v3.0 (South Korea)	18-Dec-2019		This country-specific revised protocol applies to all subjects enrolled in South Korea. The purpose of this revised protocol is to incorporate the changes from Revised Protocol 06 (global version 3.0) into the South Korea-specific Revised Protocol 03 (global version 2.0). Additionally, new language regarding biopsy sampling was added to reflect South Korea–specific endoscopic procedures.
Global Revised Protocol 06 v3.0	28-Oct-2019		Includes the following modifications: • Add a 52-week open-label extension period to provide the option of additional treatment to subjects deriving clinical benefit at Week 52; • Modify the type and/or frequency of various study assessments to improve subject safety and minimize subject burden; provide additional detail for each of the study periods, including clear guidance for management of Week 12 responders and nonresponders in the maintenance period and additional hepatitis B Virus (HBV) and hepatitis C Virus

Document	Date of Issue	Approver(s)	Summary of Changes
			(HCV) screening and monitoring information; • Modify several inclusion and exclusion criteria to increase subject eligibility, and add specific randomization criteria to aid in final determination of eligibility; • Incorporate several elements from the South Korea and Germany specific v2.0 amendments regarding age of majority, and follow-up after discontinuation and adverse events; • Revise or clarify the definitions of key study terms and endpoints; [redacted] • Revise or clarify the following study elements: prohibited and restricted treatments; use and tapering of corticosteroids during all study periods; criteria defining treatment failure; criteria leading to discontinuation; and criteria defining inadequate response, loss of response, and intolerance to previous biologic therapy; • Clarify sample size calculation [redacted]; • Remove or modify several contraception requirements to reflect recent toxicology data consistent with these changes; • Implement other revisions including modification of text regarding safety reporting requirements; and addition of several new appendices to evaluate UC disease activity [redacted]
Amendment 05 (Germany) v2.0	29-Aug-2019	[redacted]	This country-specific amendment applies to all subjects enrolled in Germany. Modifications include: • Exclusion Criterion 7)a) has been revised to exclude prisoners or

Document	Date of Issue	Approver(s)	Summary of Changes
		[redacted]	subjects who are involuntarily incarcerated from trial participation. • Section 7.1.1 (Post-Study Treatment Follow-up) has been revised to state that participants who discontinue study treatment will be followed for 28 days or longer, as required, and in line with Section 8.2.3. • Section 8.2.1 and APPENDIX 3 have been revised to state that serious adverse events (AEs) need to be reported 'immediately' to Sponsor or designee but no later than 24 hours after awareness of the event. • Section 8.2.5 (Pregnancy) has been revised to state that study drug treatment must be discontinued immediately in case of pregnancy and that the pregnancy must be reported within 24 hours of awareness of the pregnancy. • APPENDIX 3 has been revised to state that nonserious AEs that cause interruption or discontinuation of study treatment must be followed to resolution or stabilization.
Amendment 04 (Czech Republic) v2.0	01-Aug-2019		This country-specific amendment applies to all subjects enrolled in the Czech Republic. The purpose of this Amendment is to adjust the maximum age of subjects from 80 to 70 years of age, and to align Section 8.2.5 Pregnancy with local regulatory requirements for Czech Republic sites.
Amendment 03 (South Korea) v2.0	31-Jul-2019		Adding "or age of majority" to inclusion criterion to align with local regulatory requirements for South Korean sites

Document	Date of Issue	Approver(s)	Summary of Changes
Amendment 02 (Japan) v2.0	09-Apr-2019	[redacted]	This country-specific amendment applies to all subjects enrolled in Japan. The purpose of this Amendment is to incorporate local regulatory requirements for Japanese sites.
Global Revision 01 v2.0	26-Mar-2019		Includes modifications to the Schedule of Activities [redacted] added new Section 8.1.1 and language throughout protocol regarding central read versus local read of endoscopy; clarified corticosteroid use as a rescue medication; and added discontinuation criteria and study stopping rule [redacted]
Original Global Protocol v1.0	17-Dec-2018		Not applicable

[a] Document naming conventions have been updated. Legacy [redacted] numbering is provided for consistency.

OVERALL RATIONALE FOR GLOBAL PROTOCOL AMENDMENT 03

The primary purpose of this revised protocol is to include the following updates:

- Addition of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) diagnostic testing, as well as an exclusion criterion and study procedures pertaining to SARS-CoV-2 infection
- Inclusion of coronavirus disease 2019 (COVID-19) benefit-risk information and vaccination guidelines

[redacted]

- Update to study endpoints prior to database lock for primary endpoint analysis

[redacted]

The revised protocol will be implemented after the Investigator receives all appropriate agency and IRB/EC approvals.

Generally, only major additions and deletions are provided in this summary of changes document, and all minor grammatical, formatting, rephrasing, stylistic changes, or clarifications, as well as organizational changes are not included. All changes applied to the protocol body were applied to the protocol synopsis, as necessary; synopsis changes are not included in the summary of key changes table.

The rationale for the change to this Revised Protocol is provided in the summary of key changes table, as shown below:

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03

Section Number & Title	Description of Change	Brief Rationale
2 Schedule of Activities, Tables 1-4 3.3 Benefit/Risk Assessment 6.2 Exclusion Criteria, 5) Immune and Infectious Disease Exclusion Criteria 7.7.1 Prohibited and/or Restricted Treatments 8.2.1 Temporary Discontinuation (new section) [redacted] 9.8 SARS-CoV-2 Testing (new section) Appendix 19 COVID-19 Vaccines (new appendix)	Added information, instructions, and measures to be taken related to SARS-CoV-2 infection/ COVID-19, including the following: Amended exclusion criterion 5)l Added diagnostic test at screening [redacted]	Provides guidance to investigators related to SARS-CoV-2
2 Schedule of Assessments, Table 1	Removed fasting requirement for blood tests at screening	Reduces subject burden

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
2 Schedule of Assessments, Tables 2-4	Amended wording of note from Administrative Letter 1 regarding consistent endoscopy procedures	Clarified aim of previously added text
4 Objectives and Endpoints, Tables 5-7	Updated study endpoints and endpoint definitions	Adds histologic and histologic-endoscopic endpoints and definitions to reflect consensus guidelines on the measure of efficacy in UC. Due to the study's small sample size we do not wish to add additional multiplicity-controlled endpoints and therefore find histologic improvement as a better measure of efficacy than endoscopic remission
9 Study Assessments and Procedures	Clarified that study data may be used for additional analyses related to UC and other inflammatory diseases	Clarifies potential future analyses
Study Acknowledgment/Disclosure 6.5 Screen Failures 7.3.2 Circumstances for Unblinding 7.8 Treatment After the End of the Study 9.2.1 Time Period and Frequency for Collecting AE and SAE Information 9.2.5 Pregnancy [redacted] Appendix 2 Study Governance Considerations Appendix 3 Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting Appendix 4 Women of Childbearing Potential	Updated text in multiple sections of the protocol due to changes in BMS protocol standards	Reflects current BMS procedures, policies, and guidelines

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1 PROTOCOL SUMMARY

1.1 Synopsis

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

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

Study Phase: 2

Rationale: Study IM011024 is a Phase 2 randomized, double-blind study to assess the safety and efficacy of oral (PO) BMS-986165 6 mg twice daily (BID) in subjects with moderate to severe ulcerative colitis (UC). BMS 986165 will be compared to placebo to evaluate its effect on clinical remission of UC following 12 weeks of study treatment.

UC is a chronic inflammatory disease of the gastrointestinal tract that causes significant morbidity, impact on quality of life, and healthcare expenditures. 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, yet significant therapeutic challenges still remain with this and other inflammatory bowel diseases (IBDs).

Tyrosine kinase 2 (TYK2) is an intracellular signaling kinase that mediates cytokine-driven immune and proinflammatory signaling pathways that are critical in the cycle of chronic inflammation central to a number of immune-mediated diseases. TYK2 inhibition selectively blocks interleukin (IL)-23, IL-12, and Type I interferon-driven responses but not cytokine responses mediated by other Janus kinases (JAK), such as IL-6, hematopoietic growth factors, and the IL-2 family. 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, and spondyloarthropathies.

BMS-986165 is an orally administered selective TYK2 inhibitor with a unique mechanism of action distinct from other JAK inhibitors and has the potential to treat a wide spectrum of immune-mediated diseases. Inhibition of TYK2 is expected to provide therapeutic benefit for patients with UC for multiple reasons: 1) IL-12 and IL-23 have been implicated in the pathogenesis of UC; 2) Biologic agents targeting IL-23p19 and IL-12/IL-23p40 cytokines have been shown to be efficacious in UC and CD, and ustekinumab targeting IL-12/IL-23p40 has been approved for the treatment of CD and UC; and 3) BMS-986165 has been shown to be efficacious in psoriasis, an IL-23-mediated disease, in a recent Phase 2 study.

Study Population: Key inclusion criteria (Section 6.1) include:

- Male and female subjects, 18 years (or age of majority) to 80 years of age, inclusive, at the time of screening
- Documented diagnosis (endoscopic and histological) of UC of at least 3 months' duration prior to screening

- Active moderate to severe 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 subscore values:
  - A stool frequency (SF) subscore of ≥ 2, **and**
  - A rectal bleeding (RB) subscore ≥ 1, **and**
  - An endoscopic (ES) subscore of ≥ 2 (screening endoscopy)
- Active UC extending ≥ 15 cm from the anal verge and confirmed by a screening/baseline colonoscopy/sigmoidoscopy prior to the randomization visit
- 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; specific criteria and dosing details are in APPENDIX 5:
  - Oral 5-aminosalicylic acids (5-ASAs) (eg, mesalamine, sulfasalazine, olsalazine, or balsalazide)
  - Corticosteroids (eg, prednisone [or equivalent] or budesonide [or equivalent])
  - Immunomodulators (eg, azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX])
  - Anti-tumor necrosis factor-alpha (TNF-α) agents (eg, infliximab, adalimumab, or golimumab)
  - Integrin inhibitors (eg, vedolizumab)
  - Anti-IL-12/IL-23p40 antibodies (eg, ustekinumab); subjects can only be included if they were intolerant to treatment. Inadequate response or loss of response is exclusionary.

Key exclusion criteria (Section 6.2) are as follows:

- Previous/current documented diagnosis of CD, indeterminate colitis, ischemic colitis, or pseudomembranous colitis (other than associated with *Clostridium difficile* [*C. difficile*])
- Stool positive for *C. difficile* toxin at screening visit; subjects may be rescreened 30 days after completion of an institutional standard of care course with antibiotics, and subsequent negative testing for *C. difficile* stool toxin and a *C. difficile* nucleic acid amplification test
- Current or recent (within 12 weeks prior to the randomization visit) evidence of fulminant colitis, abdominal abscess, toxic megacolon, or bowel perforation
- History or evidence of any extensive colonic resection, subtotal or total colectomy, with or without presence of a stoma or ileoanal pouch. Current need for, or anticipated need for, surgical intervention for UC during the study
- History of diverticulitis within 60 days prior to the randomization visit. (Previous diverticulitis that has been successfully treated with a local standard course of antimicrobial therapy is permitted; however, the course of antimicrobial therapy must be completed at least 60 days prior to the randomization visit.)
- Current colonic adenomas, dysplasia, or past confirmed colonic dysplasia that has not been eradicated (subjects who have had UC > 8 years should have had a colonoscopy to screen for dysplasia within 1 year prior to the randomization visit, or this can be performed as part of screening colonoscopy). A subject with prior history of adenomatous polyps will be eligible if

the polyps have been completely removed (documented), and the subject is free of polyps and without evidence of dysplasia on histology at randomization.

- Prior exposure to treatment with TYK2 inhibitors
- Inadequate response or loss of response to medications that target the same pathway as BMS-986165, such as anti-IL-12/IL-23p40 antibodies (eg, ustekinumab, briakinumab) or anti-IL-23p19 antibodies (eg, guselkumab, risankizumab, tildrakizumab, brazikumab [MEDI2070], and mirikizumab [LY3074828]).
  - Subjects who have been exposed to the medications listed above, but who have not had a treatment failure (ie, an inadequate response or loss of response) may be eligible for inclusion.
  - Subjects who have experienced intolerance to the medications listed above (eg, an infusion reaction) without a treatment failure may be eligible for inclusion.
- Failure or loss of response to JAK inhibitors, such as tofacitinib. Prior exposure is not exclusionary.
- Use of other investigational agents within 4 weeks or 5 half-lives, whichever is longer, prior to randomization
- Use of immunomodulators (AZA, 6-MP, or MTX) within 4 weeks prior to randomization
- Use of a biologic agent within the minimum washout period prior to randomization (APPENDIX 7)
  - Fecal transplant is considered an "investigational" biologic agent and the washout period must be ≥ 4 weeks prior to randomization
- Use of topical rectal treatment with 5-ASA or corticosteroid within 2 weeks prior to randomization
- Current use of corticosteroid at a dose of > 20 mg/day for prednisone (or equivalent) or > 9 mg/day for budesonide (Multi-Matrix System [MMX®] colonic-release technology; eg, Uceris® or equivalent)

Objectives and Endpoints:

Efficacy (primary and secondary) and safety objectives and endpoints (Section 4) are summarized below:

Objectives	Endpoints
Efficacy	
Primary	
• To assess the effect of BMS-986165 on clinical remission at the end of the induction period	• Clinical remission (modified Mayo score[a])[b] at Week 12
Secondary	
• To assess the effect of BMS-986165 on clinical response at the end of the induction period	• Clinical response[c] at Week 12
• To assess the effect of BMS-986165 on endoscopic response at the end of the induction period	• Endoscopic response[d] at Week 12
• To assess the effect of BMS-986165 on histologic improvement at the end of the induction period	• Histologic improvement[e] at Week 12
Safety	
• To assess the safety and tolerability of BMS-986165 in subjects with moderate to severe UC	• Number and proportion of subjects experiencing AEs, SAEs, AEs leading to study discontinuation, and AEs of interest (AEIs) • Number and proportion of subjects experiencing abnormalities in laboratory testing, ECG, physical examination, and vital sign parameters over time

AE = adverse event; AEI = adverse event of interest; ECG = electrocardiogram; SAE = serious adverse event; UC = ulcerative colitis

[a] Modified Mayo Score (0 to 9 points) is the sum of 3 components: stool frequency (SF) (0 to 3), rectal bleeding (RB) (0 to 3), and endoscopic (ES) (0 to 3) subscores.

[b] Clinical remission is defined as: Mayo SF subscore ≤ 1, with ≥ 1-point decrease from baseline, **and** Mayo RB subscore = 0, **and** Mayo ES subscore ≤ 1 (obtained from centrally read endoscopy; modified, excludes friability).

[c] Clinical response is defined as: 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 Mayo RB subscore of ≥ 1 point or absolute RB subscore ≤ 1.

[d] Endoscopic response is defined as: Mayo ES subscore ≤ 1 (obtained from centrally read endoscopy)

[e] Histologic improvement is defined as: Geboes score ≤ 3.1

Overall Design:

- Study design: Parallel, placebo controlled, multicenter, proof of concept
- 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 Week 0 (Day 1) of the induction period.
  - Subjects will be randomized in a 2:1 ratio using interactive response technology (IRT) to receive oral BMS-986165 6 mg BID or placebo BID during the induction period of 12 weeks.
  - Randomization will be stratified based on corticosteroid use (yes/no) and prior exposure to biologics indicated for the treatment of UC (ie, no prior exposure, exposure to 1 biologic, or exposure to > 1 biologic). JAK inhibitors are considered as a biologic for stratification purposes. (Note: Failure or loss of response to JAK inhibitors is exclusionary, but prior exposure is not exclusionary.)
- Study periods:
  - Screening: up to 4 weeks (28 days)
  - Induction: 12 weeks (84 days)
  - Maintenance: 40 weeks (280 days)
  - Open-label extension: 52 weeks (364 days)
  - Post-treatment follow-up: 4 weeks (28 days)
- Study assessments:
  - Endoscopic (colonoscopy/sigmoidoscopy) evaluations and collection of colonic tissue biopsies will be performed during the screening period, at the end of the induction period (Week 12), at the end of the maintenance period (Week 52), and at the end of the open-label extension period (Week 104). Endoscopy should also be performed at unscheduled visits (if clinically indicated). Endoscopy is required at early termination (ET) visits that occur between Week 4 and Week 12. Endoscopy is recommended for ET visits occurring from Week 16 through Week 52 and Week 56 through Week 104. 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.
  - At Week 12, local assessment of the endoscopy will be utilized to derive the ES subscore of the modified Mayo score used for determination of treatment assignment during the maintenance period. The central read of the endoscopy will be used for efficacy analysis at all time points (Section 2 and APPENDIX 9).
  - Electronic diaries will be maintained by subjects throughout the study to collect daily stool frequency and rectal bleeding data; this will enable Mayo score calculations used in the determination of the primary and secondary efficacy endpoints (APPENDIX 9).

[redacted]

  - Assessment of adverse events (AEs), physical examinations, vital sign measurements, 12-lead electrocardiogram (ECG), and clinical laboratory evaluations will be performed at selected times throughout the study (Section 2).
  - Disease worsening will be assessed at each visit during the maintenance period using SF and RB subscores as defined in Table 5.
- Corticosteroid use and tapering:
  - Induction period: Prednisone or colonic-release budesonide are allowed, provided the dose is stable for 2 weeks prior to randomization, and thereafter stable during the induction period. Corticosteroid tapering is not allowed during the induction period.
  - Maintenance period: Subjects receiving corticosteroids during the induction period must initiate a corticosteroid taper. This is described in Section 5.1.5 for different treatment arms.
- Treatment failure: Subjects who require corticosteroid rescue therapy due to increased UC activity, fail to taper corticosteroids, or require an alternative, efficacious therapy for UC will be defined as a treatment failure (Section 5.1.6).
- 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.
- An independent Data Monitoring Committee (DMC) will be instituted to perform safety monitoring by unblinded treatment group (Section 5.1.7).

Number of Subjects: Approximately 120 subjects are planned to be randomized in a 2:1 ratio to receive BMS-986165 6 mg BID (80 subjects) or placebo (40 subjects) during the induction period of 12 weeks.

Treatment Arms and Duration:

Induction Period: On Week 0 (Day 1) of the 12-week, double-blind induction period, subjects will be randomized to receive 1 of the following study treatments:

- BMS-986165 6 mg BID
- Placebo

Maintenance Period: At Week 12, all subjects who complete the induction period will be eligible to enter the 40-week maintenance period; the treatment assignment will be based on their clinical response (assessed using the modified Mayo score with a locally read endoscopy).

Subjects who achieve clinical response at Week 12 will be categorized as a responder at Week 12, and they will enter 1 of the following study treatment arms:

- Responders at Week 12 continuing blinded treatment:
  - BMS-986165 6 mg BID → BMS-986165 6 mg BID
  - Placebo → Placebo

Subjects who do not achieve clinical response at Week 12 will be categorized as a nonresponder at Week 12, and they will enter 1 of the following study treatment arms (or they will be discontinued from the study per investigator discretion):

- Nonresponders at Week 12 continuing open-label treatment:
  - BMS-986165 6 mg BID → BMS-986165 6 mg BID
  - Placebo → BMS-986165 6 mg BID

Open-label Extension Period: After Week 52, subjects who continue to safely derive clinical benefit (as judged by the investigator) and receive open-label treatment during the 52-week, open-label extension period of the study will enter 1 of the following study treatment arms:

- Responders at Week 12, clinical benefit at Week 52 continuing open-label treatment:
  - BMS-986165 6 mg BID → BMS-986165 6 mg BID→ BMS-986165 6 mg BID
  - Placebo → Placebo→ BMS-986165 6 mg BID
- Nonresponders at Week 12, clinical benefit at Week 52 continuing open-label treatment:
  - BMS-986165 6 mg BID → BMS-986165 6 mg BID→ BMS-986165 6 mg BID
  - Placebo → BMS-986165 6 mg BID → BMS-986165 6 mg BID

The total duration of study participation is approximately 112 weeks (784 days) in 5 periods.

Study Treatment:

Study Treatment for IM011024			
Study Treatment	**Potency/Dose**	**Blinded or Open label**	**IP/Non-IP**
BMS-986165 oral tablet	6 mg	Blinded	IP
Placebo matching BMS-986165 oral tablet	Not applicable	Blinded	IP
BMS-986165 oral tablet	6 mg	Open-label	IP

IP = investigational product

Statistical Methods: Approximately 120 subjects will be randomized in a 2:1 ratio to BMS-986165 6 mg BID or placebo, respectively (80 subjects on BMS-986165 and 40 on placebo). In this proof of concept study, if the observed response rates are the same as the assumed rates reported in current UC investigative trials, the total number of 120 subjects will provide approximately 82% power to detect a 15% treatment difference in clinical remission at Week 12 with a 1-sided 0.1 level of significance.

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 study period and treatment group.

The primary efficacy analysis model for clinical remission (responder/nonresponder) will be analyzed at Week 12 using a stratified Cochran-Mantel-Haenszel test stratified by corticosteroid use (yes/no) and prior exposure to biologics (0, 1, > 1). JAK inhibitors are considered as a biologic for stratification purposes. If expected cell counts are not sufficient for each strata level, then strata levels will be combined for analysis. The assessment of statistical significance will be based upon a 1-sided, 0.1 alpha, which is in alignment with the sample size calculation. The odds ratio and corresponding 2-sided 95% confidence interval (CI) will be provided for descriptive purposes.

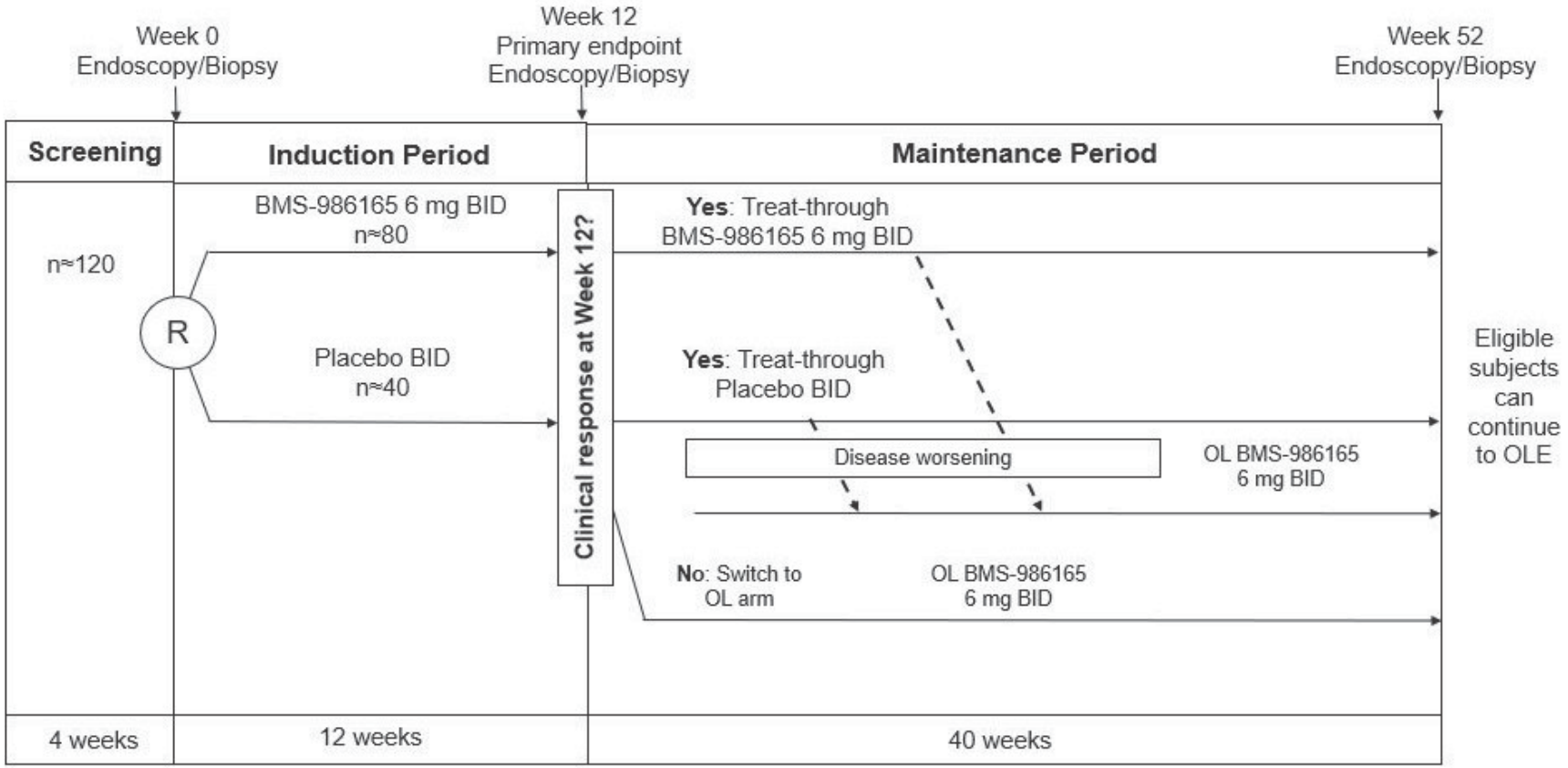
Supportive analyses using logistic regression may be performed to incorporate additional covariates of interest and to confirm primary analysis results. The model will include treatment, geographic region, corticosteroid use (yes/no), prior exposure to biologics (0, 1, > 1), as well as other covariates as applicable. The odds ratio and the corresponding 2-sided 95% CI will also be provided.

Statistical analysis of the secondary endpoints will use the same approach as the primary endpoint analysis with missing data being imputed as nonresponders. Testing strategy of secondary endpoints will be performed in a hierarchical fashion to control for Type I error rate inflation. The statistical testing of the primary endpoint will be the serial gatekeeper for proceeding to the testing of the secondary endpoints. Each secondary endpoint will be tested sequentially in a fixed-sequence order using a 1-sided alpha = 0.1 for significance testing. No further testing will be performed once a test fails to show significance at the alpha level stated above.

Safety endpoint analyses will be descriptive in nature.

1.2 Schema

The study design schematic for the induction and maintenance periods is presented below:

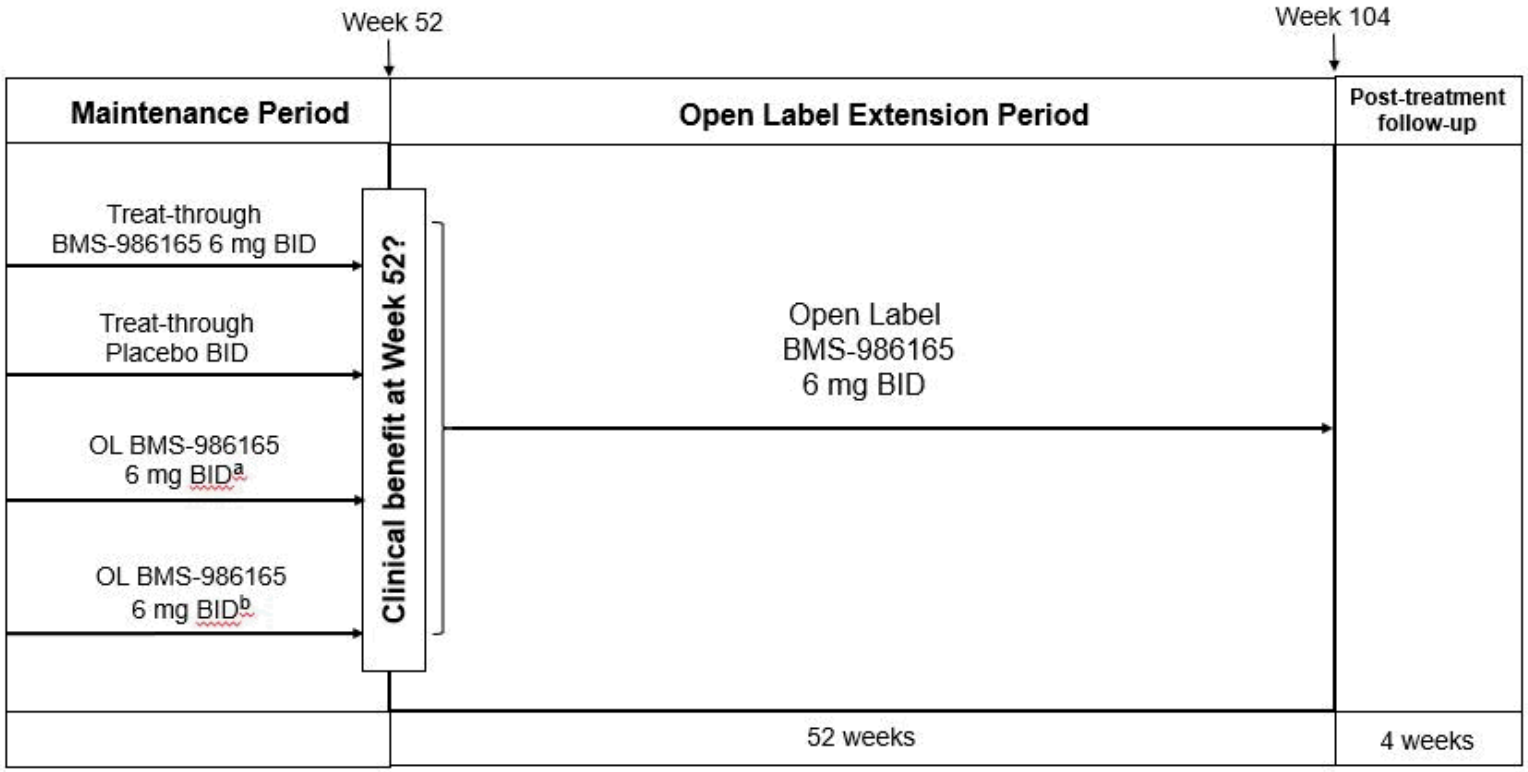


BID = twice daily; OL = open-label; OLE = open-label extension; R = randomization

At Week 12, clinical response is determined using the modified Mayo score (see Table 5 and Section 9.1.1). Subjects who achieve clinical response at Week 12 and continue into the maintenance period will continue to receive their double-blind treatment from the induction period. Subjects who subsequently experience disease worsening (Table 5) can enter the Week 12 responder open-label arm at any time from Week 13 through Week 52.

Subjects who do not achieve clinical response at Week 12 are eligible to enter the Week 12 nonresponder open-label arm.

The study design schematic for the open-label extension period is presented below:



BID = twice daily; IP = investigational product; OL = open-label

[a] Subjects in this arm are those who achieved clinical response at Week 12 of the induction period, but they subsequently lost clinical response to IP between Week 13 and Week 52 of the maintenance period and switched to the Week 12 responder open-label arm (Section 5.1.3.2).

[b] Subjects in this arm are those who did not achieve clinical response at Week 12 of the induction period and switched to the Week 12 nonresponder open-label arm.

2 SCHEDULE OF ACTIVITIES

The schedules of procedures are described in Table 1 for the screening period, Table 2 for the induction period, Table 3 for the maintenance period, and Table 4 for the open-label extension period.

2.1 Screening Period Activities and Assessments

Table 1 Screening Procedural Outline (IM011024)

Procedure	Screening Visit Day -28 to -1	Notes
Eligibility and Disease Assessments		
Informed Consent	X	A subject will be considered enrolled only when the ICF is signed.
Enroll subject	X	Obtain number from IRT; contact IRT to screen fail those not eligible.
Inclusion/Exclusion criteria	X	Section 6
Medical history	X	Include any toxicities or allergy related to previous treatments.
Ulcerative colitis (UC) disease history	X	
Dispense electronic subject diary	X	
Subject diary training	X	Includes training for entry of stool frequency (SF) and rectal bleeding (RB) assessments into the electronic subject diary. Instructions for recording the number of stools and worst rectal bleeding (each over a 24-hour period) are in Table 26 (APPENDIX 9).
Baseline SF	X	Establish the baseline SF. This is 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, he/she 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 (APPENDIX 9).
Enter SF and RB subscores for baseline Mayo score calculations	X	SF and RB subscores are calculated using the electronic subject diary and entered into the eCRF (APPENDIX 9).
Endoscopy (colonoscopy/sigmoidoscopy)	X	Colonoscopy/sigmoidoscopy examination must be performed within Day - 21 and Day - 1 of the screening period and should be scheduled as close as possible to the Week 0 (Day 1) visit. The Week 0 (Day 1) visit must occur within 14 days of the screening endoscopy. Instructions for review of SF and RB diary entries to assess if a subject is likely to meet inclusion criteria and should continue screening prior to commencing bowel preparation for the endoscopy are in APPENDIX 9.

Table 1 Screening Procedural Outline (IM011024)

Procedure	Screening Visit Day -28 to -1	Notes
		At the screening endoscopy, collection of colonic tissue biopsies will be performed as described in the rows below. Full colonoscopy will be required in these situations: • If normal margins are not apparent from sigmoidoscopy or if proximal colonic involvement is suspected • In subjects with a history of UC ≥ 8 years, if one was not performed in the prior 12 months
Colon histology [redacted]	X	Two biopsy samples will be obtained from each of the 4 colonic segments (rectum, descending colon/sigmoid, transverse colon, ascending colon) if colonoscopy is performed or from each of the 2 segments (rectum, descending colon/sigmoid) if sigmoidoscopy is performed for the histologic assessments (Section 9.1) [redacted].
[redacted]		
Baseline modified Mayo score calculation	X	The modified Mayo score is used to determine subject eligibility. A score of 5 to 9 points, inclusive, is required at screening, and it must include all of the following subscores: • A stool frequency (SF) subscore of ≥ 2 and • A rectal bleeding (RB) subscore of ≥ 1, and • A screening endoscopic (ES) subscore (central read) of ≥ 2 Instructions for calculating the modified Mayo score for eligibility are provided in APPENDIX 9.
[redacted]		

Table 1 Screening Procedural Outline (IM011024)

Procedure	Screening Visit Day -28 to -1	Notes
[redacted]		
Confirm washout of prohibited medication and dose stabilization of allowed medication (if applicable)	X	Prohibited medications are described in Section 7.7.1. Washout periods for specific immunomodulatory and biologic agents required before a participant can be randomized are in APPENDIX 7; the use of therapeutic drug monitoring (TDM) to confirm washout is also described in APPENDIX 7. Note: The washout periods shown in APPENDIX 7 may be longer than the 4-week screening period. This needs to be considered at enrollment. Prednisone dose stabilization requirements are described in Section 5.1.5.1. The dose equivalents to prednisone of commonly used corticosteroids are provided in APPENDIX 6.
Tobacco use history	X	
Prior and current concomitant medications	X	Section 7.7
Safety Assessments		
Physical examination	X	General, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdominal, extremities, neurologic, skin, musculoskeletal. If the screening physical examination is performed within 7 days prior to dosing on Week 0 (Day 1), then a single exam may count as both the screening and predose evaluation.
Physical measurements	X	Height and weight
Vital signs	X	Body temperature, respiratory rate, and seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been resting quietly for at least 5 minutes.
Electrocardiogram	X	Single 12-lead ECG reading recorded after the subject has been supine for at least 5 minutes
Chest x-ray	X	Also acceptable within 6 months of the screening visit with documentation on file
Diagnostic testing for SARS-CoV-2	X	To be performed locally, as close as possible to randomization. Diagnostic testing for SARS-CoV-2 infection refers to a molecular test (eg, PCR or NAAT) or antigen test. PCR testing is preferred (Section 9.8).
Monitor for SAEs or nonserious AEs	X	SAE reporting begins at the time of signing of the ICF; nonserious AEs are collected starting with the initiation of study treatment (Section 9.2 and APPENDIX 3).

Table 1 Screening Procedural Outline (IM011024)

Procedure	Screening Visit Day -28 to -1	Notes
		However, all AEs related to SARS-CoV-2 infection should be collected from time of signing the ICF.
Breast and cervical cancer screening	X	Investigators are encouraged to confirm if screening is up-to-date according to local guidelines (women only). Screening for cervical and breast cancer prior to randomization is encouraged as per local guidelines due to the small inherent risk of increased malignancy with immunomodulatory agents, but this screening is at the investigator's discretion.
Laboratory Tests		
Hematology, chemistry, urinalysis, and coagulation	X	Blood and urine samples (must be repeated and verified to ensure that subjects meet study inclusion criteria and no exclusion criteria if performed more than 28 days prior to randomization) (Section 9.4.3).
Serology	X	Hepatitis B Virus (HBV): HBsAg, HBsAb, HBcAb with reflex to HBV DNA in subjects with HBsAg negative, HBcAb positive serology. (APPENDIX 8) Hepatitis C Virus (HCV): Anti-HCV; if positive or indeterminate, HCV RNA testing will be performed using a separate blood draw (APPENDIX 8). Human Immunodeficiency Virus (HIV): HIV-1 and -2 antibody (Section 6.2); HIV-1 and -2 serology may be performed centrally, or locally in regions where central laboratory testing for HIV is not available.
Tuberculosis screening	X	In accordance with standard testing (details are provided in Section 6.2 and 9.4.2)
Pregnancy test (urine or serum)	X	WOCBP only (APPENDIX 4). If the urine pregnancy test is positive, a serum pregnancy test should be done for confirmation prior to enrolling the subject. Study treatment should not be administered until the results of the confirmatory test are known.
Follicle-stimulating hormone (FSH)	X	Postmenopausal women only to confirm status (APPENDIX 4)
Stool culture (performed locally)	X	If a subject is positive for enteric pathogens (not including flora that are considered commensal within a study region), he/she can be rescreened 30 days after completing a full course of standard treatment for bacterial enterocolitis and being deemed clinically improved by the investigator.
Stool C. difficile toxin (performed centrally)	X	If a subject is positive for C. difficile toxin, he/she can be rescreened as described in Section 6.5.1.

Table 1 Screening Procedural Outline (IM011024)

Procedure	Screening Visit Day -28 to -1	Notes
Therapeutic drug monitoring (TDM)	X	Optional test for subjects who recently received infliximab, adalimumab, golimumab, vedolizumab (> 14 weeks treatment duration), or ustekinumab (> 12 weeks treatment duration) and are subject to a washout period for those medications (APPENDIX 7). This washout period will be waived for subjects who have an undetectable drug level for that specific medication on TDM testing at screening or prior to screening.

AE = adverse event; anti-HCV = hepatitis C virus antibody; *C. difficile* = *Clostridium difficile*; DNA = deoxyribonucleic acid; ECG = electrocardiogram; eCRF = electronic case report form; ES = endoscopic; FSH = follicle-stimulating hormone; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HIV-1 and -2 = human immunodeficiency virus -1 and -2; ICF = informed consent form; [redacted] IRT = interactive response technology; NAAT = nucleic acid amplification test; PCR = polymerase chain reaction; RB = rectal bleeding; RNA = ribonucleic acid; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SF = stool frequency; TDM = therapeutic drug monitoring; UC = ulcerative colitis; WOCBP = women of childbearing potential

2.1.1 Induction Period Activities and Assessments

Table 2 Induction Period On-treatment Procedural Outline Up to Week 12 (Day 85) (IM011024)

Procedure/Visit Weeks (Days)	0 (1) a	2 (15)	4 (29)	8 (57)	12 (85)	Notes
Visit window (± n days)	0	3	3	3	3	
Study Treatment						
Eligibility/randomization criteria	X					Confirm eligibility criteria (Section 6.1and Section 6.2) and assess randomization criteria (Section 6.3). All procedures to be completed before dosing unless otherwise specified.
Dispense clinical drug supplies (blinded)	X		X	X	X	Subjects are to receive blinded IP twice daily PO (Section 5.1.2). See Section 5.1.3.1 and 5.1.3.2 regarding IP based on clinical response at Week 12.
Study treatment (blinded)	X----------				----------X	
Review study drug compliance		X	X	X	X	Section 7.6
Safety Assessments						
Physical examination	X				X[b]	General, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdominal, extremities, neurologic, skin, musculoskeletal.
Physical measurement	X				X[b]	Weight only
Vital signs	X	X	X	X	X[b]	See Note in the screening period procedures (Table 1).
Electrocardiogram					X[b]	Single 12-lead ECG should be recorded after the subject has been supine for at least 5 minutes.
Concomitant medication use	X	X	X	X	X	Section 7.7
Tobacco use	X	X	X	X	X	
Monitor AEs	X	X	X	X	X	Monitoring for AEs will occur at every study visit (Section 9.2).
Monitor SAEs	X	X	X	X	X	Monitoring for SAEs will occur at every study visit (Section 9.2). All SAEs will be followed until resolution, until the condition stabilizes,

Table 2 Induction Period On-treatment Procedural Outline Up to Week 12 (Day 85) (IM011024)

Procedure/Visit Weeks (Days)	0 (1) a	2 (15)	4 (29)	8 (57)	12 (85)	Notes
						until the event is otherwise explained, or until the subject is lost to follow-up (Section 8.3).
Laboratory Tests						
Hematology, chemistry, urinalysis, and coagulation	X	X	X	X	X[b]	
HBV DNA			X	X	X[b]	To be performed only in subjects with the following HBV serology at screening: HBsAg negative, HBcAb positive, HBV DNA undetectable (APPENDIX 8)
Serum Igs	X		X		X[b]	IgG, IgM, IgA, and IgE
TBNK panel	X		X		X[b]	
Serum hsCRP	X	X	X	X	X[b]	
Fasting lipid panel	X				X[b]	Subjects are required to fast for ≥ 10 hours prior to the collection of specimens for the fasting lipid panel.
Fasting glucose	X				X[b]	Subjects are required to fast for ≥ 10 hours prior to the collection of specimens for the fasting glucose evaluation.
Pregnancy test (urine or serum)	X	X	X	X	X	WOCBP only (APPENDIX 4). If the urine pregnancy test is positive, a serum pregnancy test should be done for confirmation prior to discontinuing the subject. Study treatment should not be administered until the results of the confirmatory test are known.
[redacted]						

Table 2 Induction Period On-treatment Procedural Outline Up to Week 12 (Day 85) (IM011024)

Procedure/Visit Weeks (Days)	0 (1) a	2 (15)	4 (29)	8 (57)	12 (85)	Notes
[redacted]						
Efficacy Assessments						
[redacted]						
Review subject diary for SF and RB values	X	X	X	X	X	Prior to each scheduled visit, review subject diary to ensure SF and RB data have been entered daily. Prior to each scheduled visit at which Mayo scores are to be calculated, ascertain whether an adequate number of days of diary entries have been made (APPENDIX 9). If adequate entries have not been made, the

Table 2 Induction Period On-treatment Procedural Outline Up to Week 12 (Day 85) (IM011024)

Procedure/Visit Weeks (Days)	0 (1) a	2 (15)	4 (29)	8 (57)	12 (85)	Notes
						site should contact the subject to reschedule the visit, and the subject should be counseled about proper study procedures.
Enter SF and RB subscores for Mayo score calculation					X	APPENDIX 9
Endoscopy (colonoscopy/sigmoidoscopy)					X	After bowel preparation, endoscopic examination will be performed within a 7-day window prior to the Week 12 (Day 85) visit. Endoscopy is required at ET visits that occur between Week 4 and Week 12. If colonoscopy is conducted at screening assessment, every effort should be made to ensure colonoscopy is done at subsequent assessment. Screening and surveillance as per local guidelines may be completed during study related colonoscopy.
Colon histology [redacted]					X	Two biopsy samples will be obtained from each of the 4 colonic segments (rectum, descending colon/sigmoid, transverse colon, ascending colon) if colonoscopy is performed or from each of the 2 segments (rectum, descending colon/sigmoid) if sigmoidoscopy is performed for the histologic assessments (Section 9.1) [redacted].
[redacted]						
Efficacy/Mayo Scoring						
Modified Mayo score					X	Composite score of ES (central read), SF, and RB subscores. SF and RB subscores will be calculated using electronic subject diary data. See Section 9.1 and APPENDIX 9.

Table 2 Induction Period On-treatment Procedural Outline Up to Week 12 (Day 85) (IM011024)

Procedure/Visit Weeks (Days)	0 (1) a	2 (15)	4 (29)	8 (57)	12 (85)	Notes
[redacted]						

[a] Week 0/Day 1/Randomization Visit

[b] This assessment can be performed at either the Week 12 endoscopy visit **or** the Week 12 visit. NOTE: All other assessments are to be performed **only** at the Week 12 visit, except for the endoscopy and related procedures, which are to be performed within a 7-day window prior to the Week 12 (Day 85) visit.

AE = adverse event; DNA = deoxyribonucleic acid; ECG = electrocardiogram; [redacted] ES = endoscopic; ET = early termination; HBcAb = hepatitis B virus core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; hsCRP = high-sensitivity C-reactive protein; IBD = inflammatory bowel disease; [redacted] Ig = immunoglobulin; IgA = immunoglobulin A; IgE = immunoglobulin E; IgG = immunoglobulin G; IgM = immunoglobulin mu; [redacted] IP = investigational product; [redacted] PO = oral; [redacted] RB = rectal bleeding; [redacted] SAE = serious adverse event; [redacted] SF = stool frequency; TBNK = T cells, B cells, and natural killer cells; UC = ulcerative colitis; WOCBP = women of childbearing potential; [redacted]

In the event multiple procedures are required at a single time point, the ECG may be obtained up to 20 minutes earlier, vital signs may be obtained up to 20 minutes earlier or later, and clinical laboratory sample may be obtained up to 10 minutes earlier than the nominal time poin[redacted].

2.1.2 *Maintenance Period Activities and Assessments*

Table 3 Maintenance Period On-treatment Procedural Outline Up to Week 52 (IM011024)

Procedure/Visit Weeks (Days)	16 (113)	20 (141)	24 (169)	32 (225)	40 (281)	52 (365)	Notes
Visit window (± n days)	3	3	3	3	3	3	
Study Treatment							
Dispense clinical drug supplies (blinded)*	X	X	X	X	X		Section 5.1.3 *At Week 52, open-label IP will be dispensed to subjects who enter the OLE period.
Dispense clinical drug supplies (open-label)	X	X	X	X	X	X	Open-label IP will only be dispensed to subjects who have entered an open-label treatment arm during the maintenance period. Blinded IP must be dispensed to all other subjects (Section 5.1.3). At Week 52, open-label IP will only be dispensed to subjects who enter the OLE period.
Study treatment (blinded or open-label)	X----------X						See Notes above in "Dispense Clinical Drug Supplies."
Review study treatment compliance	X	X	X	X	X	X	Section 7.6
Safety Assessments							
Physical examination	X	X	X	X	X	X	General, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdominal, extremities, neurologic, skin, musculoskeletal
Physical measurement			X			X	Weight only
Vital signs	X	X	X	X	X	X	See Notes in the screening period procedures (Table 1).
Electrocardiogram						X	See Notes in the induction period procedures (Table 2).
Concomitant medication use	X	X	X	X	X	X	
Tobacco use	X	X	X	X	X	X	

Table 3 Maintenance Period On-treatment Procedural Outline Up to Week 52 (IM011024)

Procedure/Visit Weeks (Days)	16 (113)	20 (141)	24 (169)	32 (225)	40 (281)	52 (365)	Notes
Visit window (± n days)	3	3	3	3	3	3	
Monitor AEs	X	X	X	X	X	X	Monitoring for AEs will occur at every study visit (Section 9.2).
Monitor SAEs	X	X	X	X	X	X	Monitoring for SAEs will occur at every study visit (Section 9.2). All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (Section 8.3).
Laboratory Tests							
Hematology, chemistry, urinalysis, and coagulation	X	X	X	X	X	X	
HBV DNA (Week 12 responder arms)			X		X	X	For subjects with the following HBV serology at screening: HBsAg negative, HBcAb positive, HBV DNA undetectable (APPENDIX 8)
HBV DNA (Week 12 responder arms, with subsequent disease worsening and entry to the open-label treatment arm)	See Note						For subjects with the following HBV serology at screening: HBsAg negative, HBcAb positive, HBV DNA undetectable. Subjects who have a clinical response at Week 12 and who subsequently experience disease worsening and enter the open-label treatment arm: Obtain HBV DNA at the following 3 study visits, and thereafter according to the schedule for the Week 12 responder arm (see above). (APPENDIX 8)
HBV DNA (Week 12 nonresponder arm)	X	X	X	X	X		For subjects with the following HBV serology at screening: HBsAg negative, HBcAb positive, HBV DNA undetectable (APPENDIX 8)
Serum Igs	X		X	X	X	X	IgG, IgM, IgA, and IgE
TBNK panel			X			X	
Serum hsCRP	X	X	X	X	X	X	
Fasting lipid panel			X		X	X	See Notes in the induction period procedures (Table 2).

Table 3 Maintenance Period On-treatment Procedural Outline Up to Week 52 (IM011024)

Procedure/Visit Weeks (Days)	16 (113)	20 (141)	24 (169)	32 (225)	40 (281)	52 (365)	Notes
Visit window (± n days)	3	3	3	3	3	3	
Fasting glucose			X		X	X	See Notes in the induction period procedures (Table 2).
Pregnancy test (urine or serum)	X	X	X	X	X	X	WOCBP only (APPENDIX 4). If the urine pregnancy test is positive, a serum pregnancy test should be done for confirmation prior to discontinuing the subject. Study treatment should not be administered until the results of the confirmatory test are known.
[redacted]							
Efficacy Assessments							
[redacted]							

Table 3 Maintenance Period On-treatment Procedural Outline Up to Week 52 (IM011024)

Procedure/Visit Weeks (Days)	16 (113)	20 (141)	24 (169)	32 (225)	40 (281)	52 (365)	Notes
Visit window (± n days)	3	3	3	3	3	3	
[redacted]							
Review subject diary for SF and RB values	X	X	X	X	X	X	Prior to each scheduled visit, review subject diary to ensure SF and RB data have been entered daily. Prior to each scheduled visit at which Mayo scores are to be calculated, 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, and the subject should be counseled about proper study procedures.
Enter SF and RB subscores for Mayo score calculation						X	APPENDIX 9
Enter SF and RB subscores for disease worsening	X	X	X	X	X	X	Disease worsening is defined as an increase of the sum of the SF and RB subscores ≥ 2 compared to Week 12 (Table 5 and Sections 5.1.3.2 and 5.1.3.3)
Endoscopy (colonoscopy/sigmoidoscopy)						X	After bowel preparation, endoscopic examination will be performed within a 7-day window of the Week 52 (Day 365) visit.

Table 3 Maintenance Period On-treatment Procedural Outline Up to Week 52 (IM011024)

Procedure/Visit Weeks (Days)	16 (113)	20 (141)	24 (169)	32 (225)	40 (281)	52 (365)	Notes
Visit window (± n days)	3	3	3	3	3	3	
							Endoscopy is recommended at ET visits that occur between Weeks 16 and 52. If colonoscopy is conducted at screening assessment, every effort should be made to ensure colonoscopy is done at subsequent assessment. Screening and surveillance as per local guidelines may be completed during study related colonoscopy.
Colon histology [redacted]						X	See Notes in the induction period procedures (Table 2). [redacted]
[redacted]							
Efficacy/Mayo Scoring							
Modified Mayo score						X	Composite score of ES (central read), SF, and RB subscores. SF and RB subscores will be calculated using electronic subject diary data. See Section 9.1 and APPENDIX 9.
[redacted]							

AE = adverse event; DNA = deoxyribonucleic acid; ES = endoscopic; ET = early termination; [redacted] HBcAb = hepatitis B virus core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; hsCRP = high-sensitivity C-reactive protein; IBD = inflammatory bowel disease; [redacted] Ig = immunoglobulin; IgA = immunoglobulin A; IgE = immunoglobulin E; IgG = immunoglobulin G; IgM = immunoglobulin mu; [redacted] IP = investigational product; OLE = open-label extension; [redacted]

[redacted] RB = rectal bleeding; [redacted] SAE = serious adverse event; [redacted] SF = stool frequency; TBNK = T cells, B cells, and natural killer cells; UC = ulcerative colitis; WOCBP = women of childbearing potential; [redacted]

In the event multiple procedures are required at a single time point, the ECG may be obtained up to 20 minutes earlier, vital signs may be obtained up to 20 minutes earlier or later, and clinical laboratory sample may be obtained up to 10 minutes earlier than the nominal time poin [redacted].

2.1.3 Open-label Extension Period Activities and Assessments

Table 4 Open-label Extension Period On-treatment Procedural Outline Up to Week 104 (IM011024)

Procedure/Visit Weeks (Days)	56 (393)	60 (421)	64 (449)	78 (547)	90 (631)	104 (729)/ET	108 (757) or Post-treatment Follow-up	Unscheduled Visit a	Notes
Visit Window (± n days)	3	3	3	3	3	3			
Study Treatment									
Dispense clinical drug supplies (open-label)	X	X	X	X	X				
Study treatment	X----------X								
Review study treatment compliance	X	X	X	X	X	X		X	Section 7.6
Safety Assessments									
Physical examination	X	X	X	X	X	X	X	X	General, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdominal, extremities, neurologic, skin, musculoskeletal
Physical measurement			X			X	X		Weight only
Vital signs	X	X	X	X	X	X	X	X	See Notes in the screening period procedures (Table 1).
Electrocardiograms			X			X			See Notes in the induction period procedures (Table 2).
Concomitant medication use	X	X	X	X	X	X	X	X	
Tobacco use	X	X	X	X	X	X	X		
Monitor for AEs	X	X	X	X	X	X	X	X	Monitoring for AEs will occur at every study visit (Section 9.2).

Table 4 Open-label Extension Period On-treatment Procedural Outline Up to Week 104 (IM011024)

Procedure/Visit Weeks (Days)	56 (393)	60 (421)	64 (449)	78 (547)	90 (631)	104 (729)/ET	108 (757) or Post-treatment Follow-up	Unscheduled Visit a	Notes
Visit Window (± n days)	3	3	3	3	3	3			
Monitor for SAEs	X	X	X	X	X	X	X	X	Monitoring for SAEs will occur at every study visit (Section 9.2). All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (Section 8.3).
Laboratory Tests									See notes in the screening period procedures (Table 1) and Section 9.4.3.
Hematology, chemistry, urinalysis, and coagulation*	X	X	X	X	X	X	X	X	*Coagulation is to be collected at Week 56 only.
HBV DNA	X	X	X	X	X	X		X	For subjects with the following HBV serology at screening: HBsAg negative, HBcAb positive, HBV DNA undetectable (APPENDIX 8)
Tuberculosis testing	X							X	In accordance with standard testing (details are provided in Section 5.2 4) and Section 9.4.2)
Serum Igs				X		X		X	IgG, IgM, IgA, and IgE
TBNK panel				X		X		X	
Serum hsCRP	X	X	X	X	X	X		X	
Fasting lipid panel			X	X		X			Subjects are required to fast for ≥10 hours prior to the collection of specimens for the fasting lipid panel.

Table 4 Open-label Extension Period On-treatment Procedural Outline Up to Week 104 (IM011024)

Procedure/Visit Weeks (Days)	56 (393)	60 (421)	64 (449)	78 (547)	90 (631)	104 (729)/ET	108 (757) or Post-treatment Follow-up	Unscheduled Visit a	Notes
Visit Window (± n days)	3	3	3	3	3	3			
Fasting glucose			X	X		X			Subjects are required to fast for ≥ 10 hours prior to the collection of specimens for the fasting glucose panel.
Pregnancy test (urine or serum)	X	X	X	X	X	X	X	X	WOCBP only (APPENDIX 4). If the urine pregnancy test is positive, a serum pregnancy test should be done for confirmation prior to discontinuing the subject. Study treatment should not be administered until the results of the confirmatory test are known
[redacted]									

Table 4 Open-label Extension Period On-treatment Procedural Outline Up to Week 104 (IM011024)

Procedure/Visit Weeks (Days)	56 (393)	60 (421)	64 (449)	78 (547)	90 (631)	104 (729)/ET	108 (757) or Post-treatment Follow-up	Unscheduled Visit a	Notes
Visit Window (± n days)	3	3	3	3	3	3			
[redacted]									
Efficacy Assessments									
[redacted]									
Review subject diary for SF and RB values	X	X	X	X	X	X			Prior to each scheduled visit, review subject diary to ensure SF and RB data have been entered daily. Prior to each scheduled visit at which Mayo scores are to be calculated, 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, and the subject should be counseled about proper study procedures.
Enter SF and RB subscores for Mayo score calculation						X			See APPENDIX 9

Table 4 Open-label Extension Period On-treatment Procedural Outline Up to Week 104 (IM011024)

Procedure/Visit Weeks (Days)	**56 (393)**	**60 (421)**	**64 (449)**	**78 (547)**	**90 (631)**	**104 (729)/ET**	**108 (757) or Post-treatment Follow-up**	**Unscheduled Visit a**	**Notes**
Visit Window (± n days)	3	3	3	3	3	3			
Enter SF and RB subscores for disease worsening	X	X	X	X	X	X			Disease worsening is defined as an increase of the sum of the SF and RB subscores ≥ 2 compared to Week 12 (Table 5)
Endoscopy (colonoscopy/ sigmoidoscopy)						X			After bowel preparation, endoscopic examination will be performed within a 7-day window of the Week 104 (Day 729) visit. Endoscopy is recommended at ET visits that occur between Weeks 56 and 104. If colonoscopy is conducted at screening assessment, every effort should be made to ensure colonoscopy is done at subsequent assessment. Screening and surveillance as per local guidelines may be completed during study related colonoscopy.
Colon histolog [redacted]						X			See Notes in the induction period procedures (Table 2). [redacted]
[redacted]									
Efficacy/Mayo Scoring									

Table 4 Open-label Extension Period On-treatment Procedural Outline Up to Week 104 (IM011024)

Procedure/Visit Weeks (Days)	56 (393)	60 (421)	64 (449)	78 (547)	90 (631)	104 (729)/ET	108 (757) or Post-treatment Follow-up	Unscheduled Visit a	Notes
Visit Window (± n days)	3	3	3	3	3	3			
Modified Mayo score						X			Composite score of ES (central read), SF, and RB subscores. SF and RB subscores will be calculated using electronic subject diary data. See Section 9.1 and APPENDIX 9.
[redacted]									

[a] Additional procedures/assessments will be done per investigator's discretion

AE = adverse event; DNA = deoxyribonucleic acid; ECG = electrocardiogram; [redacted] EOT = end of treatment; ES = endoscopic; ET = early termination; HBcAb = hepatitis B virus core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; hsCRP = high-sensitivity C-reactive protein; IBD = inflammatory bowel disease; [redacted] Ig = immunoglobulin; IgA = immunoglobulin A; IgE = immunoglobulin E; IgG = immunoglobulin G; IgM = immunoglobulin M; [redacted] RB = rectal bleeding; SAE = serious adverse event; [redacted] SF = stool frequency; TBNK = T cells, B cells, and natural killer cells; [redacted] WOCBP = women of childbearing potential

In the event multiple procedures are required at a single time point, the ECG may be obtained up to 20 minutes earlier, vital signs may be obtained up to 20 minutes earlier or later, and clinical laboratory sample may be obtained up to 10 minutes earlier than the nominal time poin[redacted].

3 INTRODUCTION

3.1 Study Rationale

Study IM011024 is a Phase 2 randomized, double-blind study designed to assess the safety and efficacy of oral (PO) BMS-986165 6 mg twice daily (BID) in subjects with moderate to severe ulcerative colitis (UC). The primary objective is to assess the effect of BMS-986165 on the primary endpoint of clinical remission, which is defined as a modified Mayo score with the following subscores: stool frequency (SF) subscore ≤ 1 with ≥ 1 point decrease from baseline, rectal bleeding (RB) subscore = 0, and endoscopic (ES) subscore ≤ 1 (modified, excludes friability); at the end of the induction period (Week 12).

3.2 Background

Ulcerative colitis (UC) is a chronic inflammatory disease of the gastrointestinal tract that causes significant morbidity, impact on quality of life, and healthcare expenditures. 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, yet significant therapeutic challenges still remain with this and other inflammatory bowel diseases (IBDs). The current treatment regimens often fail, induce only a partial response, or are poorly tolerated. For example, studies with tumor necrosis factor inhibitors (TNFi) report 10% to 30% of subjects do not respond to their first treatment and 23% to 46% of subjects lose their response over time.[1] Therefore, there is still a critical unmet need for novel, safe, well-tolerated, and orally administered therapies with a different mechanism of action that can effectively modify the disease course.

Tyrosine kinase 2 (TYK2) is a protein involved in interleukin (IL)-12, IL-23, and Type I interferon (IFN) signaling, and it is required for the activation of downstream signaling pathways.[2] TYK2 is a widely expressed, non-receptor tyrosine kinase that catalyzes the phosphorylation of signal transducer and activator of transcription (STAT) proteins downstream of the receptors for the p40-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.[3, 4, 5] TYK2-dependent cytokines (eg, IL-12, IL-23 and Type I IFNs) are distinct from those dependent on closely related Janus kinase (JAK) family members JAK1, JAK3 (eg, IL-2, IL-15, IL-7, IL-6) or JAK2 (eg, erythropoietin, thrombopoietin, and granulocyte-monocyte colony-stimulating factor). Consequently, a TYK2 inhibitor is expected to have a highly differentiated profile from inhibitors of other JAK family kinases. TYK2 dependent pathways and the cytokine networks they modulate (eg, IL-23, IL-17, IFNα) 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.[6, 7] Inhibition of TYK2 is expected to provide therapeutic benefit for patients with UC for multiple reasons: 1) IL-12 and IL-23 have been implicated in the pathogenesis of

UC[8, 9, 10, 11]; 2) Biologic agents targeting IL-23p19 and IL-12/IL-23p40 cytokines have been shown to be efficacious in UC and CD, and ustekinumab targeting IL-12/IL-23p40 has been approved for the treatment of CD[12] and UC[13]; and 3) BMS-986165 has been shown to be efficacious in psoriasis, an IL-23-mediated disease, in a recent Phase 2 study.[14]

This Phase 2 study (IM011024) will provide safety and efficacy data for BMS-986165 in subjects with moderate to severe UC. Approximately 120 subjects will be randomized in this study. After a 28-day screening period, eligible subjects will be randomized in a 2:1 ratio to receive oral BMS-986165 6 mg BID or placebo BID during the induction period of 12 weeks. Randomization will be stratified based on corticosteroid use (yes/no) and prior exposure to biologics indicated for the treatment of UC (ie, no prior exposure, exposure to 1 biologic, or exposure to > 1 biologic). JAK inhibitors are considered as a biologic for stratification purposes. (Note: Failure or loss of response to JAK inhibitors is exclusionary, but prior exposure is not exclusionary.) The induction period lasts from Week 0 through Week 12. The primary outcome for the study will be assessed at Week 12 (Day 85).

The maintenance period lasts from Week 12 through Week 52. This study has a treat-through study design. Subjects who achieve clinical response at Week 12 (Day 85), with an appropriate safety profile, are eligible to continue into the maintenance period, during which they will continue to receive the same blinded study treatment regimen (BMS-986165 6 mg BID or placebo BID) that they received during the induction period. An open-label study arm is available within the maintenance period for subjects who do not achieve a clinical response at Week 12 and for subjects in the treat-through study arms who experience disease worsening between Week 13 and Week 52. The open-label extension period lasts from Week 52 through Week 104 and is available to subjects who complete per protocol assessments and who continue to derive clinical benefit from the investigational product (IP), as judged by the investigator, at that time.

A detailed description of the chemistry, pharmacology, efficacy, and safety of BMS-986165 is provided in the Investigator's Brochure (IB).[15]

3.2.1 Nonclinical Toxicology

The projected systemic exposure multiples presented in this section are expressed relative to the highest anticipated mean steady-state systemic exposure in human following oral dosing at 6 mg BID (mean AUC[0-24h] = 857 ng•h/mL) and 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 single-dose oral toxicity studies, BMS-986165 was well tolerated up to the highest administered doses of 75, 100, and 30 mg/kg in rats, dogs, and monkeys, respectively.

In repeat-dose oral toxicity studies in rats, BMS-986165 was tolerated at all doses (5, 15, or 75 mg/kg/day for 1 month; 2, 5, or 15 mg/kg/day for 3 months; and 5, 15, or 50 mg/kg/day for 6 months). All doses were associated with on-target pharmacodynamic (PD) effects. Systemic exposures to BMS-986165 increased approximately dose proportionally, with no substantial sex differences, accumulation, or loss of exposure in all studies. In the 6-month rat toxicity study with

2-month postdose recovery period, BMS-986165 was tolerated by rats for 6 months at oral doses ≤ 50 mg/kg/day (mean sex-combined AUC[0-24h] ≤ 117 µg•h/mL; ≤ 137-fold AUC multiple). Consistent with BMS-986165-mediated pharmacologic immunomodulation, the primary findings at ≥ 5 mg/kg/day were decreased peripheral blood lymphocyte counts, lymphoid cellularity in lymph nodes and spleen, and/or suppression of T-cell dependent antibody response (TDAR) to keyhole limpet hemocyanin (KLH) immunogen. No BMS-986165-related infections were noted. Additional BMS-986165-related findings considered adverse at ≥ 15 mg/kg/day (mean sex-combined AUC[0-24h] ≥ 19.7 µg•h/mL; ≥ 23-fold AUC multiple) included decreased mean body weights and body weight gains, decreased red blood cell (RBC) mass parameters, reticulocytes, platelets, and bone marrow cellularity. All BMS-986165-related changes were reversible except for the decreased food consumption and body weights, decreased spleen weights, and nonadverse increased incidence of macrophage aggregation in the lung. In conclusion, based on the absence of adverse findings, the NOAEL was considered to be 5 mg/kg/day (mean sex-combined AUC[0-24h] 4.31 µg•h/mL; 5-fold AUC multiple).

In repeat dose (≤ 3 months) oral toxicity studies in monkeys, BMS-986165 was well tolerated at all doses (0.5, 1.5, or 5 mg/kg/day for 1 month; 0.75, 1.5, or 5 mg/kg/day for 3 months). All doses were associated with on-target PD effects. Exposures to BMS-986165 increased approximately dose proportionally, with no substantial sex differences, loss of exposure or accumulation noted. There were no BMS-986165-related mortalities at any dose during any monkey toxicity studies. In the 9-month monkey toxicity study (doses of 0, 1, 3, or 10 mg/kg/day; the 10-mg/kg dose was changed to 5 mg/kg due to observed toxicity) with 2 month postdose recovery period, the principal BMS-986165-related findings at all doses included generally dose-dependent skin changes, which were likely infectious in etiology, and secondary to BMS 986165-mediated pharmacologic immunomodulation. The various skin changes (swollen, dry, lesion, flaking, papule, red, white, scab) were located throughout the body, and could be seen as early as Week 1 in some monkeys. The skin changes were noted at necropsy as abrasions, discoloration, foci, nodule, scab, scale, and/or thick, and correlated with microscopic findings in the epidermis (hyperkeratosis, erosion, and/or crusts) and/or dermis (mixed cell infiltrates and/or subacute inflammation). Although no definitive microbial pathogens were confirmed as the causative agents, the skin changes were considered likely infectious in etiology, as they improved following antibiotic and antiseptic treatments, and were present in the context of BMS-986165 mediated immunomodulation. Additional findings at all doses included transient slight to severe liquid feces, which improved clinically with veterinary treatments, dose-dependent decreased RBC mass parameters, and suppression of TDAR to KLH, and at ≥ 3 mg/kg/day (mean sex-combined AUC[0-24h] ≥ 15.4 µg•h/mL; ≥ 18-fold AUC multiple) decreased activity, hunched posture, pale gums, and increased body temperature, with decreased platelets and occult blood in urine at 10 followed by 5 mg/kg/day (mean sex-combined AUC[0-24h] 30.7 µg•h/mL; 36-fold AUC multiple). Following the 2-month recovery period, all BMS-986165-related findings were partially or fully reversible. The NOAEL was not identified due to the presence of adverse skin findings at doses ≥ 1 mg/kg/day (mean sex-combined AUC[0-24h] ≥ 3.38 µg•h/mL; ≥ 4-fold AUC multiple). Although the NOAEL was not determined in this study, the skin findings did not result in any unscheduled

euthanasia or preterminal deaths, were clinically monitorable, manageable with veterinary treatments, and trended toward reversibility during the 2-month post-dose recovery.

The totality of the toxicity assessments demonstrates that BMS-986165, at doses associated with robust PD effects, has a favorable dose-related safety profile in both rodents and nonrodents, toxicological findings that are either fully reversible or trending toward recovery, and are clinically monitorable and manageable.

Additional details regarding the nonclinical toxicology results are provided in the current IB.[15]

3.2.2 Early Clinical Experience

BMS-986165 has a favorable pharmacokinetic (PK) profile characterized by consistent oral absorption, dose-related increase in exposure and no evident time-dependency. The oral absorption is rapid with maximal plasma concentrations achieved in 1 to 2 hours and a high absolute bioavailability (approximately 99% with a 12 mg oral dose). No significant interaction was observed when BMS-986165 was administered with food (high fat/high calorie meal) or with pH-modulating agents like famotidine. A study is currently underway to evaluate the effect of rabeprazole on BMS-986165. BMS-986165 is moderately bound to plasma proteins and is therefore unlikely to be displaced by drugs that have a greater binding affinity.

The terminal half-life of BMS-986165 is ~10 to 15 hours and that of the active metabolite (BMT-153261) is ~12 hours. BMS-986165 accumulates ~1.5-fold with repeated administration. BMS-986165 is eliminated via multiple well-balanced mechanisms including Phase I and II metabolism along with direct renal and possibly fecal elimination. Additionally, multiple enzymes (CYP1A2, CES2, and UGT1A9) are involved in its elimination. The active metabolite, BMT-153261, whose whole blood potency is 50% of the parent, is formed via CYP1A2 metabolism. The formation of the BMT-334616 metabolite is mediated by UGT1A9. The formation of the BMT-158170 metabolite is mediated by CES2.

The clinical data available to date supporting the safety, PK, and PD of BMS-986165 are from 8 Phase 1 studies of BMS-986165 in healthy volunteers (IM011002, IM011015, IM011016, IM011025, IM011031, IM011039, IM011048 and IM011071) and a Phase 2 study in adult subjects with moderate to severe plaque psoriasis (IM011011). In addition to the current study, Phase 2 studies in CD (IM011023), psoriatic arthritis (IM011084), SLE (IM011021, IM011074), and lupus nephritis (IM011073), and Phase 3 studies in psoriasis (IM011046, IM011047, IM011065, IM011066, IM011075) are currently ongoing.

Study IM011002 (Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, PK, and PD of BMS-986165 in Healthy Subjects) used 1, 3, 10, 20, and 40 mg doses for the single-dose part, and 2, 4, 6, or 12 mg BID or 12 mg every day (QD) for 14 days for the multiple ascending dose part. All reported adverse events (AEs) were mild or moderate in severity, and approximately half of subjects overall had at least 1 AE that was considered potentially related to study treatment. The most frequently reported AEs with single dosing were headache and dyspepsia. The most frequently reported AEs with multiple dosing were headache, skin rash and acne, and upper respiratory tract infection. Dose-limiting AEs in the form of skin rashes and

acneiform lesions were observed. These observations were largely reported for subjects in the 24 mg/day (12 mg BID) group and were reported for most subjects dosed at this level. These AEs were mild or moderate in nature and resolved with topical treatments (corticosteroid applications, benzoyl peroxide cream, clindamycin solution, chlorhexidine ointment). All events requiring treatment responded appropriately, and rarely resulted in discontinuation of study drug. Overall, BMS-986165 was found to have an acceptable safety profile in healthy volunteers, and the acneiform lesions that were seen at the highest doses were manageable with topical treatments, were reversible, and were not serious or severe.

The study to evaluate the cardiodynamic effects of BMS-986165 was conducted at 12 mg and 36 mg, and included a positive control (moxifloxacin) and placebo. The study demonstrated that BMS-986165 at these doses does not have a clinically relevant effect on electrocardiogram (ECG) parameters. Using concentration-QTc analysis, a QTcF effect (ΔΔQTcF) exceeding 10 msec can be excluded up to BMS-986165 plasma concentrations of ~500 ng/mL. Assay sensitivity was demonstrated by the QT effect of moxifloxacin with a statistically significant slope of the concentration-ΔΔQTc relationship and the lower bound of the 2-sided 90% confidence interval (CI) of the predicted effect at the observed geometric Cmax above 5 msec. The study therefore constitutes a negative TQT study.

Study IM011011 was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel group Phase 2 study to evaluate the clinical efficacy, safety, and PD of BMS-986165 after 12 weeks of treatment with 4 weeks' follow-up in 267 subjects with moderate to severe plaque psoriasis.[14] The study met its primary and secondary efficacy endpoints of clinically relevant improvement in Psoriasis Activity and Severity Index (PASI) and static Physician Global Assessment (PGA) scores for 4 of the 5 doses investigated (only the 3 mg every other day dose did not meet the primary endpoint). Treatment with BMS-986165 at doses of > 3 mg once daily were associated with significantly greater clinical responses compared with placebo at Week 12, as measured by a ≥ 75% reduction in the Psoriasis Area and Severity Index (PASI 75) score. At Week 12, the percentage of patients with a PASI 75 response was 7% (3 of 45 patients) with placebo, 39% (17 of 44 patients) with 3 mg QD, 69% (31 of 45 patients) with 3 mg BID, 67% (30 of 45 patients) with 6 mg BID, and 75% (33 of 44 patients) with 12 mg QD (P value < 0.001 for each comparison). Treatment with BMS-986165 at doses > 3 mg BID was also associated with a numerically greater proportion of patients achieving ≥ 90% reduction in PASI score (PASI 90), compared with placebo at Week 12. The most common AEs reported overall were nasopharyngitis, upper respiratory tract infection, diarrhea, and nausea. The majority of the AEs reported in the study were mild or moderate in intensity. AEs of acneiform dermatitis were observed in a few subjects that appeared to be dose-related, and most were reported for subjects at the 2 highest dose groups. Most of the lesions were completely resolved (a few were almost completely resolved) with topical treatments and did not result in discontinuation of the study treatment. In summary, BMS-986165 has demonstrated promising clinical efficacy in the treatment of subjects with moderate to severe plaque psoriasis.[14]

3.3 Benefit/Risk Assessment

BMS-986165 is being developed as an oral treatment for UC, CD, psoriasis, psoriatic arthritis, SLE, and lupus nephritis. Based on its mechanism of action as an inhibitor of TYK2-mediated signaling pathways downstream of well-characterized pharmaceutical targets for the treatment of UC, the IL-12/T_H1 and IL-23/T_H17 axis, it is predicted that subjects with UC may benefit from treatment with BMS-986165. Further, the first-in-human (FIH) study of BMS-986165 (Study IM011002) in healthy subjects demonstrated IL-12 signaling inhibition by BMS-986165. These data suggest that subjects with UC are likely to derive clinical benefit after treatment with BMS-986165.

The effects of TYK2 inhibition by BMS-986165 have been documented in pharmacology studies, and the potential for benefit in UC is supported through in vivo studies showing BMS-986165 is efficacious in murine models for lupus, colitis, and psoriasis. In all models, efficacy was observed at doses providing continuous coverage of the mouse whole blood half-maximal inhibitor concentration (IC50) value over the dosing interval.

The proposed dosing regimen reflects implementation of appropriate safety margins and is within the range of doses tested in the FIH study and within exposure margins based on comparisons of systemic exposure and body surface area. The dose of BMS-986165 6 mg BID is also being investigated in clinical trials for other indications.

BMS-986165 was safe when investigated in the FIH study IM011002 with healthy subjects at single doses up to 40 mg and multiple doses of 24 mg/day (12 mg BID) for 14 days. However, BMS-986165 did elicit dose-dependent, mild-to-moderate acneiform skin reactions particularly after multiple doses of 24 mg/day (12 mg BID). Importantly, all skin-related AEs were mild or moderate, with no signs or symptoms of circulatory impairment or respiratory distress in these subjects; required topical treatment in only a few cases, responded quickly and appropriately when treatment was required, and rarely required discontinuation of study drug. Based on these findings, the highest proposed dose for the Phase 2 study IM011024 in subjects with UC will be 6 mg BID. In case of the occurrence of skin-related events, subjects may receive treatment per standard practice according to investigator's discretion and followed until resolution.

The risk for PK drug-drug interactions (DDIs) with BMS-986165 was assessed using Food and Drug Administration (FDA) and European Medicines Agency guidance documents for DDI assessments. At the maximum concentrations expected in this study (in portal vein or systemic circulation, as appropriate), the potential for DDIs involving cytochrome P450 (CYP450) enzymes and most transporters is low. BMS-986165 has low turnover in in vitro metabolism studies, and a number of enzymes are involved in its metabolism. Additionally, BMS-986165 is not an inhibitor or inducer of CYP450 enzymes at the expected clinical concentrations. Therefore, the potential for DDIs resulting from CYP450 inhibition or induction is low. BMS-986165 is a breast cancer resistance protein (BCRP) inhibitor with an in vitro IC50 = 0.31 μM. However, due to overlapping substrate specificity between BCRP and other transporters not affected by BMS-986165 at the expected concentrations, the impact of BMS-986165 on the exposures of potential comedications that are BCRP substrates, such as rosuvastatin, was expected to be low. Based on data from

IM011015 DDI study, co-administration of 12 mg QD BMS-986165 and 10 mg rosuvastatin had no impact on the exposure of rosuvastatin. Data from a study evaluating the impact of BMS-986165 in women taking oral contraceptives found no impact on exposure of ethinyl estradiol or norethindrone.

Because BMS-986165 is a potential immunomodulator and in line with standard practice for immunosuppressive therapies, this study has been designed with study visits that allow for close monitoring and with inclusion/exclusion criteria aimed at minimizing the risk for serious infections and malignancies.

Additionally, the current study (Study IM011024) has been designed to closely monitor study subjects' safety throughout the duration of the study. At the investigator's discretion, rescue therapy can be initiated (Section 5.1.5), or dosing of study medication can be discontinued at any time during the study (Section 8.1). In addition to a comprehensive monitoring of safety with oversight by the investigators, medical monitors from both BMS and the partner organization, [redacted] and the BMS Safety Physician, the safety of subjects will also be monitored by an independent Data Monitoring Committee (DMC).

In summary, existing preclinical data and clinical experience in healthy subjects in combination with the design and dose selected for this Phase 2 study indicate an overall favorable benefit-risk assessment of investigating BMS-986165 as an oral treatment for subjects with UC.

Additional detailed information on the known and expected benefits and risks and reasonably anticipated AEs of BMS-986165 is provided in the IB.[15]

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 (refer to 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 AEs of interest (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 discontinuation of IP in the context of clinical suspicion of COVID-19, or a positive diagnostic test for SARS-CoV-2.

This also includes criteria for potentially recommencing IP upon complete resolution of a COVID-19 infection, confirmed by a negative diagnostic test (Section 8.2.1).

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).

4 OBJECTIVES AND ENDPOINTS

Primary and secondary endpoints and related study terms are defined in Table 5.

Table 5 Primary and Secondary Endpoint and Related Study Term Definitions

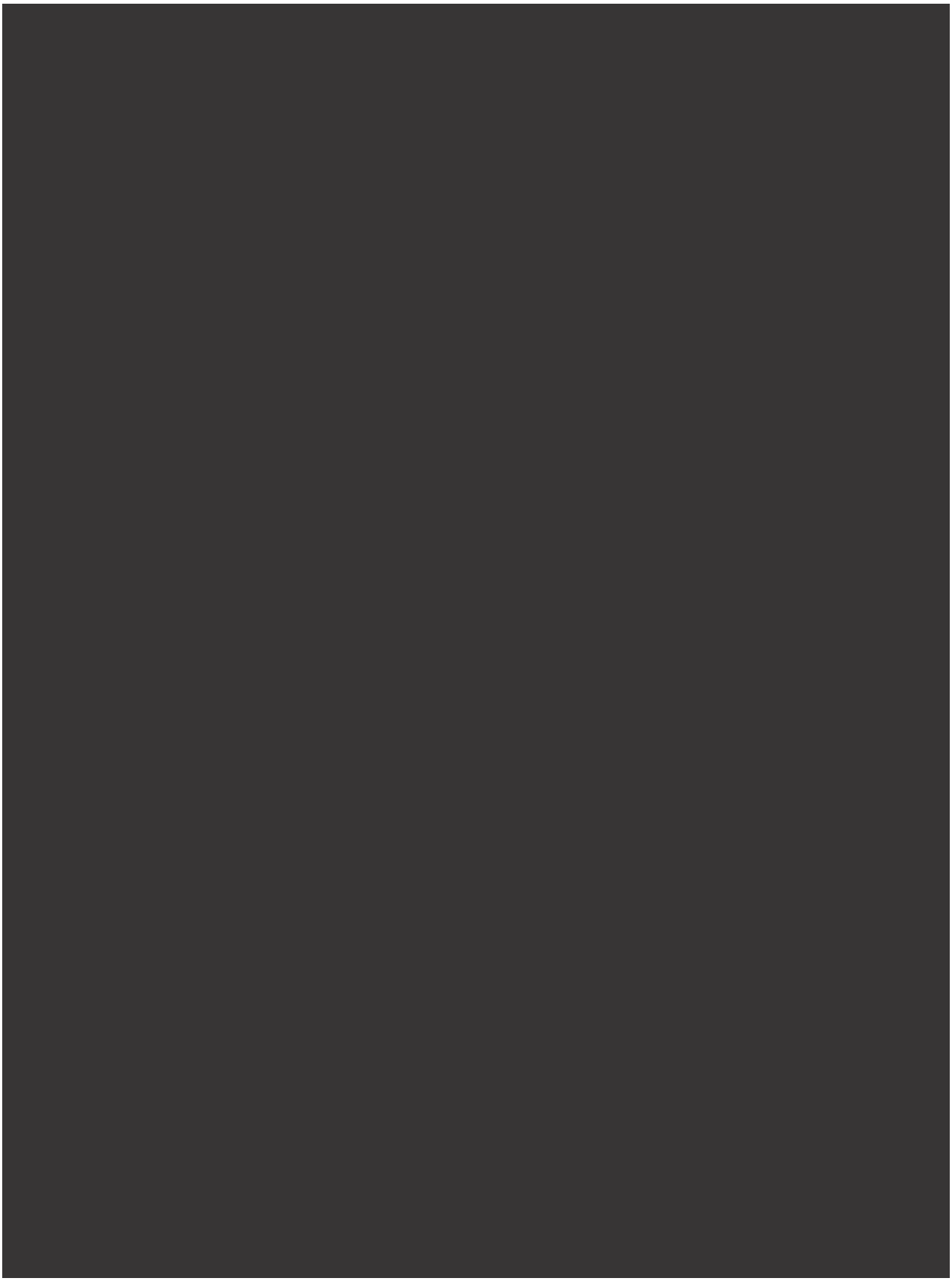
Endpoint	**Definition**
Primary	
Clinical remission (modified Mayo score)	A modified Mayo score[a] with the following: • SF subscore ≤ 1, with ≥ 1 point decrease from baseline, **and** • RB subscore = 0, **and** • ES subscore[b] ≤ 1 (modified, excludes friability)
Secondary	
Clinical response[c]	• A decrease from baseline in the modified Mayo score[a] of ≥ 2 points, **and** • A decrease from baseline in the modified Mayo score[a] ≥ 30%, **and** • A decrease in RB subscore of ≥ 1 point or absolute RB subscore ≤ 1
Endoscopic response	Mayo ES subscore[b] ≤ 1
Histologic improvement	Geboes score ≤ 3.1
Study Term	**Definition**
Disease worsening	An increase of the **sum** of the SF and RB subscores ≥ 2 compared to Week 12

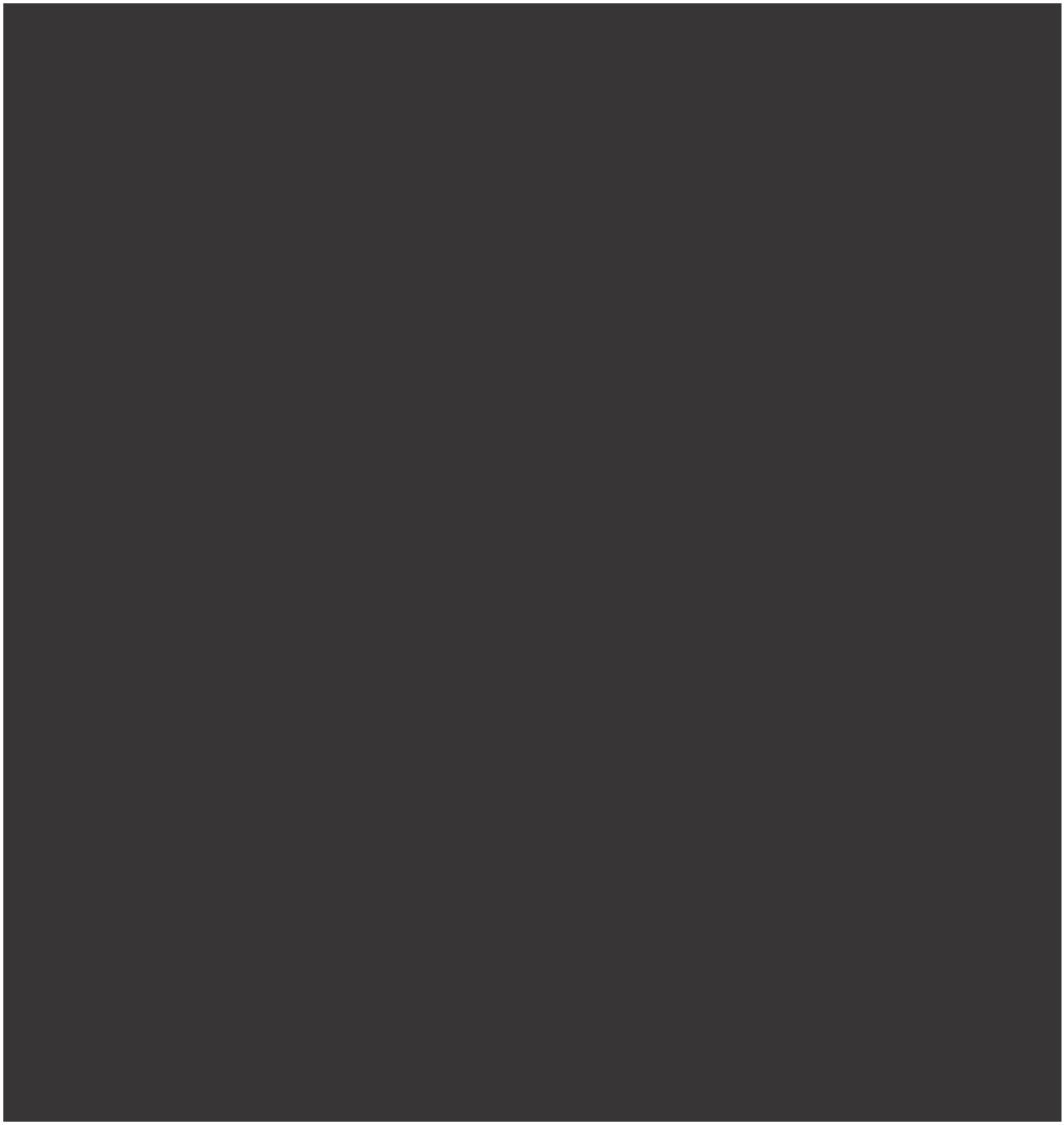
ES = endoscopic; RB = rectal bleeding; SF = stool frequency

[a] The modified Mayo score (0 to 9 points) is the sum of 3 components: the SF, RB, and ES subscores (see Section 9.1 and APPENDIX 9).

[b] Obtained from centrally read endoscopy (Section 9.1.1)

[c] Efficacy analyses will use the modified Mayo score calculated with centrally read endoscopy. At Week 12, treatment assignment in the maintenance period will be determined using clinical response based on the modified Mayo score calculated with a locally read endoscopy (Section 9.1.1).





The study objectives and endpoints are in Table 7.

Additional endpoints and analyses will be described in the statistical analysis plan (SAP), the Endoscopy Image Review Charter or the Histopathology Image Review Charter.

Table 7 Study Objectives and Endpoints

Objectives	Endpoints
Efficacy	
Primary	
• To assess the effect of BMS-986165 on clinical remission at the end of the induction period	• Clinical remission (modified Mayo score) at Week 12
Secondary	
• To assess the effect of BMS-986165 on clinical response at the end of the induction period	• Clinical response at Week 12
• To assess the effect of BMS-986165 on endoscopic response at the end of the induction period	• Endoscopic response at Week 12
• To assess the effect of BMS-986165 on histologic improvement at the end of the induction period	• Histologic improvement at Week 12
Safety	
• To assess the safety and tolerability of BMS-986165 in subjects with moderate to severe UC	• Number and proportion of subjects experiencing AEs, SAEs, AEs leading to study discontinuation, and AEs of interest (AEIs) • Number and proportion of subjects experiencing abnormalities in laboratory testing, ECG, physical examination, and vital sign parameters over time
[redacted]	

Table 7 Study Objectives and Endpoints

Objectives	Endpoints
[redacted]	

Table 7 Study Objectives and Endpoints

Objectives	Endpoints
[redacted]	

Table 7 Study Objectives and Endpoints

Objectives	Endpoints
[redacted]	

Table 7 Study Objectives and Endpoints

Objectives	Endpoints
[redacted]	

Table 7 Study Objectives and Endpoints

Objectives	Endpoints
[redacted]	

AE = adverse event; AEI = adverse event of interest; ECG = electrocardiogram; [redacted] hsCRP = high-sensitivity C-reactive protein; IgG = immunoglobulin G; [redacted] RB = rectal bleeding; SAE = serious adverse event; SF = stool frequency; UC = ulcerative colitis; [redacted]

5 STUDY DESIGN

5.1 Overall Design

This is a Phase 2 randomized, double-blind, placebo-controlled, multicenter clinical trial to assess the safety and efficacy of BMS-986165 6 mg BID in subjects with moderate to severe active UC. The primary objective is to assess the effect of BMS-986165 on clinical remission at Week 12.

The duration of study participation is approximately 112 weeks (784 days) in 5 periods, as follows:

- Screening Period: up to 4 weeks (28 days; Section 5.1.1)
- Induction Period: 12 weeks (84 days; Section 5.1.2)
- Maintenance Period: 40 weeks (280 days; Section 5.1.3)
- Open-label Extension Period: 52 weeks (364 days; Section 5.1.4)
- Post-treatment Follow-up Period: 4 weeks (28 days; Section 5.1.4.1)

Physical examinations, vital sign measurements, 12-lead ECG, and clinical laboratory evaluations will be performed at selected times throughout the study, as indicated in the Schedule of Activities (Section 2). Subjects will be closely monitored for AEs throughout the study. [redacted]

Clinical efficacy is assessed using the modified Mayo score, which uses a combination of patient-reported outcomes (PRO) (SF and RB captured by the subject in their electronic diary) and endoscopic assessments (centrally read endoscopy). Subjects should receive and be trained on an electronic patient diary at the screening visit. Subjects are expected to complete the electronic diary on a daily basis through the screening period, and then throughout their ongoing participation in the study.

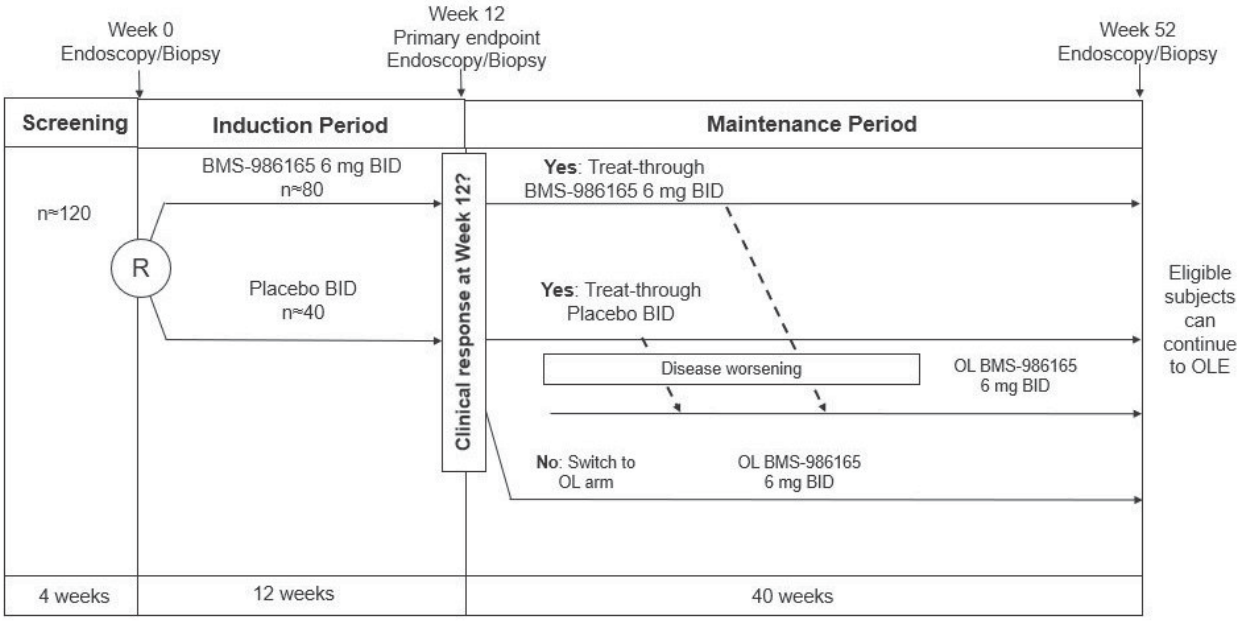
Endoscopic (colonoscopy/sigmoidoscopy) evaluations and collection of colonic tissue biopsies will be performed during the screening period, at Weeks 12, 52, and 104, at unscheduled visits (if clinically indicated) and at early termination (ET) visits that occur at least 4 weeks after the last per protocol-required endoscopy. Endoscopic assessment is required for ET visits occurring between Week 4 and Week 12 (induction period) and optional but recommended for ET visits occurring between Weeks 16 and Week 52 (maintenance period), and between Weeks 56 and 104 (open-label extension [OLE] period). 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 post-treatment follow-up period (Section 5.1.4.1).

An independent DMC will be instituted to assess safety data by unblinded treatment group (Section 5.1.7).

The study design schematics for the induction/maintenance periods and the open-label extension period are in Figure 1 and Figure 2, respectively.

Figure 1 **Study Design Schematic: Induction and Maintenance Periods**

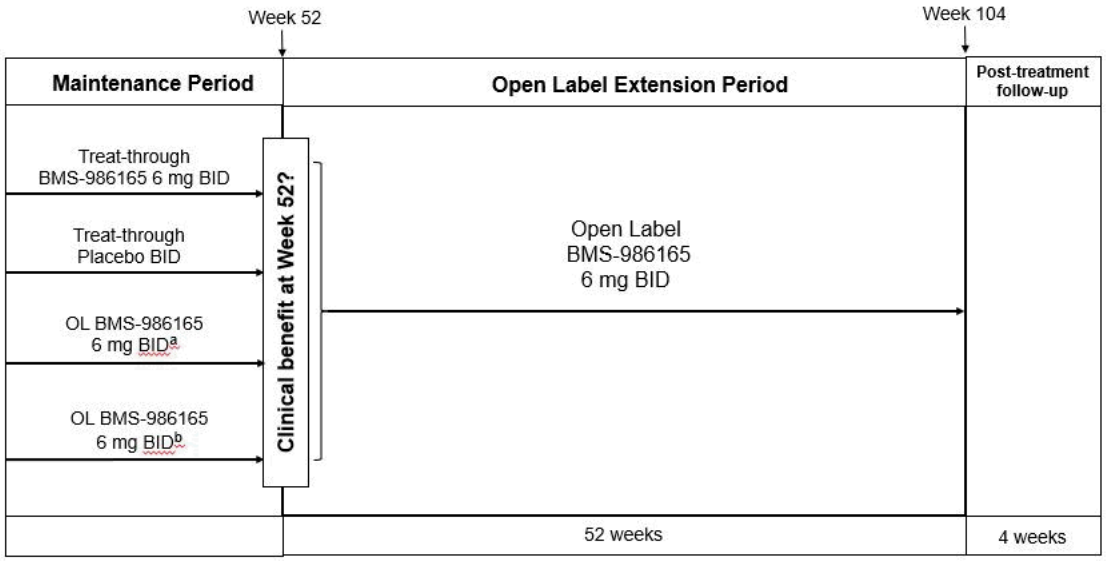


BID = twice daily; OL = open-label; OLE = open-label extension; R = randomization

At Week 12, clinical response is determined using the modified Mayo score (see Table 5and Section 9.1.1). Subjects who achieve clinical response at Week 12 and continue into the maintenance period will continue to receive their double-blind treatment from the induction period. Subjects who subsequently experience disease worsening (Table 5) can enter the Week 12 responder open-label arm at any time from Week 13 through Week 52.

Subjects who do not achieve clinical response at Week 12 are eligible to enter the Week 12 nonresponder open-label arm.

Figure 2 **Study Design Schematic: Open-label Extension Period**



BID = twice daily; IP = investigational product; OL = open-label

a Subjects in this arm are those who achieved clinical response at Week 12 of the induction period, but they subsequently lost clinical response to IP between Week 13 and Week 52 of the maintenance period and switched to the Week 12 responder open-label arm (Section 5.1.3.2).

b Subjects in this arm are those who did not achieve clinical response at Week 12 of the induction period and switched to the Week 12 nonresponder open-label arm.

5.1.1 Screening Period

Once subjects sign the informed consent form (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 (Table 1) to determine if they continue to meet eligibility criteria (Section 6).

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

Subjects are expected to complete a daily diary throughout the screening period. SF and RB data recorded in the daily diary contribute to disease activity assessment throughout the study. The minimum daily diary requirements for modified Mayo score calculations are outlined in APPENDIX 9. To ensure that a subject can be successfully randomized, sites should confirm prior to each study visit that subjects are successfully entering and uploading daily diary data (see APPENDIX 9 and Table 26).

A screening endoscopy (sigmoidoscopy or colonoscopy) will be performed to determine if a subject has active intestinal inflammation (assessed by central reading) and to obtain biopsies for histological [redacted] assessment [redacted]. In order to avoid unnecessary endoscopies, best practice is to complete other screening investigations first, and to check the results of those

investigations for abnormalities before a subject begins bowel preparation for endoscopy. This ensures that a subject continues to be potentially eligible for the study before they commence bowel preparation. Subjects must be randomized within 14 calendar days of the screening endoscopy.

Note: a **full colonoscopy will be required** 1) if normal margins are not apparent from sigmoidoscopy or proximal colonic involvement is suspected; or 2) in subjects with a history of UC > 8 years, if endoscopy was not performed in the prior 12 months.

When operationalizing the screening period, please consider the following:

i. Study procedures cannot be performed before the subject signs the ICF. Once the ICF is signed at the screening visit, sites should consider obtaining a medical history, vital signs and physical examination, and other per protocol screening visit investigations such as blood tests, ECG, and chest x-ray (if required); giving the subject the electronic study diary and training on the diary; and also scheduling the screening endoscopy and Week 0 (Day 1) visit. Sites should consider the turnaround time for the centrally read endoscopy result when scheduling the endoscopy and Week 0 (Day 1) visits.

ii. The study diary requirements for the calculation of the modified Mayo score are outlined in APPENDIX 9. To ensure that a modified Mayo score can be determined, sites should confirm prior to each study visit that subjects are successfully entering and uploading daily diary data and that an appropriate number of valid entry days is available for the calculation of the SF and RB subscores (APPENDIX 9).

iii. Sites should check the results of screening investigations to confirm that a subject remains potentially eligible for inclusion before they commence bowel preparation for the screening endoscopy.

iv. Once the screening endoscopy is performed, subjects must be randomized within 14 days.

To be eligible for randomization, subjects must have had an inadequate response, loss of response, or intolerance to a standard treatment course of 1 or more of the medications outlined in the Inclusion Criteria in Section 6.1 2) Type of Subject and Target Disease Characteristics.

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 as defined in Section 6.1 must be recorded in source documents and the UC medications electronic case report form (eCRF).

The medications outlined in APPENDIX 7 must be discontinued prior to randomization on Week 0 (Day 1) and include immunomodulators (eg, methotrexate [MTX], 5-azathioprine [AZA], 6-mercaptopurine [6-MP]) and biologic medications (eg, infliximab, adalimumab, golimumab, vedolizumab, and ustekinumab). To be eligible for randomization, subjects taking the medications listed in APPENDIX 7 must discontinue them prior to randomization and comply with the required washout periods listed in APPENDIX 7.

Corticosteroids (prednisone ≤ 20 mg QD PO or equivalent [APPENDIX 6] or budesonide ≤ 9 mg QD PO Multi-Matrix System [MMX®] colonic-delivery technology; eg, Uceris® or equivalent), probiotics, and 5-aminosalicylic acids (5-ASAs) are allowed, subject to dose stabilization rules outlined in Section 6.3.

5.1.1.1 Therapeutic Drug Monitoring

Some subjects will require adequate washout of biologics to be eligible for randomization. Therapeutic drug monitoring (TDM) 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 on a TDM assay, performed either in routine clinical practice or during the screening period: (i) infliximab, (ii) adalimumab, (iii) golimumab, (iv) vedolizumab (> 14 weeks of vedolizumab therapy), or (v) ustekinumab (> 12 weeks of ustekinumab therapy). If a TDM assay is used to waive the washout period for any of the biologics listed above, the result of the TDM assay must be available in source documents, **and** the subject cannot receive another dose of that biologic prior to randomization.

5.1.2 Induction Period

On Week 0 (Day 1) of the induction period, subjects who have completed the screening procedures and met the inclusion/exclusion criteria will be randomized in a 2:1 ratio to receive BMS-986165 6 mg BID or placebo BID, respectively (see Section 6.3 for randomization criteria). During the induction period, subjects will receive study treatment over 12 weeks. Allowed concomitant medication for UC (eg, 5-ASAs, probiotics, oral corticosteroids) must remain at the prerandomization stable dose, unless reduced or discontinued due to an AE. Corticosteroid use during the induction period is detailed in Section 5.1.5.1.

Endoscopy for the assessment of efficacy at Week 12 will occur within a window of 7 days prior to the Week 12 visit. The subject study diary requirements for the calculation of the modified Mayo score are outlined in APPENDIX 9.

At Week 12, the centrally read endoscopy will be used for determination of efficacy within the study. However, clinical response calculated using the locally read endoscopy will be used to determine treatment assignment of a subject in the maintenance period (See Section 9.1.1).

Rescue therapy is not offered during the induction period. If, in the opinion of the investigator, a subject requires rescue therapy for UC during the induction period, the subject must permanently discontinue study treatment (Section 8.1), complete an ET visit, and enter the post-treatment follow-up period (see Section 5.1.6 and Section 5.1.4.1). Endoscopy is required at the ET visit for subjects who permanently discontinue study medication between Weeks 4 and 12. Discontinuation criteria are further detailed in Section 8.

Some study-related procedures may be performed on the day of endoscopy prior to the Week 12 visit. Please refer to the Schedule of Activity table (Table 2) for timing of specific Week 12 assessments.

Subjects who discontinue study treatment will remain in the study and 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 subject to provide this information (see Section 8).

5.1.3 Maintenance Period

The maintenance period will last up to 40 weeks.

During the maintenance period, subjects who were on a stable dose of corticosteroids must begin a dose taper by Week 14. See Section 5.1.5.2 and Table 8 for recommended tapering schedules.

Subjects who require prohibited rescue treatment for UC (ie, outside of the protocol allowance; see Section 5.1.6 and Section 7.7.1) during the maintenance period must permanently discontinue study treatment, complete an ET visit, and enter post-treatment follow-up (Section 5.1.4.1). An exit endoscopy is recommended for all subjects who undergo an ET visit between Weeks 16 and 52 (i.e. exit endoscopy is not required for ET visits within 4 weeks of the Week 12 endoscopy).

5.1.3.1 Week 12 (Day 85), End of Induction Period

Subjects who achieve a protocol-defined clinical response at Week 12 (assessed using the modified Mayo score with a locally read endoscopy) are eligible to enter the maintenance period and continue to receive the same blinded study regimen they received in the induction period. Blinded study treatment will continue until the subject completes Week 52, experiences disease worsening (Section 5.1.3.2) and switches to open-label treatment, or discontinues from the study.

At Week 12, subjects who do not achieve a clinical response will be offered the opportunity to switch to open-label BMS-986165 treatment (6 mg BID PO), regardless of the initial treatment regimen received during the induction period. Subjects receiving corticosteroids during the induction period who enter this open-label treatment arm must initiate a corticosteroid taper by Week 24, or earlier. See Section 5.1.5.3 and Table 8 for recommended tapering schedules.

5.1.3.2 Week 12 Responders: Disease Worsening in the Maintenance Period

Subjects who achieve clinical response at Week 12 and continue on blinded study treatment will be judged to have disease worsening (as defined in Table 5) if they experience a worsening of clinical disease activity between Weeks 13 and 52.

These subjects are eligible to enter the Week 12 responder open-label arm, during which they will receive BMS-986165 6 mg BID PO through Week 52.

Subjects who switch to open-label treatment and experience disease worsening based on the definition in Table 5 should discontinue from the study (Section 8.1). Investigators should have a low threshold for evaluating whether these subject should continue based on their clinical judgment.

5.1.3.3 Week 12 Nonresponders: Disease Worsening in the Maintenance Period

Subjects who do not achieve clinical response at Week 12 are eligible to enter the open-label BMS-986165 6 mg BID PO arm and continue into the maintenance period through Week 52. Alternatively, nonresponder subjects may be discontinued from the study per investigator discretion.

Nonresponder subjects who switch to open-label treatment and experience disease worsening between Weeks 13 and 52 (Table 5) should discontinue from the study (Section 8.1).

See Section 5.1.5.3 regarding subjects receiving corticosteroids in this open-label treatment arm who experience disease worsening at Week 36 (and thereafter).

5.1.3.4 Week 52 (Day 365): End of Maintenance Period

Endoscopy for the assessment of efficacy at Week 52 will occur within a window of 7 days prior to the Week 52 visit. The subject study diary requirements for the calculation of the modified Mayo score are outlined in APPENDIX 9.

5.1.4 Open-label Extension Period

Subjects who continue to safely derive a clinical benefit from IP at Week 52, as judged by the investigator, are eligible to receive BMS-986165 6 mg BID PO in the open-label extension period. The open-label extension period will last 52 weeks, to Week 104. Study visits in this period occur every 4 weeks for the first 3 months, then approximately every 3 months afterwards, to Week 104.

Subjects in the open-label extension period who meet any of the discontinuation criteria as defined in Section 8.1 should discontinue from the study (Section 8.2). An exit endoscopy is recommended for all subjects who undergo an ET visit between Weeks 56 and 104.

The final endoscopy for the assessment of efficacy at Week 104 will occur within a window of 7 days prior to the Week 104 visit. The subject study diary requirements for the calculation of the modified Mayo score are outlined in APPENDIX 9.

5.1.4.1 Post-treatment Follow-up

Subjects who complete the Week 104 visit, or who permanently discontinue study drug at any time during the study (Section 8), will enter a 4-week post-treatment follow-up period.

For subjects who continue to demonstrate clinical benefit after Week 104, a separate long-term extension study may become available in the future, subject to regulatory and Institutional Review Board (IRB) approval (Section 7.8).

5.1.5 Corticosteroid Use and Tapering Schedules

5.1.5.1 Corticosteroid Use in the Induction Period

Prednisone ≤ 20 mg/day or budesonide MMX ≤ 9 mg/day are allowed, provided the dose is stable for 2 weeks prior to randomization (Section 7.7.2), and thereafter stable during the induction period. Corticosteroid tapering is not allowed during the induction period.

5.1.5.2 Corticosteroid Tapering in the Maintenance Period

Subjects receiving corticosteroids during the induction period who achieve a clinical response at Week 12 must initiate a corticosteroid taper by Week 14, according to a standardized tapering schedule. Corticosteroids must be discontinued by Week 24, unless the subject has evidence of adrenal insufficiency.

If a subject experiences disease worsening during the corticosteroid taper, the corticosteroid dose may be increased back to the baseline corticosteroid dose (ie, the dose the subject received at Week 0 [Day1]), if clinically indicated. This may only be done **once**. The investigator must recommence the corticosteroid taper as soon as possible, with the intention of tapering corticosteroids by Week 24.

Failure to discontinue corticosteroids by Week 24 will be considered a treatment failure (defined in Section 5.1.6), unless the subject requires glucocorticoid treatment for adrenal insufficiency. Subjects who remain on corticosteroids at Week 24 to treat adrenal insufficiency must be discussed with the medical monitor to continue on the study.

The recommended tapering schedules for prednisone (or equivalent oral corticosteroid) and colonic-release budesonide are in Table 8.

Table 8 Recommended Corticosteroid Tapering Schedule

Medication	Starting Dose	Schedule
Prednisone[a]	≥ 15 mg QD PO	Taper daily dose by 5 mg/week until 10 mg/day; continue tapering at 2.5 mg/week until 0 mg/day
Prednisone[a]	11 mg - 15 mg QD PO	Taper daily dose to 10 mg/day for 1 week; continue tapering at 2.5 mg/week until 0 mg/day
Prednisone[a]	< 10 mg QD PO	Taper daily dose by 2.5 mg/week until 0 mg/day
Budesonide MMX[b]	≤ 9 mg QD PO	9 mg every other day for 1-2 weeks; continue tapering 9 mg every third day for 1-2 weeks until 0 mg/day

MMX = Multi-Matrix System; PO = oral; QD = every day

[a] Or equivalent oral corticosteroid

[b] Uceris extended release or equivalent colonic-release corticosteroid

5.1.5.3 Corticosteroid Tapering in the Open-label Treatment Arm

Subjects receiving corticosteroids during the induction period who do not have a clinical response at Week 12 may be eligible to enter the open-label treatment arm. Such subjects must initiate a corticosteroid taper at Week 24 or earlier, according to the standardized tapering schedule described in Table 8 (Section 5.1.5.2). Corticosteroids must be discontinued by Week 36 unless the subject has evidence of adrenal insufficiency. As discussed in Section 5.1.5.2, 1 corticosteroid

dose escalation to the baseline (Week 0/Day 1) corticosteroid dose is allowed, but the corticosteroid taper must be recommenced as soon as possible, with the intention of tapering corticosteroids by Week 36. Failure to discontinue corticosteroids by Week 36 will be considered a treatment failure (defined in Section 5.1.6), unless the subject requires glucocorticoid treatment for adrenal insufficiency. Such subjects must be discussed with the medical monitor.

Subjects receiving corticosteroids in this open-label study arm who experience disease worsening (as defined in Table 5) at Week 36 (and thereafter) will permanently discontinue study treatment. They will enter the post-treatment follow-up period (see Section 5.1.4.1) and should be referred for appropriate treatment.

5.1.6 Treatment Failure

For study purposes, treatment failure will be defined as:

1) Requirement for corticosteroid rescue therapy due to increased UC activity or failure to taper corticosteroids:
   a) For subjects who are on an allowed, stable dose of corticosteroids at randomization: A requirement for the dose of corticosteroids to be increased above that baseline dose to treat UC during the **induction period** (Section 5.1.5.1) or more than 1 corticosteroid dose increase during the **maintenance period** (Section 5.1.5.2)
   b) For subjects who are **not** on corticosteroids at randomization and in subjects who have tapered corticosteroids to 0 mg/day during the maintenance period: A course of systemic corticosteroids (> 24 hours in duration) or more than 1 discrete exposure to systemic corticosteroids (< 24 hours in duration) required to treat UC
   c) Failure to taper corticosteroids during the maintenance period by Week 24 unless the subject has adrenal insufficiency (in which case, the subject must be discussed with the medical monitor)
   d) Failure to taper corticosteroids during the maintenance period by Week 36 in the Week 12 nonresponder open-label arm, unless the subject has adrenal insufficiency (in which case, the subject must be discussed with medical monitor)
2) Requirement for an alternative, efficacious therapy for UC

5.1.7 Data Monitoring Committee and Other External Committees

An external DMC will be used in this study to perform safety monitoring by unblinded treatment group.

Unblinded data summaries and listings will be provided to the DMC to facilitate their safety assessment at the regularly scheduled times, and on an ad hoc basis if needed. The safety review includes all AEs and events of special interest, focusing on early signal detection. Further details on the frequency, content, and methods of data reports to the DMC will be outlined in the DMC charter along with the processes and procedures the committee will follow.

5.2 Number of Subjects

Approximately 120 subjects will be randomized. The sample size justification is in Section 10.1. Subjects who have completed screening procedures and met inclusion/exclusion criteria will be randomized in a 2:1 ratio to receive BMS-986165 6 mg BID PO or placebo BID PO during the induction period of 12 weeks. Current standard of care treatments may be continued as long as the dosing has been stable and allowed per the concomitant medications section of the protocol (Section 7.7).

Randomization will be stratified based on corticosteroid use (yes/no) and prior exposure to biologics indicated for the treatment of UC (ie, no prior exposure, exposure to 1 biologic, or exposure to > 1 biologic; see Section 7.2). JAK inhibitors are considered as a biologic for stratification purposes. (Note: failure or loss of response to JAK inhibitors is exclusionary, but prior exposure without failure or loss of response is not exclusionary.)

To ensure real-world subpopulations are well represented in this study (ie, biologic-naive subjects and biologic-exposed subjects), approximately 40% biologic-naive subjects and 60% biologic-exposed subjects will be randomized.

5.3 End of Study Definition

The duration of study participation for individual subjects may be up to approximately 112 weeks (784 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 (Week 108 for collection of potential AEs and SAEs). [redacted]

5.4 Scientific Rationale for Study Design

This is a Phase 2 randomized, double-blind, placebo-controlled study to assess the safety and efficacy of BMS-986165 6 mg BID in subjects with moderate to severe UC. The primary objective is to assess the effect of BMS-986165 on clinical remission at Week 12. Subjects who have completed screening procedures and met eligibility criteria will be randomized in a 2:1 ratio to receive oral BMS-986165 6 mg BID or placebo BID during the 12-week induction period. The dose chosen for this study was done so with the intent to maintain exposure at or above the IC50 of the target engagement.

This Phase 2 study in subjects with UC will provide evidence of biologic activity of BMS-986165 in a relevant disease population and will help determine the safety and efficacy of the BMS-986165 dose of 6 mg BID.

Inhibition of TYK2 is expected to provide therapeutic benefit for patients with UC for multiple reasons: 1) IL-12 and IL-23 have been implicated in the pathogenesis of UC[8, 9, 10, 11]; 2) Biologic agents targeting IL-23p19 and IL-12/IL-23p40 cytokines have been shown to be efficacious in UC and CD, and ustekinumab targeting IL-12/IL-23p40 has been approved for the treatment of CD[12]

and UC; and 3) BMS-986165 has been shown to be efficacious in psoriasis, an IL-23-mediated disease, in a recent Phase 2 study.[14]

The eligibility and randomization criteria of this study are designed to ensure that subjects have the expected level of UC activity and to minimize the risk for serious infections that may be associated with immunosuppressive therapies.

The Mayo score is a combined endoscopic and clinical scale that is designed to assess UC severity. This score was first proposed by Schroeder et al[16] and has since become widely accepted and used in many clinical trials and in clinical practice. [redacted] The modified Mayo score is a composite of SF, RB, and ES subscores. Further details on the [redacted] modified Mayo score are in Section 9.1 and APPENDIX 9. The modified Mayo score will be used to assess disease severity for study eligibility and will be used to assess clinical remission and clinical response. [redacted]

A plan for corticosteroid tapering is included to allow subjects to discontinue corticosteroid throughout the maintenance period of the study (Section 5.1.5.2). Corticosteroid doses are required to be stable for at least 2 weeks prior to the randomization visit and must be at or below the allowed doses prior to the first dose of study treatment on Week 0 (Day 1) of the induction period (see Section 7.7.2). Subjects who take corticosteroid under the above mentioned conditions during the induction period and who achieve clinical response at Week 12 (Day 85) are to undergo recommended corticosteroid tapering during the start of the maintenance period (Section 5.1.3 and Table 8). This eventual corticosteroid withdrawal will make it possible to isolate the effects of assigned study treatments and to assess the effect of the IP in eliminating the need for corticosteroid use while maintaining disease control.

5.5 Justification for Dose

Subjects randomized for treatment in the induction period will receive 1 of 2 treatments: BMS-986165 at 6 mg BID or placebo BID during the induction period.

The following points were considered for dose selection:

1. The preclinical studies of BMS-986165 showed an exposure-response relationship between BMS-986165 PK, target engagement assays, and efficacy indicators of interest in animal models of IBD.
2. Psoriasis is a disease highly dependent upon IL-17/IL-23 pathway;[19] thus, the observed efficacy and dose response observed in psoriasis are assumed to be informative for dose selection in UC. In data from the psoriasis trial IM011011, an association was shown between the average concentration (Cavg) of BMS-986165 and efficacy. Based on this finding and the very limited information available to identify the exposure measure that best correlates with efficacy for TYK2 inhibition, the assumption that Cavg is correlated with efficacy is the most

reasonable assumption to make. Because preclinical studies of BMS-986165 indicate that 24-hour coverage of the IC50 of the target engagement assay is correlated with a robust response, additional consideration was given to trough observed plasma concentration (Ctrough) to ensure that an adequate range of Ctrough spanning the IC50 was also captured in this trial.

3. The primary target engagement measurement used for dose selection based on the IL-12/IL-23 pathway was the inhibition of IL-12/IL-18 induced interferon gamma (IFNγ) production measured in an ex-vivo assay in the FIH study. It is assumed that the inhibition of IL-12/IL-18 assay is associated with efficacy in IBD. This assumption is supported by preclinical studies of BMS-986165 and the clinical improvements observed in UC and CD clinical trials conducted using biologic therapies directed against either the p40 subunit shared between IL-12 and IL-23 or p19, IL-23 only. Using the PK and target engagement data from the single ascending dose and multiple ascending dose portions of the FIH studies, a direct effect (Emax) model was developed to characterize the concentration-response relationship in the FIH study. Results of the analysis showed that the estimated IC50 for IL-12/IL-18-induced IFNγ production was approximately 6 ng/mL. With the assumption that the IC50 should be similar between healthy subjects and those with UC, the selected treatment level of 6 mg BID is expected to provide a median Cavg up to approximately 5.8 × the IC50 for this selected assay. The selected dose is also expected to provide a median Ctrough of approximately 2.6 × the IC50 for the assay.

The ideal amount of target inhibition in patients with UC using a selective inhibitor of TYK2 is not known because BMS-986165 is the first compound of this class. A higher dose (6 mg BID) was chosen as UC typically requires higher doses than in psoriasis (eg, ustekinumab) and greater target engagement to observe efficacy.

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.

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 confirm eligibility or record reasons for screening failure, as applicable. Procedures conducted as part of the subject's routine clinical management (eg, blood count) and obtained before signing of the ICF may be used for pre-screening purposes to allow predicting for potential eligibility during the screening period.

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 medical monitor. Rules for retesting and rescreening are provided in Section 6.5.1.

To be eligible for the study, subjects must meet all criteria in Sections 6.1 and 6.2. To be randomized into the study on Week 0 (Day 1), subjects must meet the criteria in Section 6.3.

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 Subject and Target Disease Characteristics

a) Not applicable (N/A) per Revised Global Protocol v3.0

b) N/A per Revised Global Protocol v3.0

c) Active UC extending ≥ 15 cm from the anal verge and confirmed by a screening/baseline colonoscopy/sigmoidoscopy prior to the randomization visit

d) N/A per Revised Global Protocol v3.0

e) N/A per Revised Global Protocol v3.0

f) Documented diagnosis of UC of at least 3 months' duration prior to screening, confirmed by:

1. Source: Medical records with report of an endoscopy, which shows features consistent with UC, as determined by the procedure performing physician, AND

2. Source: Medical record documentation of a histopathology report showing features consistent with UC, as determined by the local pathologist

Note: If a histopathology report is not available, histologic samples can be obtained at the screening endoscopy and sent to a local laboratory to confirm diagnosis of UC before proceeding to randomization. The screening endoscopy must show features consistent with UC, and medical records must still document a clinical diagnosis of UC of at least 3 months' duration prior to screening.

g) Must have active moderate to severe UC, as defined by a modified Mayo score of 5 to 9 points (inclusive; see APPENDIX 9), which includes all of the following subscore values:

- A stool frequency (SF) subscore of ≥ 2, **and**
- A rectal bleeding (RB) subscore ≥ 1, **and**
- A screening endoscopic (ES) subscore of ≥ 2

h) 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; specific criteria and dosing details are in APPENDIX 5:

- Oral 5-aminosalicylic acids (5-ASAs) (eg, mesalamine, sulfasalazine, olsalazine, or balsalazide)
- Corticosteroids (eg, prednisone [or equivalent] or budesonide [or equivalent])
- Immunomodulators (eg, azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX])

- Anti-tumor necrosis factor-alpha (TNF-α) agents (eg, infliximab, adalimumab, or golimumab)
- Integrin inhibitors (eg, vedolizumab)
- Anti-interleukin (IL)-12/IL-23p40 antibodies (eg, ustekinumab); subjects can only be included if they were intolerant to treatment. Inadequate response or loss of response is exclusionary.

i) Subjects currently using concomitant salicylates, probiotics, or oral corticosteroid (≤ 20 mg prednisone or equivalent, ≤ 9 mg budesonide MMX or equivalent) at stable doses prior to the randomization visit are eligible provided they are on stable doses for the time period specified in Section 7.7.2

3) Age and Reproductive Status

a) N/A per Revised Global Protocol v3.0

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the start of study treatment.

c) Women must not be breastfeeding, lactating, or planning pregnancy during the study period.

d) N/A per Revised Global Protocol v3.0

e) N/A per Revised Global Protocol v3.0

f) Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

g) Males and females ages 18 (or age of majority) to 80 years, inclusive, at the time of screening

h) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment(s) (BMS-986165 or placebo).

Investigators shall counsel WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective or less than highly effective methods of contraception (APPENDIX 4).

6.2 Exclusion Criteria

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

1) Target Disease

a) N/A per Revised Global Protocol v3.0

b) Current or recent (within 12 weeks prior to the randomization visit) evidence of fulminant colitis, abdominal abscess, toxic megacolon, or bowel perforation

c) History or evidence of any extensive colonic resection, subtotal or total colectomy, with or without presence of a stoma or ileoanal pouch. Current need for, or anticipated need for, surgical intervention for UC during the study

d) N/A per Revised Global Protocol v3.0

e) N/A per Revised Global Protocol v3.0

f) Current or recent (within 3 months before the first dose) gastrointestinal disease, including gastrointestinal surgery, which could impact the absorption of study treatment, or current or recent (within 6 months before the first dose) gastrointestinal resections

g) Previous/current documented diagnosis of CD, indeterminate colitis, ischemic colitis, or pseudomembranous colitis other than associated with Clostridium difficile (C. difficile). (See Section 6.2 5)h) Physical and Laboratory Test Findings for specific C. difficile exclusion criterion.)

h) History of diverticulitis within 60 days prior to the randomization visit. (Previous diverticulitis that has been successfully treated with a local standard course of antimicrobial therapy is permitted; however, the course of antimicrobial therapy must be completed at least 60 days prior to the randomization visit.)

i) Current colonic adenomas, dysplasia, or past confirmed colonic dysplasia that has not been eradicated (subjects who have had UC > 8 years should have had a colonoscopy to screen for dysplasia within 1 year prior to the randomization visit, or this can be performed as part of the screening colonoscopy). A subject with prior history of adenomatous polyps will be eligible if the polyps have been completely removed (documented), and the subject is free of polyps and without evidence of dysplasia on histology at randomization.

j) Receiving tube feeding, defined formula diets, or total parenteral alimentation

2) Medical Conditions and History

a) Women who are pregnant or breastfeeding

b) Any major illness/condition 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

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

d) 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

e) 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)

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) Female subjects with a breast cancer screen suspicious for malignancy, and in whom the possibility of malignancy cannot be reasonably excluded after additional clinical, laboratory, or other diagnostic evaluations

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

j) Inability to tolerate oral medication

k) Inability to undergo venipuncture and/or tolerate venous access

l) Drug or alcohol abuse, as determined by the investigator, within 6 months prior to Week 0 (Day 1). (Note: medical marijuana is not allowed.)

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

3) Prior/Concomitant Therapy

a) Inability to comply with restrictions and prohibited treatments, as listed in Section 7.7

b) Previous exposure to BMS-986165 in any study

c) Prior exposure to treatment with TYK2 inhibitors

d) N/A per Revised Global Protocol v3.0

e) Failure or loss of response to JAK inhibitors, such as tofacitinib. Prior exposure is not exclusionary.

f) N/A per Revised Global Protocol v3.0

g) N/A per Revised Global Protocol v3.0

h) Use of topical rectal treatment with 5-ASA or corticosteroid within 2 weeks prior to the randomization visit

i) Current use of corticosteroid at a dose of > 20 mg/day for prednisone or equivalent or > 9 mg/day for budesonide MMX or equivalent

j) N/A per Revised Global Protocol v3.0

k) N/A per Revised Global Protocol v3.0

l) Previous stem cell transplantation

m) Receipt of either lymphocyte apheresis or selective monocyte, granulocyte apheresis (eg, Cellsorba™) is prohibited within 12 months prior to the randomization visit.

n) Use of therapeutic enema or suppository, other than required for ileocolonoscopy, within 7 days prior to the randomization visit

o) N/A per Revised Global Protocol v3.0

p) Inadequate response or loss of response to medications that target the same pathway as BMS-986165, such as anti-IL-12/IL-23p40 antibodies (eg, ustekinumab, briakinumab) or anti-IL-23p19 antibodies (eg, guselkumab, risankizumab, tildrakizumab, brazikumab [MEDI2070], and mirikizumab [LY3074828]). However, subjects who have been exposed to the medications listed above, but who have not had a treatment failure (ie, an inadequate response or loss of response) 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.

q) Use of other investigational agents within 4 weeks or 5 half-lives, whichever is longer, prior to randomization (APPENDIX 7)

r) Use of immunomodulators (AZA, 6-MP, or MTX) within 4 weeks prior to randomization (APPENDIX 7)

s) Use of a biologic agent within the minimum washout period prior to randomization, as listed in APPENDIX 7

t) Fecal transplant is considered an "investigational" biologic agent, and the washout period must be ≥ 4 weeks prior to the randomization visit.

4) Infections/Immune-related Exclusions

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

- History of active TB prior to the screening visit, regardless of completion of adequate treatment
- Has signs or symptoms of active TB as judged by the investigator
- A chest x-ray obtained during the screening period or anytime within 6 months before screening, with documentation, with evidence of current active or old active pulmonary TB
- Latent TB infection (LTBI) defined as positive IFNγ release assay (IGRA) such as QuantiFERON® - TB Gold, QuantiFERON® - TB Gold Plus, or T-Spot® at screening, or other diagnostic test in the absence of clinical manifestations

  Note: such subjects 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 rescreened now after 1 month of treatment. The subject must agree to complete a locally recommended course of treatment for LTBI to continue in the study.

- An indeterminate IGRA result at screening with no signs or symptoms of active TB
- Note: A subject with an indeterminate IGRA test result must be retested for confirmation. If the second result is again 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.

b) N/A per Revised Global Protocol v3.0

c) N/A per Revised Global Protocol v3.0

d) Positive for human immunodeficiency virus (HIV) by antibody testing (HIV-1 and 2 Ab) at screening. NOTE: Subjects who are newly found to be HIV-positive should be directed to appropriate follow-up.

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

f) History of congenital or acquired immunodeficiency

g) N/A per Revised Global Protocol v3.0

h) Previous history of herpes zoster, herpes simplex, or influenza infection within 12 weeks before the first dose of study treatment or a history of disseminated/complicated herpes zoster infection (multidermatomal involvement, ophthalmic zoster, central nervous system involvement, or post-herpetic neuralgia)

i) Administration of a live vaccine within 90 days or an inactivated vaccine within 30 days before the first dose of study treatment administration. Heat-killed, or otherwise inactivated or protein vaccines (eg, influenza and pneumococcal vaccines) may be received at any time on study. Furthermore, live vaccines should not be used during the study and within the 2 months following last dose, and any other inactivated vaccines (eg, tetanus, etc.) should be used according to local guidelines during the treatment period.

j) Evidence of, or positive test for, hepatitis B virus (HBV) at screening as defined per APPENDIX 8.

k) Evidence of, or positive test for, hepatitis C virus (HCV) at screening. A positive test for HCV is defined as:

(1) Positive for HCV antibody (anti-HCV) and

(2) Positive via a confirmatory test for HCV (eg, detectable HCV RNA, HCV polymerase chain reaction) (see APPENDIX 8).

l) 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.

(1) 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 must be no sequelae that would place the participant at a higher risk of receiving BMS-986165. See Section 9.8 for additional information regarding retesting subjects who have prior SARS-CoV-2 infection.

5) Physical and Laboratory Test Findings

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

b) Clinically significant abnormalities on chest x-ray or ECG

c) N/A per Revised Global Protocol v3.0

d) N/A per Revised Global Protocol v3.0

e) Any other significant laboratory abnormalities that, in the opinion of the investigator, might place the subject at unacceptable risk for participation in this study

f) Clinically significant abnormalities in laboratory testing including:

- Serum alanine aminotransferase (ALT) > 2× upper limit of normal (ULN)
- Serum aspartate aminotransferase (AST) > 2× ULN
- Serum total bilirubin > 2× ULN (Exception: subjects can be included if they have a confirmed diagnosis of Gilbert Syndrome that is documented, and when other causes of isolated bilirubin elevation have been excluded.)
- Alkaline phosphatase > 2.5× ULN

- Serum creatinine > 2× ULN and/or renal impairment based on an estimated glomerular filtration rate (eGFR) <45 mL/min (calculated using the Modification of Diet in Renal Disease [MDRD] equation)
- Hemoglobin level < 9.0 g/dL
- Absolute white blood cell count < 3000/mm3
- Absolute lymphocyte count < 750/mm3
- Neutrophil count < 1000/mm3
- Platelet count < 100,000/mm3

g) Positive stool culture for enteric pathogens (not including flora that are considered commensal within a study region) at screening visit; subjects may rescreen 30 days after completion of a standard treatment course with antimicrobial agents without recurrence of clinical symptoms.

h) Stool positive for C. difficile toxin at screening visit; subjects may be rescreened 30 days after completion of an institutional standard of care course with antibiotics, and subsequent negative testing for C. difficile stool toxin and a C. difficile nucleic acid amplification test. Test results should be discussed with the medical monitor prior to rescreening.

6) Allergies and Adverse Drug Reaction

a) N/A per Revised Global Protocol v3.0

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

7) Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a subject. Strict conditions apply, and Bristol-Myers Squibb approval is required.)

b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

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

6.3 Randomization Criteria

Eligible subjects must meet the following criteria on Week 0 (Day 1) before randomization and the first dose of study treatment:

1) The subject continues to satisfy all eligibility criteria
2) Previous therapy must follow the rules outlined below:
   a) Dose stabilization:
      - 5-ASAs must be at stable doses for at least 2 weeks prior to randomization.
      - Probiotics must be at stable doses for at least 2 weeks prior to randomization.
      - Prednisone ≤ 20 mg QD PO (or equivalent) or budesonide MMX ≤ 9 mg QD PO (eg, Uceris extended release or equivalent) must be stable for at least 2 weeks prior to randomization.

b) Washout periods for immunomodulator and biologic treatments: Subjects must comply with the washout periods outlined in APPENDIX 7.

6.4 Lifestyle Restrictions

No 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. However, subjects are required to fast for a minimum of 10 hours before visits on which fasting lipid and fasting glucose samples will be drawn; at 2 of these visits (Week 0 [Day 1] and Week 12 [Day 85]) [redacted].

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. 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.

6.5.1 Retesting During the Screening Period and Rescreening

This study permits the rescreening of a subject who has been deemed as ineligible (screen failure) during the screening period (ie, the subject has not been randomized/has not been treated). The subject must be re-consented.

For laboratory parameters and/or assessments (Table 1) that initially do not meet eligibility requirements, a single retest within the 28-day screening period is permitted in an effort to find all possible well-qualified subjects, unless otherwise noted. Consultation with the medical monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

A subject can only be rescreened 1 time (ie, if the subject fails 1 rescreening attempt, no additional rescreening is allowed). **If a subject is rescreened, the endoscopy previously performed at the initial screening may be used for rescreening purposes. This is permitted if the randomization following rescreening occurs within 14 days of the initial screening endoscopy.**

NOTE: Use of the initial screening endoscopy for rescreening purposes should be discussed with the medical monitor before randomization occurs.

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

If a subject is positive for *C. difficile* toxin, they can be rescreened 30 days after completing a full course of standard treatment for *C. difficile* colitis and subsequently testing negative for *C. difficile*

stool toxin and a *C. difficile* nucleic acid amplification test. The subject must be re-consented and will be assigned a new identification number, and a full screening visit must be performed again.

The most current result prior to randomization is the value by which study inclusion will be assessed, as it represents the subject's most current clinical state.

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 investigational product (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.

IM011024 consists of IP study treatments BMS-986165 and placebo (see Table 9). Information about the pharmacology and previous experience with BMS-986165 is provided in Section 3.2.1 and Section 3.2.2.

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 9 Study Treatments for IM011024

Product Description/ Class and Dosage Form	Potency	IP/ Non-IP	Blinded or Open-label	Packaging/Appearance	Storage Conditions (per label)
BMS-986165 oral tablet	6 mg (as the free base)	IP	Blinded	Bottle containing 68 (6 mg) active tablets required for daily dosing	Store 15° to 25°C; Store in a tightly closed container; Protected from light
Placebo matching BMS-986165 oral tablet	Not applicable	IP	Blinded	Bottle containing 68 (6 mg) placebo tablets required for daily dosing	Store 15° to 25°C; Store in a tightly closed container; Protected from light
BMS-986165 oral tablet	6 mg (as the free base)	IP	Open-label	Bottle containing 68 (6 mg) active tablets required for daily dosing	Store 15° to 25°C; Store in a tightly closed container; Protected from light

IP = investigational product

7.1 Treatments Administered

During the induction period, subjects will take BMS-986165 6 mg BID or placebo BID over 12 weeks (Section 5.1.2), once in the morning and once in the evening. Dose information for each treatment group in the induction period is provided in Table 10. [redacted]

Study treatment will be supplied in bottles, each containing 68 film-coated active or placebo 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, that dose should be missed, and the next expected dose should be taken at the usual time.

Study treatment will be administered in the maintenance period, as described in Section 5.1.3 and illustrated in Figure 1.

Clinical Responders at Week 12: Subjects who achieve a clinical response at Week 12 (Table 5) who enter the double-blind, placebo-controlled maintenance period, will take the same blinded study treatment (BMS-986165 6 mg BID or placebo BID) that was assigned during the induction period.

Clinical Nonresponders at Week 12: Subjects who do not achieve a clinical response at Week 12 (Table 5) may be eligible to receive BMS-986165 6 mg BID in the open-label study arm, regardless of the initial treatment regimen received during the 12-week induction period.

Study treatment will be administered in the OLE period as described in Section 5.1.4 and illustrated in Figure 2.

Table 10 Selection and Timing of Dose

Study Treatment	Unit dose strength	Dosage formulation Frequency of Administration	Route of Administration
6 mg BID BMS-986165	6 mg	1 active tablet; BID	Oral
Placebo BID	Not applicable	1 placebo tablet; BID	Oral

BID = twice daily

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 informed consent 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 2:1 randomization ratio to receive oral treatment during the induction period with either BMS-986165 6 mg BID or placebo BID, according to a computer-generated block randomization scheme and in accordance with stratification criteria. Randomization numbers will be assigned prior to dosing. Randomization will be stratified by corticosteroid use (yes/no) and prior exposure to biologics indicated for treatment of UC; biologics includes JAK inhibitors for stratification purposes. Stratification groups: no prior biologic exposure (0), exposure to 1 biologic (1), or exposure to more than 1 (> 1) biologic.

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 Section 2 (Schedule of Activities).

Subjects who have completed the 12-week induction period will be eligible to enter the maintenance period. Their assigned maintenance treatment will be based on whether or not they achieved clinical response at Week 12 (Section 9.1.1). Responders will continue on their assigned double-blind treatment while nonresponders will be given the option to switch to open-label BMS-86165 6 mg BID through Week 52 or may choose to discontinue the study.

For subjects who are entered into the open-label portion of the study, BMS-986165 will be supplied in bottles of 6 mg tablets and subjects will take the requisite number of tablets for their daily dosing. These bottles will be assigned through the IRT to each subject during their dosing visits.

Subjects who have completed the 52-week maintenance period will be eligible to enter the 52-week open-label extension period. Eligibility will be based on the investigator's assessment of clinical benefit at Week 52 (Section 5.1.4).

7.3 Blinding

7.3.1 Maintaining the Blind

Blinded treatment assignments will be managed using IRT.

All tablets (BMS-986165 6 mg and placebo) are identical in appearance and will be supplied in bottles (see Section 7.1). Investigative site staff, Sponsor and designee personnel, and subjects and their families will remain blinded to treatment assignments.

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 medical monitor, but the investigator always has ultimate authority for the decision to unblind. The Principal Investigator should only call in for emergency unblinding AFTER the decision to discontinue the subject has been made.

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, the investigator shall notify the medical monitor 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 electronic case report form (eCRF). After unblinding via IRT, the investigator shall notify the medical monitor.

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

[redacted]

7.4 Dosage Modification and/or Interruption

There is no provision for dose modification of study treatment. Titration of corticosteroid and its use as rescue therapy are discussed in Section 5.1.5.2 and Section 5.1.5.3. Modification of other background UC therapies or dose regimens is not permitted during study participation. Subjects should continue to take their assigned treatment even if they experience flares and/or are unable to taper their corticosteroid dose, unless any of the criteria in Section 8.1 are met. If a subject's clinical condition worsens (eg, flares) during the induction period to the extent that rescue therapy is required based on the investigator's judgment, the subject must discontinue study treatment (IP or placebo) for appropriate alternative available treatment.

If treatment is interrupted for a subject due to an AE, study treatment can be restarted in consultation with the medical monitor.

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

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. A real-time monitoring platform may be used.

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 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 and/or Restricted Treatments

Restrictions and prohibitions on prior and concomitant medications are summarized in Table 11.

Table 11 Prohibited and/or Restricted Treatments

Prohibited Treatments	
Medication/Formulation	**Notes**
BMS-986165 or other TYK2 inhibitors	Prior exposure is prohibited
Corticosteroids: oral > 20 mg/day prednisone (or equivalent) or > 9 mg/day budesonide MMX (or equivalent)	Prohibited during the study; subjects are allowed to reduce their oral corticosteroid dose to ≤ 20 mg/day (Section 7.7.2)

Table 11 Prohibited and/or Restricted Treatments

Prohibited Treatments	
Medication/Formulation	**Notes**
	and be rescreened for study entry. Only 1 rescreening is allowed (Section 6.5.1)
Corticosteroids: IV, IM, intra-articular, intrabursal	Prohibited during the study; use of IV corticosteroid is also prohibited within 2 weeks prior to the screening period
Corticosteroid or 5-ASA/topical rectal treatment	Prohibited within 2 weeks of the randomization visit and during study
Immunomodulatory drugs	Prohibited within required washout periods (APPENDIX 7)
Biologic drugs	Prohibited within required washout periods (APPENDIX 7)
Live vaccines	Prohibited 90 days prior to the randomization visit; during the induction period, maintenance period, or OLE; or within the 2 months after the last dosea
Apheresis	Receipt of either lymphocyte apheresis or selective monocyte, granulocyte apheresis (eg, Cellsorba™) is prohibited within 12 months prior to the randomization visit
Investigational agents	Prohibited within 4 weeks or 5 half-lives (whichever is longer) before the randomization visit
Over-the-counter medications or herbal preparations	Prohibited within 1 week prior to the randomization visit; any exceptions to this must be cleared by the medical monitor
Restricted Treatments	
Medication	**Notes**
Corticosteroids/topical or inhaled to treat non-UC medical conditions	Allowed but must be discussed with the medical monitor
Systemic corticosteroids (< 7 days in duration) to treat non-UC medical conditions	Allowed but must be discussed with the medical monitor to determine if the intercurrent illness affects the safety of the subject, or if the corticosteroid treatment is likely to confound efficacy assessment
Nonsteroidal anti-inflammatory drugs (NSAIDs) for indications other than UC-related pain (eg, headache)	May be used on an as-needed basis during the study, but use is not recommended. If a subject enters the study on a stable dose of NSAIDs, they may continue this dose throughout the study after discussing with the medical monitor. NSAID dosing may be decreased or discontinued if due to NSAID toxicity

5-ASA = 5-aminosalicyclic acid; COVID-19 = coronavirus disease 2019; IM = intramuscular; IV = intravenous; MMX = Multi-Matrix System; NSAID = nonsteroidal anti-inflammatory drug; OLE = open-label extension; TYK2 = tyrosine kinase 2; UC = ulcerative colitis

[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. For COVID-19 vaccine information refer to APPENDIX 19.

7.7.2 Existing Therapies for Ulcerative Colitis

Use of concomitant 5-ASAs, probiotics, and oral corticosteroids (prednisone ≤ 20 mg/day or equivalent, or budesonide MMX [≤ 9 mg/day or equivalent]) is permitted. All subjects will continue their existing UC treatment(s) during the study (provided the treatment complies with the eligibility criteria; Section 6), unless dose modification or discontinuation is required for subject safety reasons, as follows:

- 5-ASAs: Must be at stable doses for at least 2 weeks prior to the randomization visit; stable doses must be maintained during the induction period. During the maintenance period, a dose decrease is permitted if due to moderate to severe drug-related toxicity.
- Probiotics: Must be at stable doses for at least 2 weeks prior to the randomization visit; stable doses must be maintained during the induction period. During the maintenance period, a dose decrease is permitted if due to moderate to severe probiotics related toxicity.
- Oral corticosteroids: Prednisone ≤ 20 mg QD PO (or equivalent) or budesonide MMX ≤ 9 mg QD PO (eg, Uceris extended release or equivalent) must be stable for at least 2 weeks prior to the randomization visit; stable doses must be maintained during the induction period (Section 5.1.5.1). Corticosteroid tapering must occur in the maintenance period, as described in Section 5.1.5.2.
- If a subject has recently stopped taking any of the above medications (5-ASAs, probiotics, oral corticosteroids), he/she must have been stopped for ≥ 4 weeks prior to the randomization visit.
- Prior exposure to immunomodulator and biologic treatments: Subjects must comply with the washout periods outlined in Section 5.1.1 and APPENDIX 7.

7.8 Treatment After the End of the Study

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive BMS-supplied study treatment. Study treatment will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS.

BMS reserves the right to terminate access to BMS supplied study 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 post-treatment

follow-up procedures (Section 5.1.4.1). 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.

- Subject meets 1 of the following criteria for laboratory abnormalities in 2 sequential laboratory measurements taken 3 to 5 days apart:
- White blood cell count < 1.5 × 109/L (< 1,500/mm3)
- Absolute neutrophil count < 0.75 × 109/L (< 750/mm3)
- Absolute lymphocyte count < 0.5 × 109/L (< 500/mm3)
- Hemoglobin < 8.0 g/dL or a decrease of > 30% from baseline
- Platelet count < 75 × 109/L (< 75,000/mm3)
- An increase in serum creatinine > 50% over the average of screening and baseline (Week 0/Day1) values and an absolute increase in serum creatinine > 0.5 mg/dL (> 44.2 µmol/L)
- Creatine kinase elevations > 10 × ULN, unless the causality is known not to be medically serious (eg, exercise induced)
- Subject who develops a serious infection during the study defined as any infection (viral, bacterial, and fungal) requiring parenteral antimicrobial therapy, hospitalization for treatment, or meeting other criteria that require the infection to be classified as an SAE
- Any drug-related rash or hypersensitivity reaction (eg, anaphylaxis, angioedema, urticaria, Stevens-Johnson syndrome, Drug Rash with Eosinophilia and Systemic Symptoms [DRESS], Toxic Epidermal Necrolysis [TEN]) deemed by the investigator to be severe or life threatening
- 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
- 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 expresses an interest in becoming pregnant (Refer to Section 9.2.5 Pregnancy)
- Requirement for any rescue therapy during the induction period
- Requirement for additional rescue therapy during the maintenance period, other than as specified in Section 5.1.5.2
- Requirement for any rescue therapy during the open-label extension period
- Subject meets any of the criteria for treatment failure defined in Section 5.1.6
- Abnormal liver tests suggestive of drug-induced liver injury (DILI), as defined Section 9.2.7, or if the investigator believes that it is in the best interest of the subject

Refer to the Schedule of Activities (Section 2, Table 4) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that would be completed.

All subjects who discontinue study treatment should comply with protocol-specified 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 post-treatment 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). Replacement of subjects is not permitted (Section 8.4).

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 Post-Study Treatment Study Follow-Up

Subjects who discontinue study treatment will continue to be followed for 28 days post last dose of study medication, or longer, as required, and in line with Section 9.2.3 (Follow-up of AEs and SAEs).

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 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 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.

8.2.1 Temporary Discontinuation

The following criteria for temporary interruption of study treatment apply:

- 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).
- 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.

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 informed consent, 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 Discontinuation of Study Conduct/Study Stopping Rules

There will be a DMC to provide oversight of the safety in this trial as outlined in Section 5.1.7 of the protocol. The DMC is responsible for assessing the ongoing acceptability of the benefit/risk profile for the study drug in an unblinded manner. Subjects, investigators, site staff, and Sponsor all remain blinded to study treatment throughout the conduct of the trial.

The DMC will review unblinded study treatment information and safety data to adjudicate study treatment relatedness and to make a recommendation regarding the appropriateness of continuing the study, with or without study modifications, or stopping the study under the following circumstances, which are not clearly related to the underlying UC:

- Two or more subjects experience an SAE of the same preferred term 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

Full details of the DMC data review can be found in the DMC Charter.

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 medical monitor 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, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities (Section 2).

The study data includes all the information that is collected as a result of the study, including subject demographics, disease characteristics (eg, Montreal classification), clinical information, blood tests, [redacted] endoscopic videos, intestinal biopsies obtained during endoscopy, and other tests listed in Section 2. Study data collected during this study will be used to help understand how BMS-986165 works in people with UC and related health conditions. The study data may also be used to help understand the biology of UC and related health conditions, study test performance 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.

Baseline assessments must be performed per protocol (standard of care assessments may not be used for baseline). 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 following procedures or tools will be used to assess subjects' UC activity during the study (see Schedule of Activities in Section 2):

- Mayo Scores: Details regarding the calculation of the modified [redacted] Mayo score[redacted] and the recording of the individual Mayo score components (SF, RB, ES[redacted]) are provided in APPENDIX 9. Electronic diaries will be provided to each subject for daily recording of SF and RB. Each day, a subject will enter his/her number of stools and RB assessment into the electronic subject diaries, according to instruction in APPENDIX 9. Should the subject miss daily entries prior to a visit, the investigator will assess if the visit should be rescheduled to ensure an adequate number of daily entries are recorded.
  - Modified Mayo Score18: The modified Mayo score is an adapted total Mayo score that is a composite of the following components (each scored on a scale of 0 to 3 points):
    - SF subscore
    - RB subscore
    - ES subscore

The modified Mayo score is a 9-point scale in which a score of 5 to 9 points denotes moderate to severe disease.

Timings of SF and RB assessments, endoscopy, and the modified Mayo score calculations are provided in the Schedule of Activities (Section 2).

[redacted]

- Geboes Score[21]: Biopsies for histological assessment will be taken on the days indicated in the Schedule of Activities (Section 2). This assessment will be carried out by the [redacted] group. Further details on the biopsy collection and processing for this histological assessment are provided in the Histopathology Image Review Charter.

[redacted]

[redacted]

- Serum hsCRP levels

[redacted]

The [redacted] group is the central vendor responsible for reading and scoring all endoscopies and biopsies [redacted]. These procedures are described in the Endoscopy Image Review Charter and Histopathology Image Review Charter.

9.1.1 Clinical Response Assessment

Clinical response for efficacy analysis will be determined with the modified Mayo score (defined in Section 9.1 and APPENDIX 9) calculated with an ES subscore derived from the central read of endoscopies. The central read of the endoscopy will be used for efficacy analysis at all time points.

At Week 12, clinical response for the determination of maintenance period treatment assignment will be determined with the modified Mayo score calculated with an ES subscore derived from a local read of endoscopies.

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 until the follow-up visit at Week 108 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 Day 1. The Reference Safety Information in Sections 5.6.1 and 5.6.2 of the IB should be used to determine the expectedness of SAEs for expedited reporting.[15]

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures, and within 30 days of discontinuation of dosing.

All AEs and SAEs related to SARS-CoV-2 infection must be collected from the time of signing the consent to the end of the safety follow-up period (30 days after treatment discontinuation) or roll-over into an extension 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 will be recorded and reported immediately to 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

Adverse events 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 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 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 suspected, unexpected serious adverse reaction (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 at least 5 half-lives after study product administration, the investigator must immediately notify [redacted] Drug

Safety of this event and complete and forward a Pregnancy Surveillance Form to [redacted] Drug Safety within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in APPENDIX 3.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject.

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 (see APPENDIX 3).

Any pregnancy that occurs in a female partner of a male study subject should be reported to [redacted] Drug Safety. 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 in APPENDIX 3.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the AE eCRF page:

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

If a laboratory test result meets the definition of an AE or SAE, the laboratory test result should be reported as an AE or SAE and submitted to [redacted] Drug Safety, as specified in APPENDIX 3.

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)

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).

Potential DILI is defined as:

1. ALT or AST elevation > 3 × ULN,
3) AND
4. Total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

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

9.2.8 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 AEIs. Adverse events of interest may be serious or nonserious. Such events may require further investigation to better characterize and understand them. In the BMS-986165 clinical development program, certain skin-related AEs (eg, acne) and infection AEs have been identified as potential AEIs; however, there has been no definitive assessment on the causal relationship between these events and treatment with BMS-986165.

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 should 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.

For purposes of reporting these AEIs, specialized eCRF pages will be required to collect additional information related to characterization, social/family history, risk factors, signs/symptoms, diagnostics, and treatments.

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

For this study, any dose of BMS-986165 that is more than 2-days' worth of study treatment within a 24-hour time period will be considered an overdose.

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

1. Contact the medical monitor 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 medical monitor 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), 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 may be performed by a Doctor of Medicine (MD), or 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 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

A chest x-ray and physical examination are part of the process to assess a subject's eligibility, as outlined in Section 2, and as defined in the Exclusion Criteria, Section 5.2). A chest x-ray at the screening visit is required if not already performed and documented within 6 months of obtaining written informed consent. A subject must not have active signs or symptoms of TB, as judged by the investigator, to be eligible for the study.

In addition to a complete physical examination and medical history to evaluate exposure to TB, all subjects will have a screening test, an IGRA (eg, T-spot® or QuantiFERON®-TB Gold, or QuantiFERON®-TB Gold Plus) performed centrally. If unable to obtain central laboratory results, an IGRA test could be obtained locally, after consultation with the medical monitor. A subject with an indeterminate IGRA test result must be retested for confirmation. If the second result is again indeterminate, the subject will be excluded from the study. If the second result is positive, the subject should be treated as having LTBI provided there are no signs or symptoms of active TB. If the second result is negative, the subject may be eligible provided no other exclusion criterion for TB is met.

9.4.3 Clinical Safety Laboratory Assessments

- A central laboratory will perform safety laboratory assessments (except pregnancy tests) and provide reference ranges and laboratory reports.
- 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 laboratory parameters to be assessed are as follows:

- Hematology: hemoglobin, hematocrit, total leukocyte count (including absolute neutrophil count and absolute lymphocyte count), platelet count, RBC count, and manual differential (separate smear)
- Chemistry: AST, ALT, gamma glutamyltransferase, total bilirubin, direct bilirubin, alkaline phosphatase, lactate dehydrogenase, creatinine, blood urea nitrogen, uric acid, total protein, albumin, sodium, potassium, chloride, calcium, phosphorus, magnesium, creatine kinase, creatinine clearance (screening only) with eGFR calculated using the MDRD equation, and thyroid-stimulating hormone (TSH) blood test (with reflex T3/T4 testing for abnormal TSH results at screening)
- Coagulation: prothrombin time, international normalized ratio, and either partial thromboplastin time or activated partial thromboplastin time
- Tests performed after a ≥ 10-hour fast: lipid panel (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides) and glucose
- Urinalysis: protein, glucose, blood, leukocyte esterase, specific gravity, pH; microscopic examination of the sediment if blood, protein, or leukocyte esterase are positive on dipstick; spot urine will be assessed for urine protein and urine creatinine
- Serology to be performed at screening: hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb) (only in Japan and selected countries), hepatitis B core antibody (HBcAb), reflex to HBV deoxyribonucleic acid (DNA); anti-HCV, HCV ribonucleic acid (RNA) if anti-HCV is positive or indeterminate; HIV-1 and HIV- 2 antibody; and IGRA testing
- Quantitative serum immunoglobulins (Igs): IgG, IgM, IgA, and IgE
- T cells, B cells, and natural killer cells (TBNK)
- Serum high-sensitivity C-reactive protein (hsCRP)

Urine and/or serum pregnancy testing will be performed for WOCBP, and FSH will be measured to confirm postmenopausal status (as applicable; at screening only).

9.4.4 Imaging Safety Assessment

Not applicable.

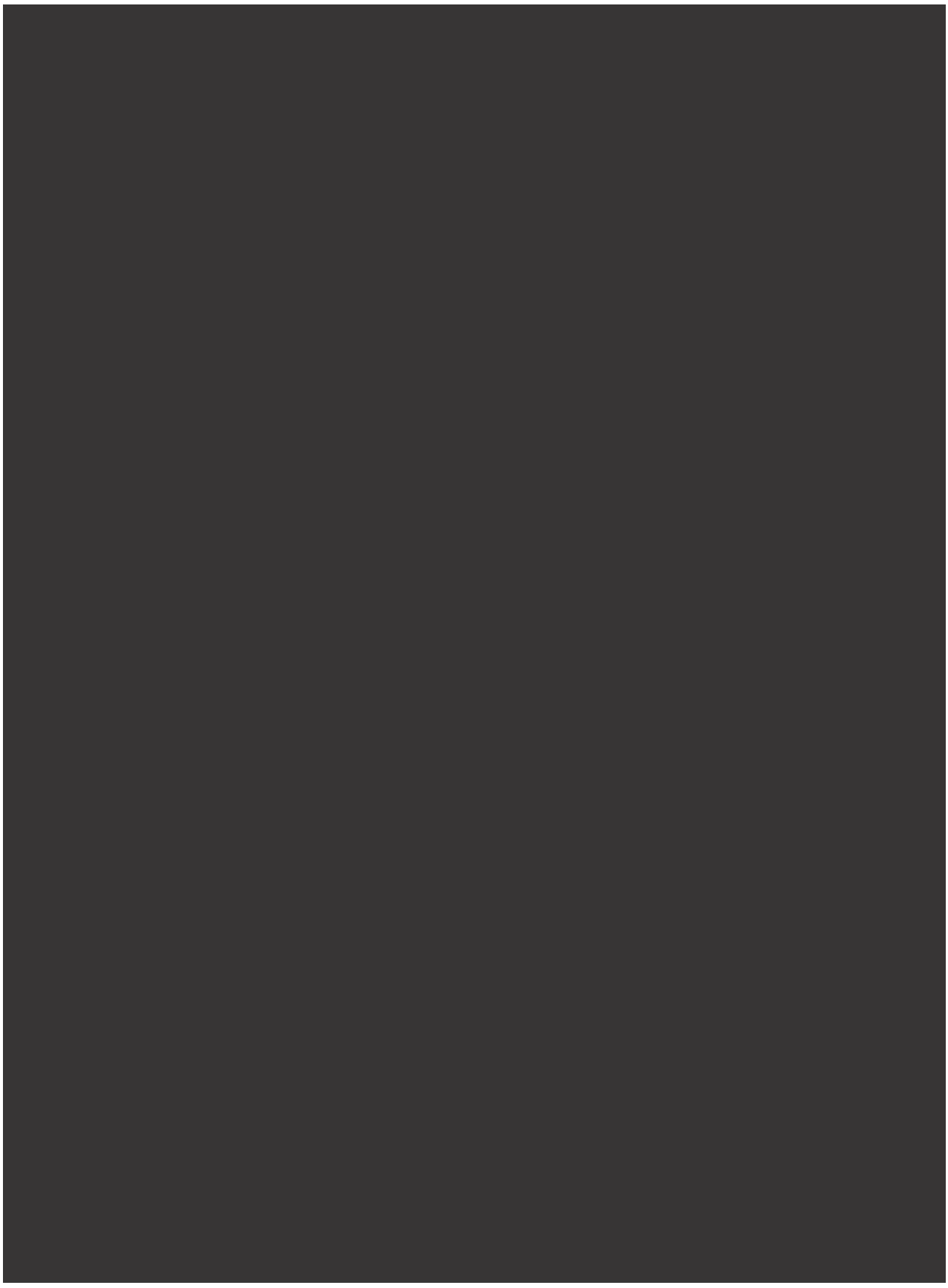
9.4.5 Vital Signs

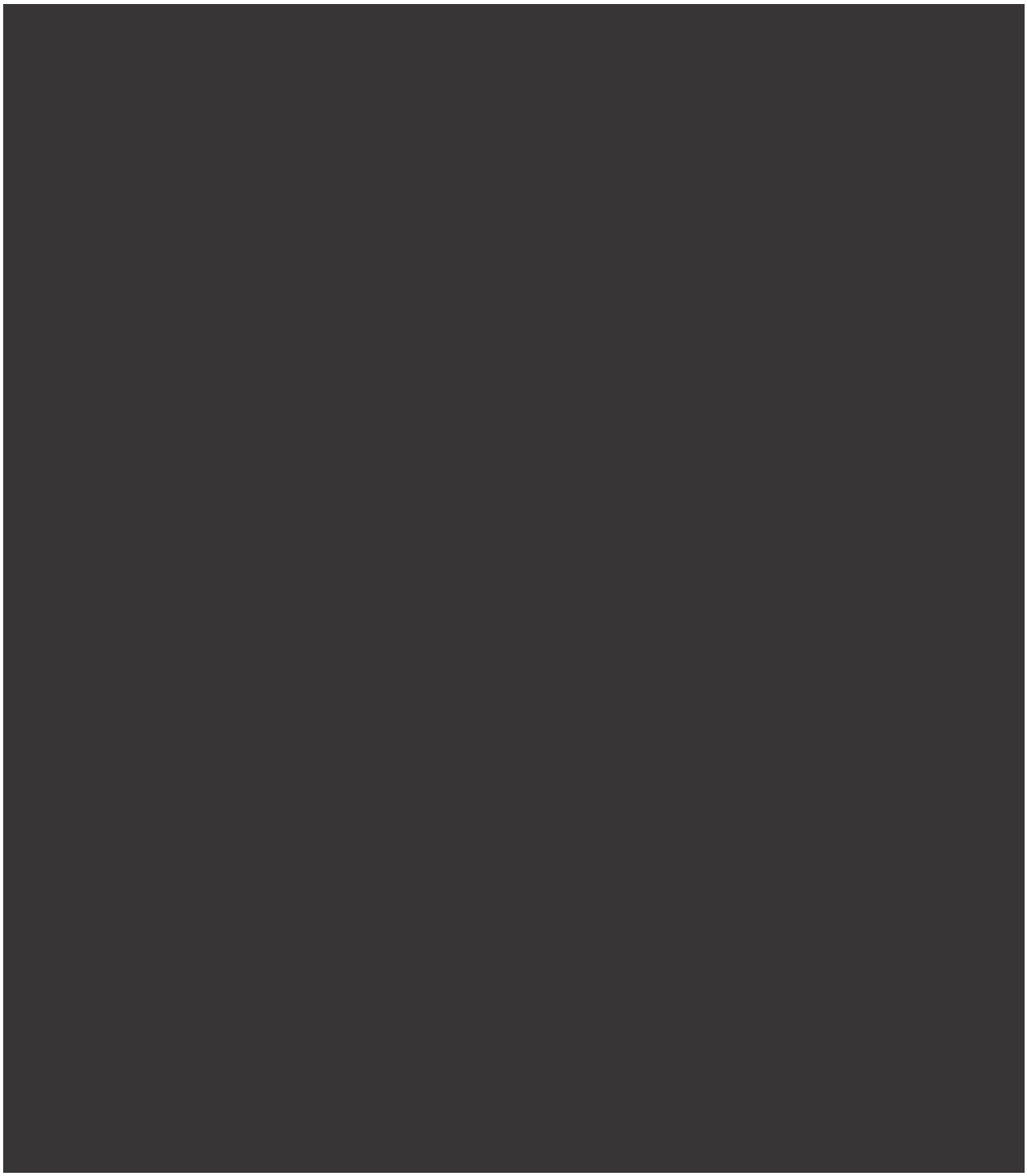
Refer to Schedule of Activities in Section 2.

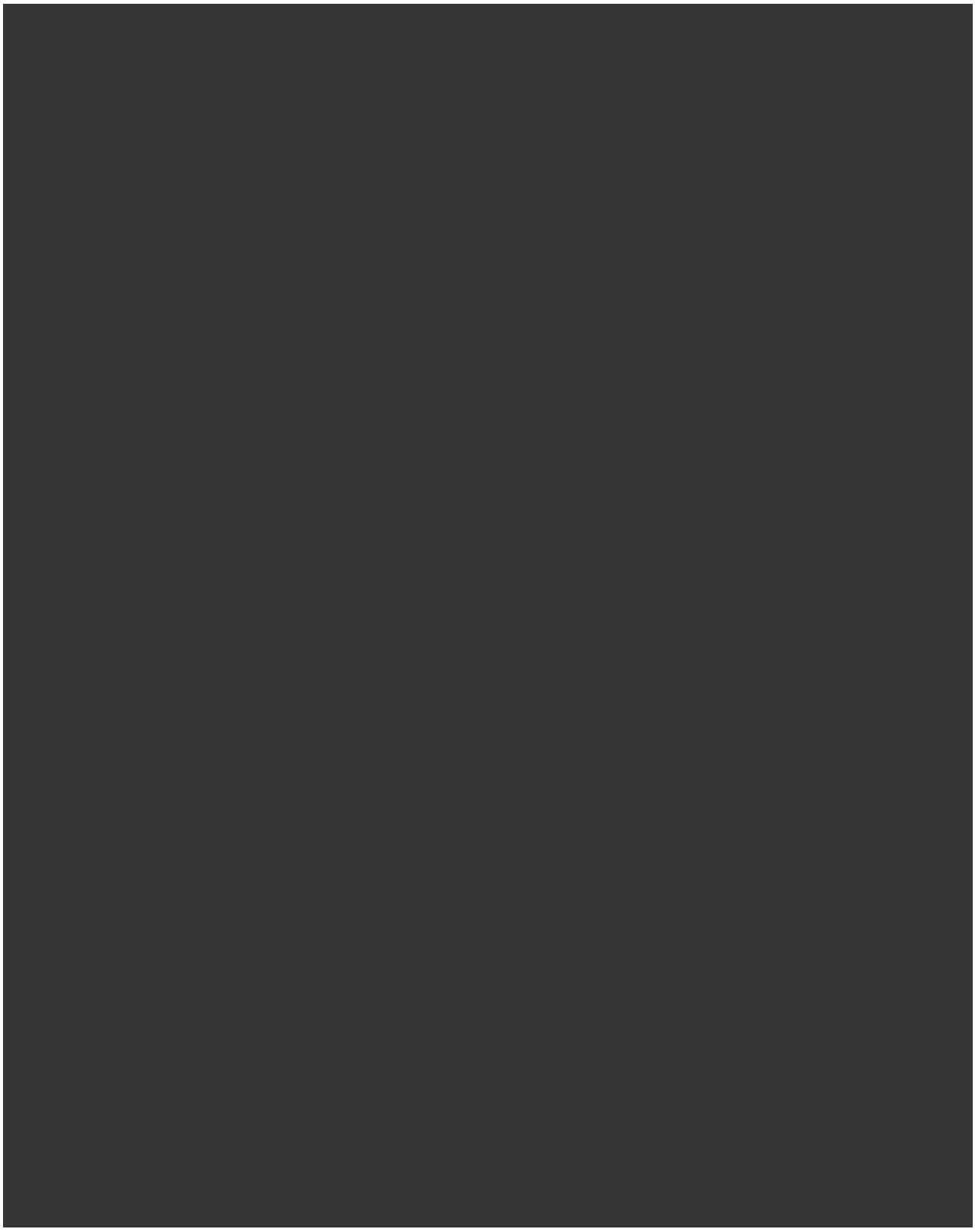
9.4.6 Electrocardiograms

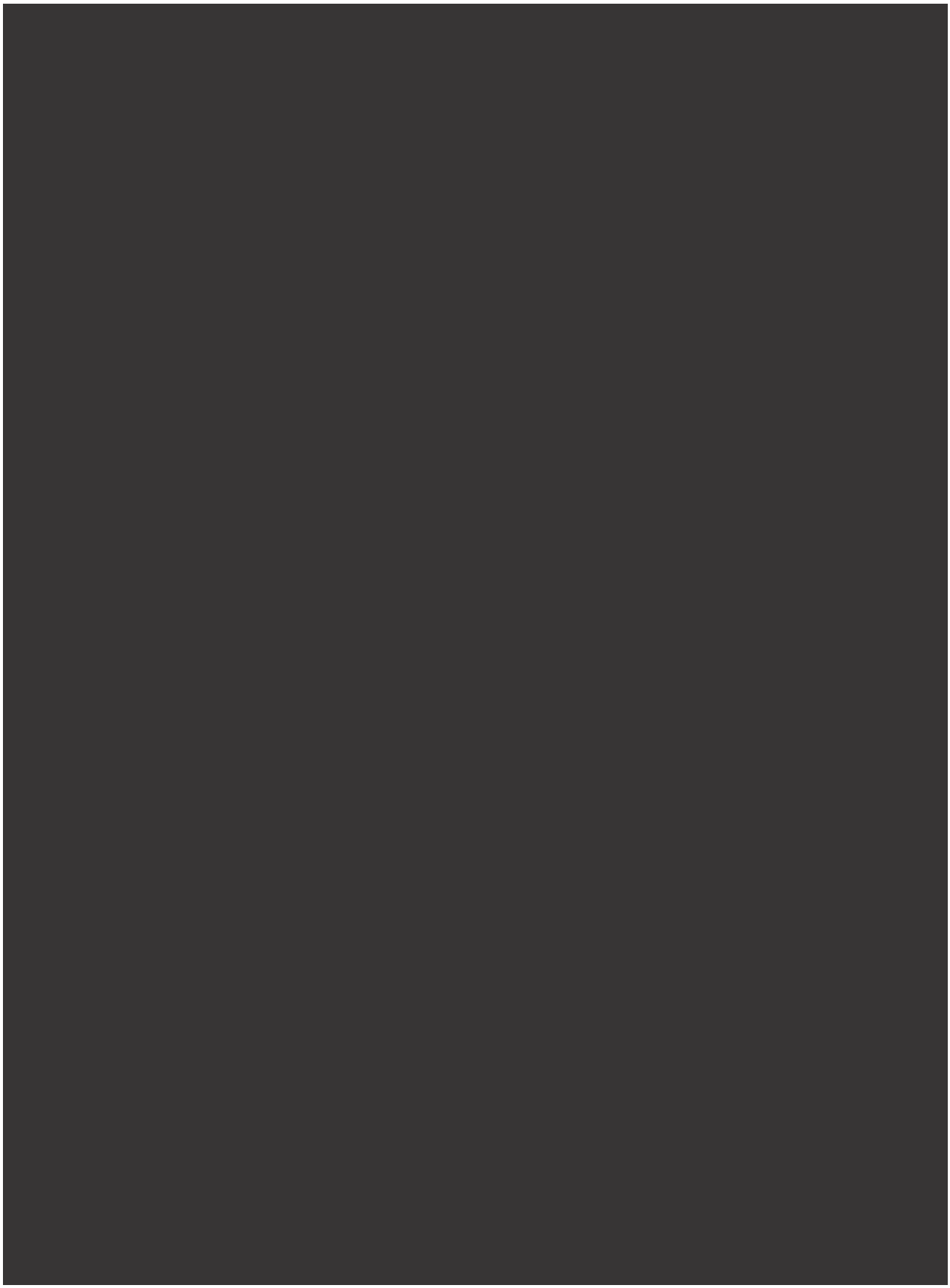
Refer to Schedule of Activities in Section 2.

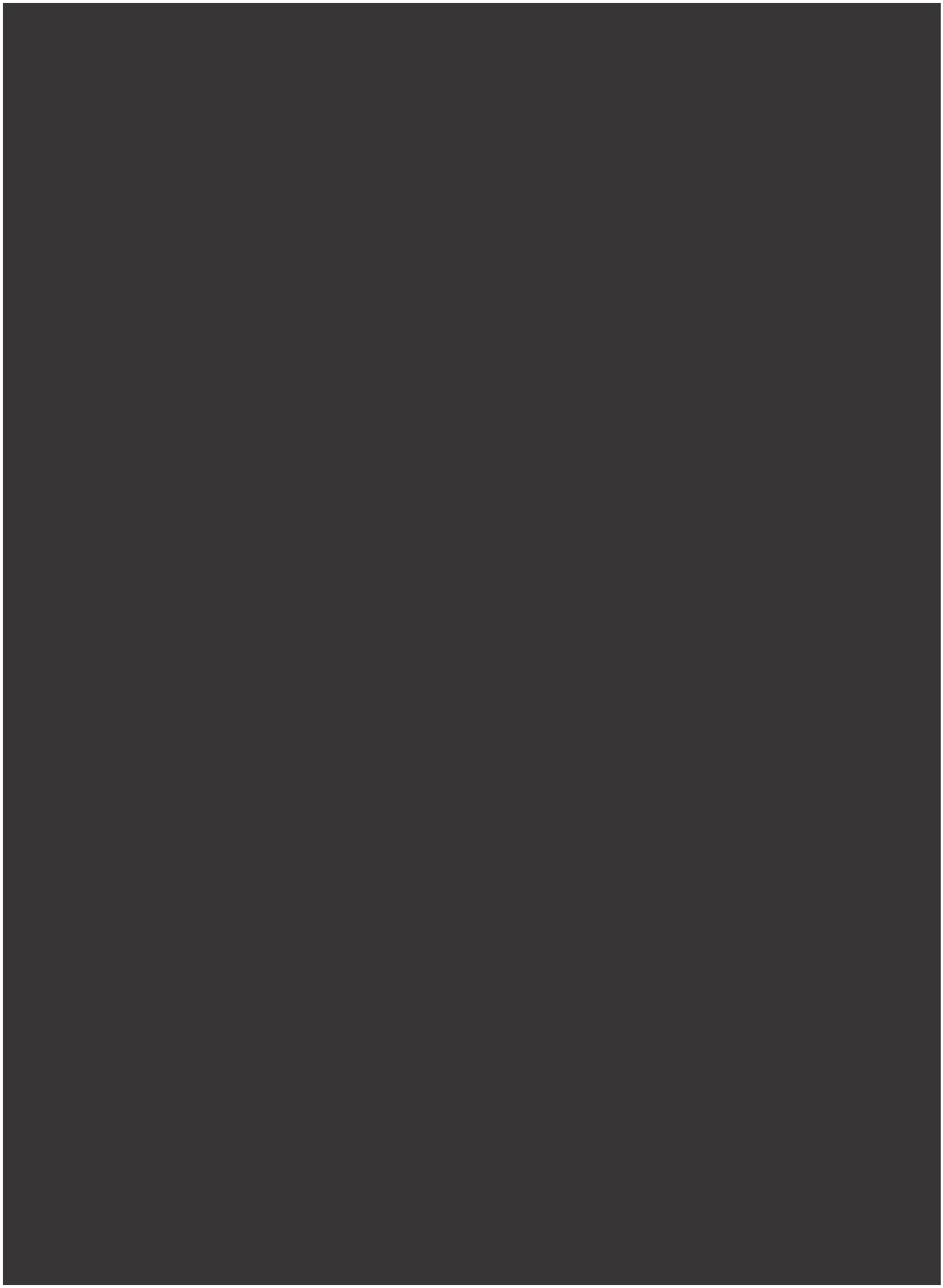
[redacted]

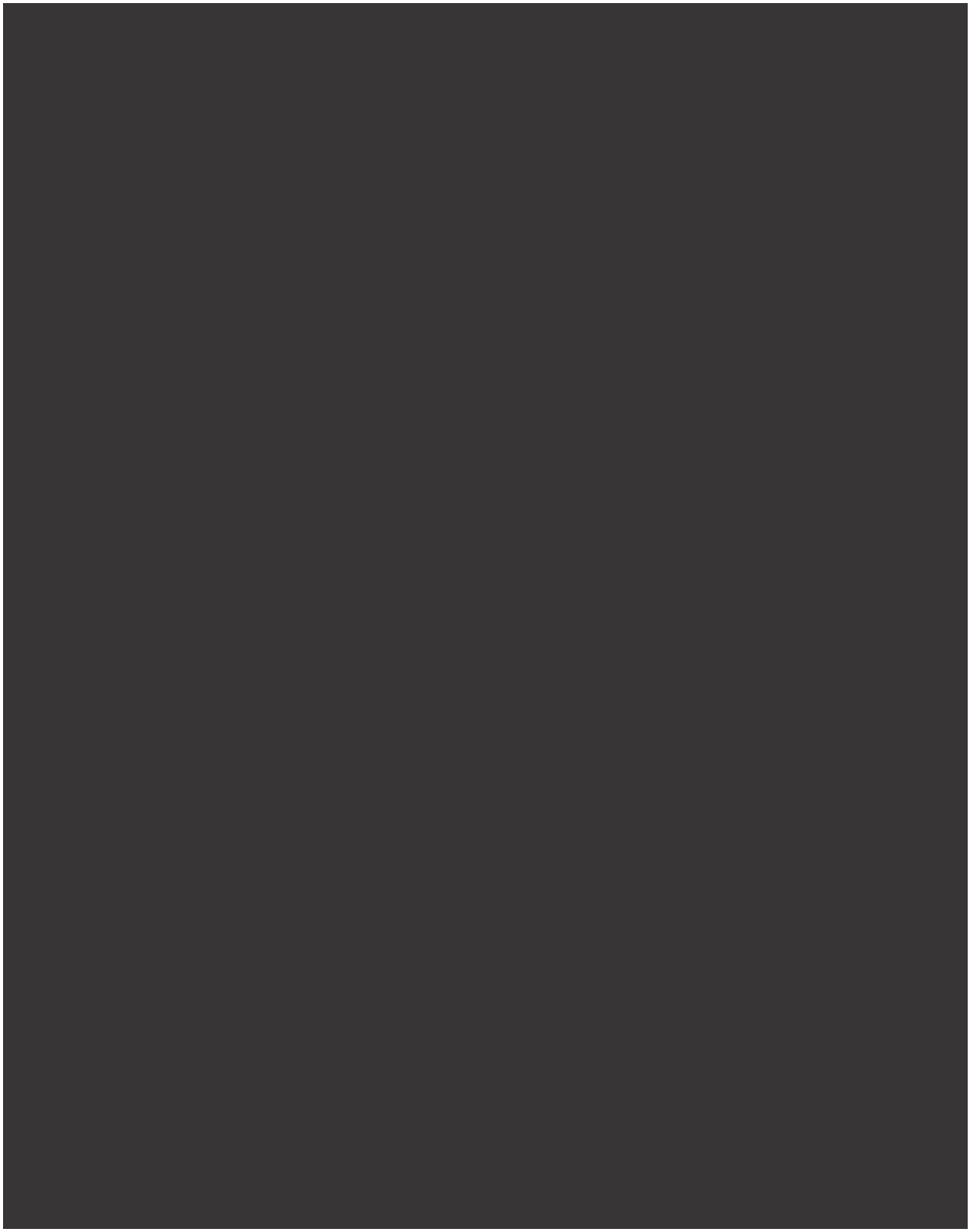


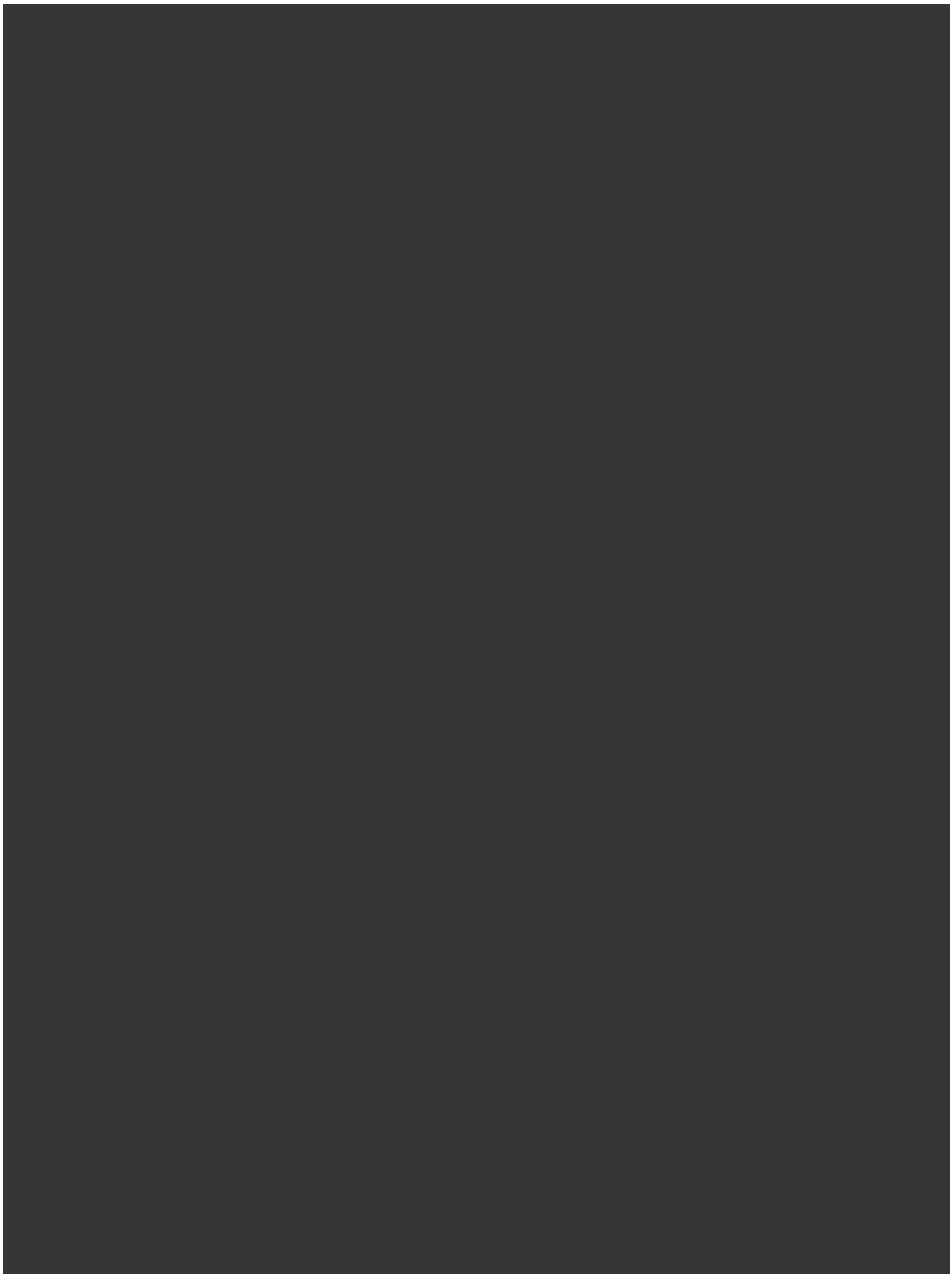


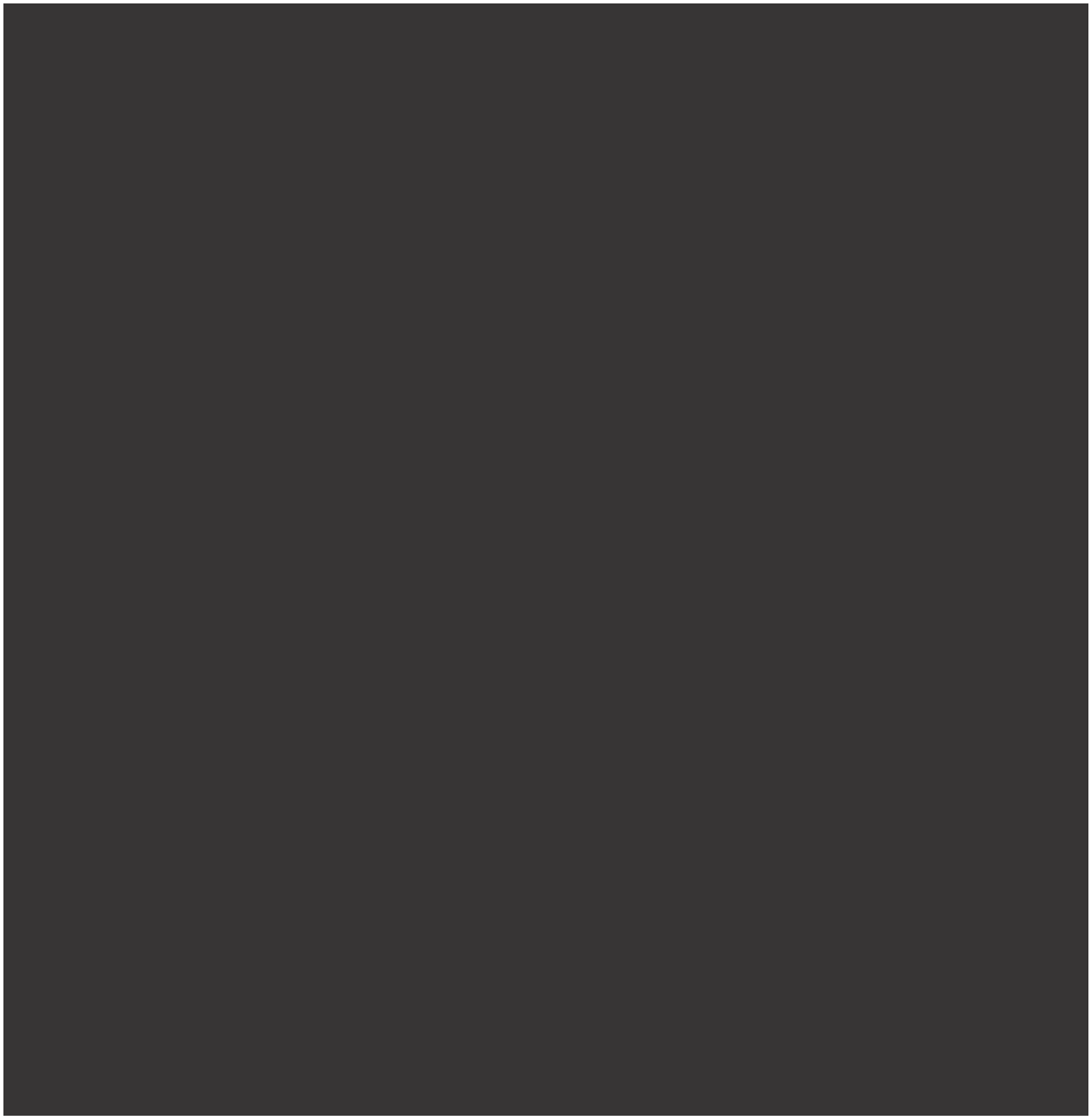












9.8 SARS-CoV-2 Testing

Diagnostic testing for SARS-CoV-2 infection refers to a molecular test (PCR or nucleic acid amplification test [NAAT]) or an antigen test for SARS-CoV-2 infection, performed according to local standard of care. PCR testing is preferred. Antibody 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.

Investigational product 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.

Investigational product 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 test for COVID-19 based on institutional, local, or regional guidelines, and
- 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

Sample size was determined based on providing exposure to a sufficient number of subjects to be able to observe a true difference in the rate of clinical remission (modified Mayo score) after 12 weeks of treatment. With the assumption that the observed placebo population will have similar clinical remission rate as seen in current UC investigative trials (mirikizumab),[9] it is expected that the placebo response rate will be 5%. Assuming that BMS-986165 will provide similar efficacy as

observed in current UC trials (mirikizumab and upadacitinib),[9,28] the expected treatment difference of BMS-986165 6 mg BID vs placebo is assumed to be 15%.

Approximately 120 subjects will be randomized in a 2:1 ratio to BMS-986165 6 mg BID or placebo, respectively (80 subjects on BMS-986165 and 40 on placebo). In this proof of concept study, if the observed response rates are the same as the assumed rates given above, the total number of 120 subjects (80 subjects on BMS-986165 and 40 on placebo) will provide approximately 82% power to detect a 15% treatment difference in clinical remission at Week 12 with a 1-sided 0.1 level of significance.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined in Table 23

Table 23: Analysis Populations

Population	Description
Enrolled Set	All subjects who sign informed consent.
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]	

FAS = full analysis set; 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 database lock 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, standard deviation, median, minimum, and maximum unless otherwise specified.

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

- BMS-986165 6 mg BID
- Placebo

After Week 12, subjects continuing into the maintenance period of the study (see Section 5.1.3 for details) will have their data presented as follows:

- Responders at Week 12 continuing blinded treatment:
  - BMS-986165 6 mg BID → BMS-986165 6 mg BID
  - Placebo → Placebo
- Nonresponders at Week 12 continuing open-label treatment:
  - BMS-986165 6 mg BID → BMS-986165 6 mg BID
  - Placebo → BMS-986165 6 mg BID

After Week 52, subjects with clinical benefit continuing open-label treatment during the open-label extension period of the study (see Section 5.1.4 for details) will have their data presented as follows:

- Responders at Week 12, clinical benefit at Week 52 continuing open-label treatment:
  - BMS-986165 6 mg BID → BMS-986165 6 mg BID→ BMS-986165 6 mg BID
  - Placebo → Placebo→ BMS-986165 6 mg BID
- Nonresponders at Week 12, clinical benefit at Week 52 continuing open-label treatment:
  - BMS-986165 6 mg BID → BMS-986165 6 mg BID→ BMS-986165 6 mg BID
  - Placebo → BMS-986165 6 mg BID → BMS-986165 6 mg BID

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 study period and treatment group.

A summary of planned statistical analyses of the primary and secondary endpoints is in Table 24.

Baseline values are defined as the last non-missing value prior to the first dose of study drug unless otherwise indicated.

Table 24 Planned Statistical Analyses of the Primary and Secondary Endpoints

Endpoint	Statistical Analysis Methods
Primary	General Analysis Methodology The proportion of subjects who achieve the primary endpoint, clinical remission (modified Mayo score), will be analyzed using a stratified Cochran-Mantel-Haenszel test. Clinical remission (modified Mayo score) responder rates at Week 12 between the BMS-986165 6 mg BID group and placebo group will be compared adjusting for the randomization stratification factors (corticosteroid use [yes/no] and prior exposure to biologics [0, 1, > 1]); JAK inhibitors are considered as a biologic for stratification purposes. If expected cell counts are not sufficient for each strata level, then strata levels will be combined for analysis. The assessment of statistical significance will be based upon a 1-sided, 0.1 alpha, which is in alignment with the sample size calculation. The odds ratio and corresponding 2-sided 95% CI will be provided for descriptive purposes. Supportive analyses using logistic regression may be performed to incorporate additional covariates of interest and to confirm primary analysis results. The model will include treatment, geographic region, corticosteroid use (yes/no), prior exposure to biologics (0, 1, > 1) as well as other covariates as applicable. The odds ratio and the corresponding 2-sided 95% CI will be provided. Imputation Method Occurrence of intercurrent events may have an impact on the estimand of interest. For the following types of subjects: • Subjects who discontinue treatment or study early (ie, prior to Week 12) • Subjects who start a protocol prohibited medication/therapy prior to the evaluation of the primary endpoint (clinical remission [modified Mayo score]) at Week 12 • Subjects who are lost to follow-up or have otherwise missing endpoint data at or prior to the Week 12 assessment The primary endpoint (clinical remission [modified Mayo score]) will be determined using the "Composite Strategy" as defined in International Council for Harmonisation (ICH) E9R1 addendum[29]. Subjects with the identified intercurrent events will have their clinical remission endpoint imputed as being a "nonresponder." This is commonly known as nonresponder imputation (NRI). Sensitivity analyses using different imputation methods may be performed and will be defined in the SAP.

Table 24 Planned Statistical Analyses of the Primary and Secondary Endpoints

Endpoint	Statistical Analysis Methods
Secondary	General Analysis Methodology The secondary endpoints will use the same analysis approach as the primary endpoint analysis with missing data, due to the incurrent events as defined above, being imputed as nonresponders. Testing Strategy for Secondary Endpoints Statistical analysis of secondary endpoints will be performed in a hierarchical fashion to control for Type I error rate inflation. The statistical testing of the primary endpoint will be the serial gatekeeper for proceeding to the testing of the secondary endpoints. Each secondary endpoint will be tested sequentially in a fixed-sequence order, as outlined below, using a 1-sided alpha = 0.1 for significance testing. No further testing will be performed once a test fails to show significance at the alpha level stated above. Secondary endpoints will be tested in the following order: 1. Clinical response 2. Endoscopic response 3. Histologic improvement
[redacted]	

BID = twice daily; CI = confidence interval; ICH = International Council for Harmonisation; JAK = Janus kinase; SAP = statistical analysis plan

10.4.1.1 Subgroup Analyses

Subgroup analyses will be conducted for the primary and secondary efficacy endpoints on the FAS population. Subgroups will not be further stratified based on the factors used for randomization. Subgroups to be evaluated include the following:

1. Sex
2. Age categories (< 65, ≥ 65)
3. Race
4. Prior exposure to biologics (0, 1, > 1); JAK inhibitors are considered as a biologic for stratification purposes
5. Prior corticosteroid use (yes/no)
6. Subjects taking corticosteroid at baseline who discontinue use after induction period
7. Baseline modified Mayo score (≤ 7, > 7)

A complete list of subgroups will be detailed in the SAP.

10.4.2 Safety Analyses

Safety data for each period will be summarized separately and combined. All safety data will be listed by study period and 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 pre-existing 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 and deaths, AEs leading to study treatment discontinuation, and target AEIs will be summarized by the Medical Dictionary for Regulatory Activities system organ class and preferred term.

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 non-missing 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 post-baseline value. Incidence of abnormal, high, or low values will be summarized. Shift tables will also be provided. Baseline values are defined as the last non-missing 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.

[redacted]

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), an interim analysis may be performed after 50% of subjects, approximately 60 subjects, have reached

this milestone. The purpose of this interim analysis will be to help in early planning for further clinical development of the compound.

To maintain the overall probability of Type I error at the specified 0.1 level, a modified Haybittle-Peto method[30] will be used as the alpha-spending function, which assigns alpha = 0.001 to each interim analysis, and the remaining alpha to the final (Week 12) analysis of the primary efficacy endpoint.

The SAP for the study will be finalized prior to any interim analysis. The details (including the timing) of the interim analyses will be provided in an interim analysis plan prior to the database lock for any interim analysis. The study will not be stopped on the basis of overwhelming efficacy findings at the interim analysis. The results of the interim analysis will be reviewed by an unblinded internal BMS team that is independent of the study team responsible for the conduct of the study. The study team members, including the medical monitors and other study personnel, will remain blinded and will not have access to any unblinded interim analysis results or data until the final database lock for the Week 52 data has occurred.

10.4.5 Analysis and Reporting

A database lock (12-week database lock) will occur once all randomized subjects have completed the Week 12 efficacy assessments or have discontinued prior to Week 12. Analyses of the collected efficacy and safety results during the 12-week induction period will be performed to aid in planning for subsequent clinical development. Details of these analyses will be described in the SAP. The study team responsible for managing the study, including medical monitors, will remain blinded to treatment assignment and the results of this analysis throughout the study.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
5-ASA	5-aminosalicylic acid/aminosalicylate
6-MP	6-mercaptopurine
[redacted]	[redacted]
AE	adverse event
AEI	adverse event of interest
ALT	alanine aminotransferase
Anti-HCV	hepatitis C virus antibody
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
[redacted]	[redacted]
AZA	azathioprine
BCRP	breast cancer resistance protein
BID	twice daily
BMS	Bristol-Myers Squibb
C. difficile	*Clostridium difficile*
Cavg	average concentration
CD	Crohn's disease
CFR	Code of Federal Regulations
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	clinical study report
Ctrough	trough observed plasma concentration
CYP450	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid

Term	Definition
DRESS	Drug Rash with Eosinophilia and Systemic Symptoms
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
[redacted]	[redacted]
ES	endoscopic (Mayo score component)
ET	early termination
FAS	full analysis set
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle stimulating hormone
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
h	hour
hsCRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
IBD	inflammatory bowel disease
[redacted]	[redacted]
IC50	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
IFNγ	interferon gamma
Ig	immunoglobulin
IgA	immunoglobulin A

Term	Definition
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
IGRA	interferon gamma release assay
[redacted]	[redacted]
IL	interleukin
IM	intramuscular
IMP	investigational medicinal product
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
IV	intravenous
JAK	Janus kinase
KLH	keyhole limpet hemocyanin
LTBI	latent tuberculosis infection
MDRD	Modification of Diet in Renal Disease
Min	minute(s)
MMX	Multi-Matrix System
MTX	methotrexate
N/A	not applicable
NAAT	nucleic acid amplification test
NOAEL	no-observed-adverse-effect-level
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
OLE	open-label extension
OTC	over-the-counter
PASI	Psoriasis Activity and Severity Index
PCR	polymerase chain reaction
PD	pharmacodynamics
PGA	Physician's Global Assessment

Term	Definition
[redacted]	[redacted]
[redacted]	[redacted]
PK	pharmacokinetic(s)
PO	oral
PRO	patient-reported outcome
[redacted]	[redacted]
QD	every day
RB	rectal bleeding (Mayo score component)
RBC	red blood cell
[redacted]	[redacted]
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SF	stool frequency (Mayo score component)
SLE	systemic lupus erythematosus
STAT	signal transducer and activator of transcription
SUSAR	Suspected, unexpected serious adverse reaction
TB	tuberculosis
TBNK	T cells, B cells, and natural killer cells
TDAR	T-cell-dependent antibody response
TDM	therapeutic drug monitoring
TEAE	treatment-emergent AE
TEN	Toxic Epidermal Necrolysis
TNF	tumor necrosis factor
TNFi	tumor necrosis factor inhibitor(s)
TSH	thyroid-stimulating hormone
TYK2	tyrosine kinase 2
UC	ulcerative colitis
[redacted]	[redacted]

Term	Definition
ULN	upper limit of normal
[redacted]	[redacted]
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

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

The study will be conducted in compliance with the protocol. The protocol 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) that is likely to affect, to a significant degree, one or more of the following: (1) the rights, physical safety or mental integrity of one or more participants; (2) the scientific value of the clinical trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP regulation(s) or trial protocol(s).Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

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

- ICH guidelines,
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- European Union Directive 2001/20/EC; or

- European Regulation 536/2014 for clinical studies (if applicable),
- European Medical Device Regulation 2017/745 for clinical device research (if applicable),
- the IRB/IEC
- and all other applicable local regulations.

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by 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.

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

The investigator or his/her representative must:

- Obtain IRB/IEC written approval/favorable opinion of the written ICF and any other information to be provided to the participant prior to the beginning of the study and after any revisions are completed for new information.
- Provide a copy of the ICF and written information about the study in the language in which the participant is proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Explain the nature of the study to the participant and answer all questions regarding the study.
- Inform participant that his/her participation is voluntary. Participant will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- Allow time necessary for participant to inquire about the details of the study.
- Obtain an ICF signed and personally dated by participant and by the person who conducted the informed consent discussion.
- Include a statement in participant's medical record that written informed consent was obtained before participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Re-consent participant to the most current version of the ICF(s) during his/her participation in the study, as applicable.

Revise the ICF whenever important new information becomes available that is relevant to the 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 HIPAA Authorization.

The ICF must also include a statement that BMS and local and foreign 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

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

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

- The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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 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

If	Then
	• dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy.

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 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 electronic data capture 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 electronic data capture tool using the unique user account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals.

MONITORING

Sponsor or designee representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

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.

CLINICAL STUDY REPORT

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

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

- External 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)

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

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

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

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

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

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

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

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

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

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

ADVERSE EVENTS

Adverse Event Definition:
An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a 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 pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term.
Events NOT Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below) NOTE: The following hospitalizations are not considered SAEs in 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 8.2.7 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 8.2.5 for reporting pregnancies).

EVALUATING AES AND SAES

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, 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 Investigator's Brochure (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.

Assessment of Intensity

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

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

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

Follow-up of AEs and SAEs

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

If an ongoing SAE changes in its intensity or relationship to study 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 must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study drug, and pregnancies must be reported immediately to [redacted] Drug Safety but no later than 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE reporting is through the electronic case report form (eCRF).
  - The paper SAE Report Form is intended only as a back-up option when the electronic data capture system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile transmission.
    - When paper forms are used, the original paper forms are to remain on site.
- Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: [redacted]

SAE Fax Number:

Americas: [redacted]

Europe/East Asia Pacific: [redacted]

SAE Telephone Contact - For questions on SAE/pregnancy reporting, please call:

Americas: [redacted]

Europe/East Asia Pacific: [redacted]

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

Appendix 4 provides general information and definitions related to Woman of Childbearing Potential and methods of contraception that can be applied to most clinical trials. For information specific to this study regarding acceptable contraception requirements for female and male participants, refer to Section 5.1 of the protocol. Only the contraception methods as described in Section 5.1 are acceptable for this study.

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal 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.

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

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

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

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

End of Relevant Systemic Exposure

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

CONTRACEPTION GUIDANCE FOR FEMALE SUBJECTS OF CHILD BEARING POTENTIAL

One of the highly effective or less than highly effective methods of contraception listed below should be continued until the end of study treatment.

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

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b]
  • Oral (birth control pills)
  • Intravaginal (rings)
  • Transdermal
• Combined (estrogen- and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy.

• Progestogen-only hormonal contraception associated with inhibition of ovulation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b]
  • Oral
  • Injectable
• Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy.

Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Intrauterine device (IUD)[c] • Intrauterine hormone-releasing system (IUS)[c] • Bilateral tubal occlusion

- Vasectomized partner

  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 1.3.
- 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 amenorrhea 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 .Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol.

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

Less Than Highly Effective Contraceptive Methods That Are User Dependent

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

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

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

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 8.2.5 and APPENDIX 3.

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

Subject has demonstrated an inadequate response, loss of response, or intolerance to 1 or more of the following standard of care medications (including, but not limited to):

- 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 oral prednisone ≥ 30 mg/day (or equivalent) for 2 weeks, or intravenously (IV) for 1 week, or oral budesonide MMX 9 mg/day (or equivalent) for 2 weeks; OR
  - At least 2 failed attempts to taper corticosteroids below a dose that is equivalent to oral prednisone 10 mg/day (or equivalent) or budesonide 3 mg/day (or equivalent) on 2 separate occasions; 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-alpha (TNF-α) agents (eg, infliximab, adalimumab, or golimumab):
  - Signs and symptoms of persistently active disease despite an adequate trial of induction treatment with an anti-TNF-α 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).
- Anti-interleukin (IL)-12/IL-23p40 antibodies (eg, ustekinumab):
    - History of intolerance (including, but not limited to, infusion-related reaction, arthralgia, or liver test abnormalities).

Subjects who stop biologic treatment due to loss of funding will also be eligible for inclusion into the study.

APPENDIX 6 COMMONLY USED CORTICOSTEROID EQUIVALENTS

Medication	Dose Equivalence
Prednisone	20 mg
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 on TDM assay
Alefacept	≥ 8 weeks	
Alemtuzumab	≥ 12 months	
AMG 623	≥ 12 weeks	
Apheresis: lymphocyte apheresis or selective monocyte or granulocyte apheresis (eg, Cellsorba™)	≥ 12 months	
Atacicept (TACI-Ig)	≥ 48 weeks	
Belimumab	≥ 14 weeks	
Certolizumab pegol[a]	≥ 8 weeks	Washout period waived if undetectable levels on TDM assay
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 biologic agent for the purposes of this study.
Golimumab[a]	≥ 8 weeks	Washout period waived if undetectable levels on TDM assay
Infliximab[a]	≥ 8 weeks	Washout period waived if undetectable levels on TDM assay
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 medical monitor.
IPP-201101	≥ 12 weeks	
Janus kinase (JAK) inhibitors[c]	≥ 8 weeks	Subjects treated with a JAK inhibitor 8-12 weeks prior to first dose of study treatment must be discussed with the medical monitor.
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 medical monitor if undetectable mycophenolic acid (MMA) level on a relevant assay; test not provided within the study.
Natalizumab	≥ 8 weeks	
Ocrelizumab[a]	≥ 24 weeks	
Pimecrolimus	≥ 4 weeks	
Plasmapheresis	24 weeks	
Retinoids	≥ 4 weeks	
Rituximab	≥ 12 months	
Sirolimus (rapamycin)	≥ 4 weeks	Washout period may be waived after discussion with medical monitor 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 medical monitor 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 on TDM assay
Tocilizumab	≥ 12 weeks	

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

TDM = therapeutic drug monitoring; TNF = tumor necrosis factor

[a] The washout period for this biologic can be waived for subjects who have an undetectable drug level on a TDM assay, performed either in routine clinical practice or during the screening period. If a TDM assay is used to waive the washout period for this biologic, the result of the TDM assay must be available in source documents, and the subject cannot receive another dose of that biologic after the TDM assay is obtained (Section 4.1.1.1).

[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.

[c] Failure or loss of response to previous treatment with JAK inhibitors, such as tofacitinib, is exclusionary.

[d] Failure or loss of response to previous treatment with ustekinumab (as well as other anti-IL-12/IL-23p40 antibodies or anti-IL-23p19 antibodies) is exclusionary.

Note: Investigators should consult with the [redacted] medical monitor for information about compounds not included in this list.

APPENDIX 8 HBV AND HCV TEST RESULT INTERPRETATION

I. HBV

As BMS-986165 is predicted to have immunomodulatory effects in this study, subjects with potentially active hepatitis B (HBV) infection and subjects at risk of reactivation of HBV infection will be excluded (see Section 5.2).

Hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), and hepatitis B surface antibody (HBsAb) are evaluated at screening, with reflex to HBV DNA testing in subjects with HBsAg negative, HBcAb positive serology (as listed in the "Interpretation unclear" scenario, below). Notes on interpretation of HBV serology within this study are given below:

Susceptible – does not meet exclusion criteria on HBV:

- HBsAg negative
- HBcAb negative
- HBsAb negative

Immune due to natural infection - does not meet exclusion criteria on HBV:

- HBsAg negative
- HBcAb positive
- HBsAb positive

Immune due to hepatitis B vaccination - does not meet exclusion criteria on HBV:

- HBsAg negative
- HBcAb negative
- HBsAb positive

Acutely infected – meets exclusion criteria on HBV:

- HBsAg positive
- HBcAb positive
- IgM HBcAb positive
- HBsAb negative

Chronically infected - meets exclusion criteria on HBV:

- HBsAg positive
- HBcAb positive
- IgM HBcAb negative
- HBsAb negative

Interpretation unclear:

- HBsAg negative
- HBcAb positive
- HBsAb negative

HBV DNA testing will be performed in subjects with a negative HBsAg, but a positive HBcAb at screening. Subjects with detectable HBV DNA at screening are excluded. Subjects in this subgroup may be eligible for inclusion if HBV DNA is undetectable on this assay during screening.

Subjects with HBsAg negative, HBcAb positive serology and undetectable HBV DNA at screening will have follow-up HBV DNA testing throughout their participation in the study, as detailed in the Schedule of Activities (Section 1.3).

- During the study, subjects in this subgroup will have HBV DNA tested at Weeks 4, 8, 12, and approximately every 3 months thereafter.
- Subjects in this subgroup who have a clinical response at Week 12, who then enter the maintenance period and subsequently lose response and enter the open-label Week 12 responder arm will have additional HBV DNA testing at the first 3 study visits after entry to this treatment arm.
- Subjects in this subgroup who do not have a clinical response at Week 12 and who enter the open-label BMS-986165 6 mg BID PO study arm, will have HBV DNA testing at Weeks 16, 20 and 24, and approximately every 3 months thereafter.
- Subjects who enter the open-label extension period at Week 52 will have HBV DNA tested at Weeks 56, 60 and 64, and approximately every 3 months thereafter.
- If subjects in this subgroup have detectable HBV DNA at any time, they must permanently discontinue study treatment, enter the post-treatment follow-up period and the investigator should consider referring them for appropriate specialty care and follow-up.

II. HCV

Testing for HCV is a two-step process: (i) anti-HCV antibody, and (ii) HCV RNA.

Subjects with a negative anti-HCV antibody may be eligible for the study.

Subjects with a positive or indeterminate anti-HCV antibody require additional HCV RNA testing to determine eligibility. Subjects with negative or undetectable HCV RNA may be eligible for the study. Subjects with positive or detectable HCV RNA have HCV infection, are excluded from the study and should be referred for appropriate assessment and consideration for treatment.

Subjects who were previously treated with an approved, treatment regimen for HCV infection may be eligible to participate in the study provided they achieve a Week 24 Sustained Virologic Response; that is negative or undetectable HCV RNA 24 weeks after completion of a full course of an approved treatment regimen for HCV infection. Such subjects must be discussed with the medical monitor prior to screening.

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.[16] Scherl et al.[31] 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).[18] 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[18] or European regulatory authorities.[32]

Consequently, disease activity assessments for inclusion and efficacy assessment will use the 9-point modified Mayo score [redacted].

Table 1 outlines the components and scoring used to calculate the modified [redacted] Mayo score[redacted].

Table 1 Components of the Modified [redacted] Mayo Score[redacted]

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	None
1	Streaks of blood with stool less than half the time
2	Obvious blood with stool most of the time
3	Blood alone passed
Findings of flexible proctosigmoidoscopy (endoscopy used to determine endoscopic [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)

[redacted]

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)
- Endoscopic (ES) subscore (0 to 3)

[redacted]

The modified [redacted] Mayo score [redacted] 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, valid (not necessarily consecutive), electronic subject diary entries recorded from the 7 days prior to a study visit** will be used to calculate the SF and RB subscores.

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
- The 24 hours prior to the date of the endoscopy (to account for any preparation [eg, enema(s), laxative(s), clear liquid diet] that can affect bowel frequency or blood content of the stool)

NOTE: Formal calculation of SF and RB subscores will be done using the electronic subject diaries. The averages of the 3 most recent, valid (not necessarily consecutive) diary entries for SF and RB (recorded from the 7 days prior to a study visit) will be calculated and used to represent SF and RB subscores in Mayo score determination; averages will be rounded up and down at the 0.5 cutoff.

For the pre-endoscopy 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 calculated to determine subject eligibility.

For subsequent study visits at which Mayo Scores are calculated:

For the Week 12, Week 52, and Week 104 visits, 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, valid (not necessarily consecutive), 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, Week 52, and Week 104.

MAYO SCORES: ELECTRONIC SUBJECT DIARY ENTRY INSTRUCTIONS

Standardized instructions for recording SF and RB data (based on draft FDA Guidance for UC clinical endpoints)[18] 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.
Stool Frequency (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 should be 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. 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.

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

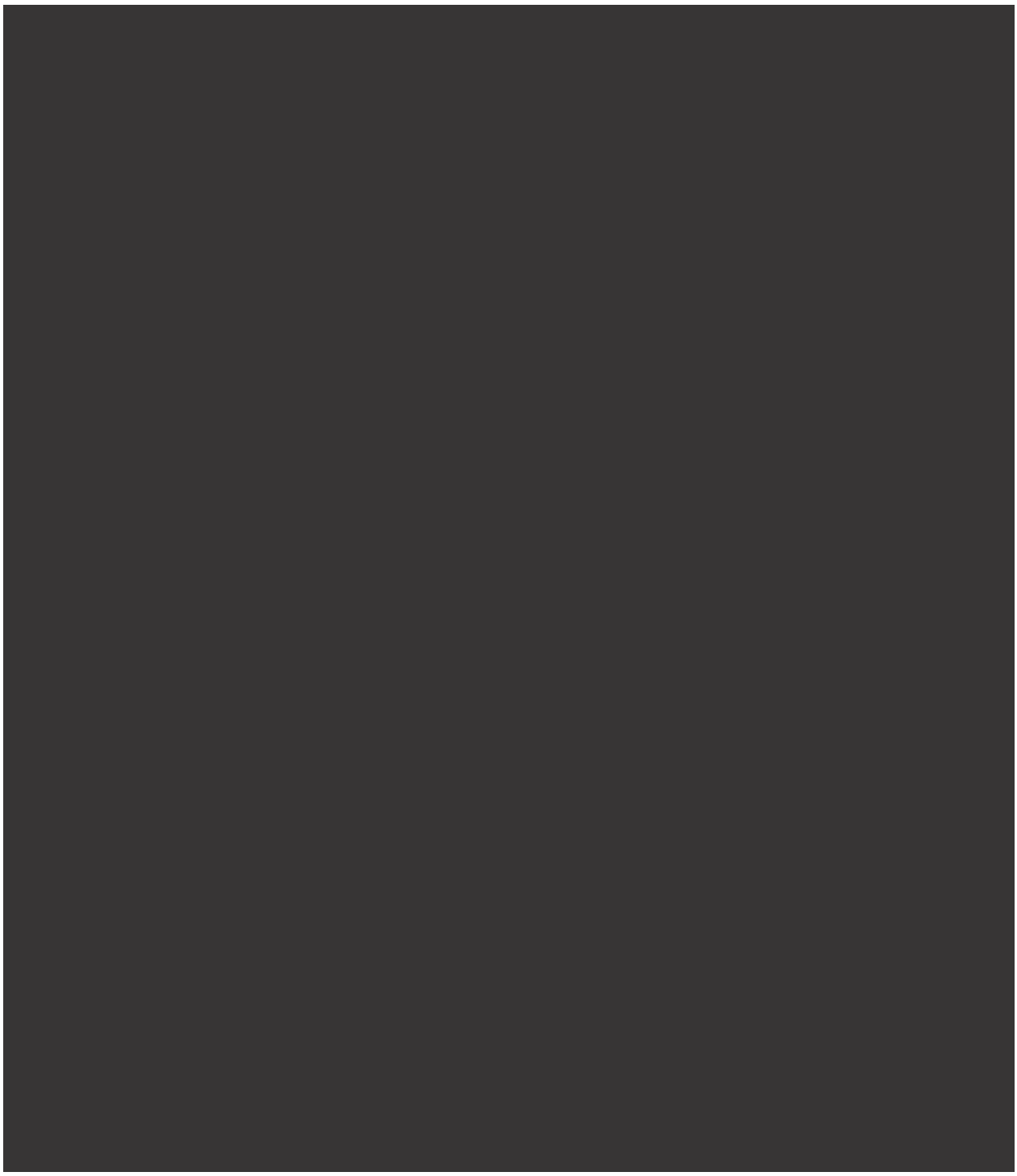
RB = rectal bleeding; SF = stool frequency; UC = ulcerative colitis

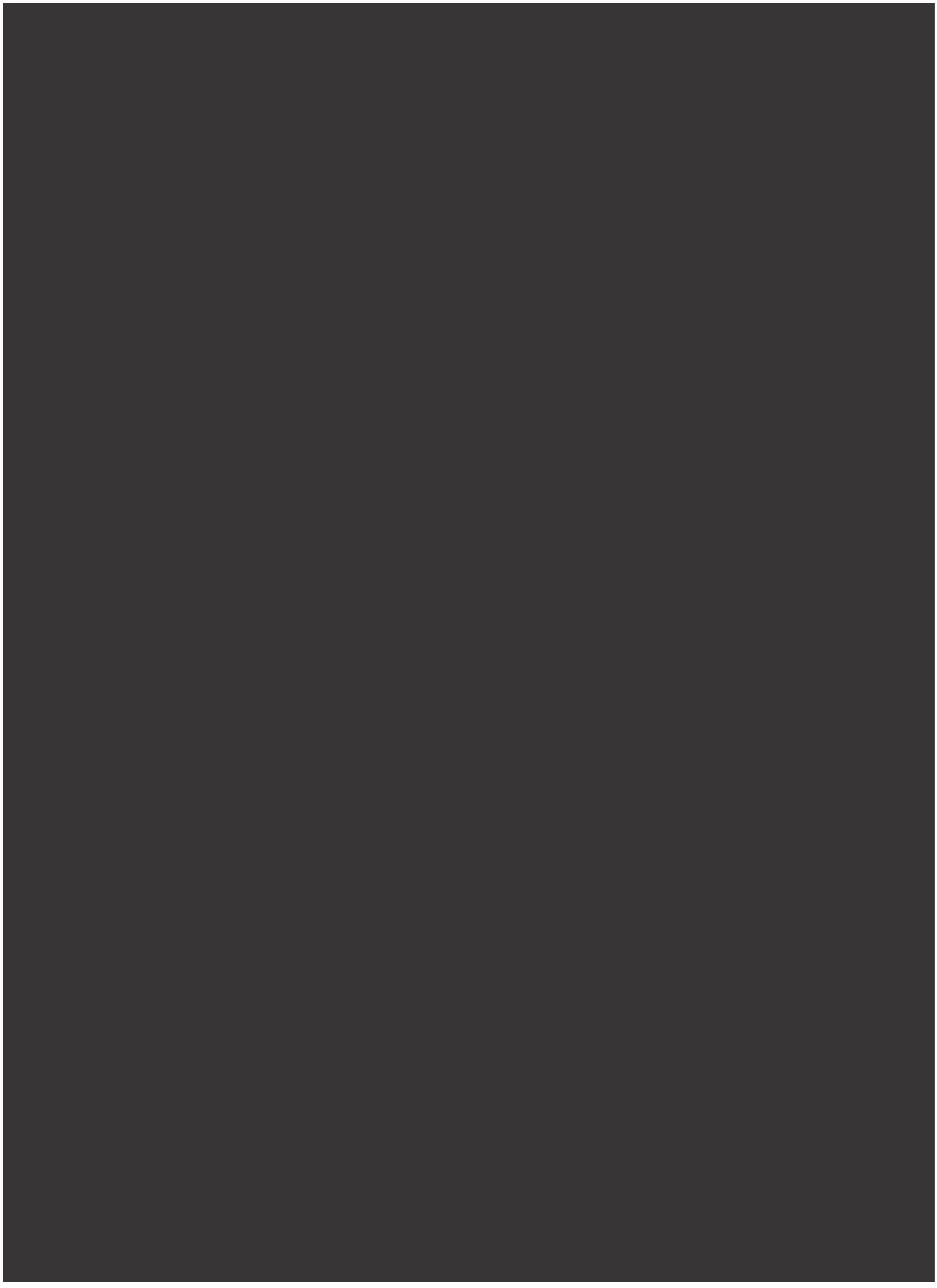
Adapted from: Draft Guidance for Industry, Ulcerative Colitis: Clinical Trial Endpoints US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Draft August 2016. Publication UCM515143.

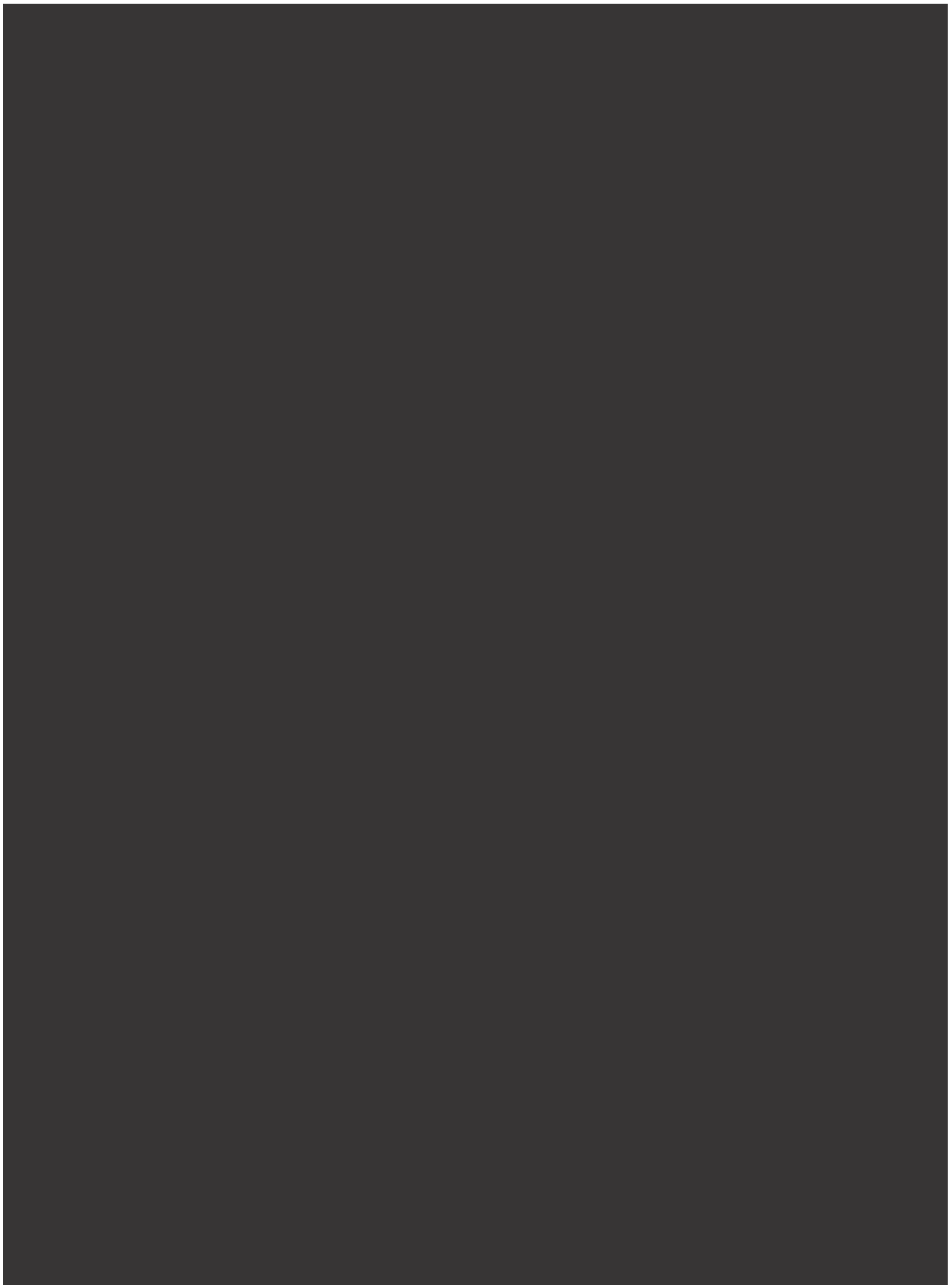
Endoscopic (ES) Subscore

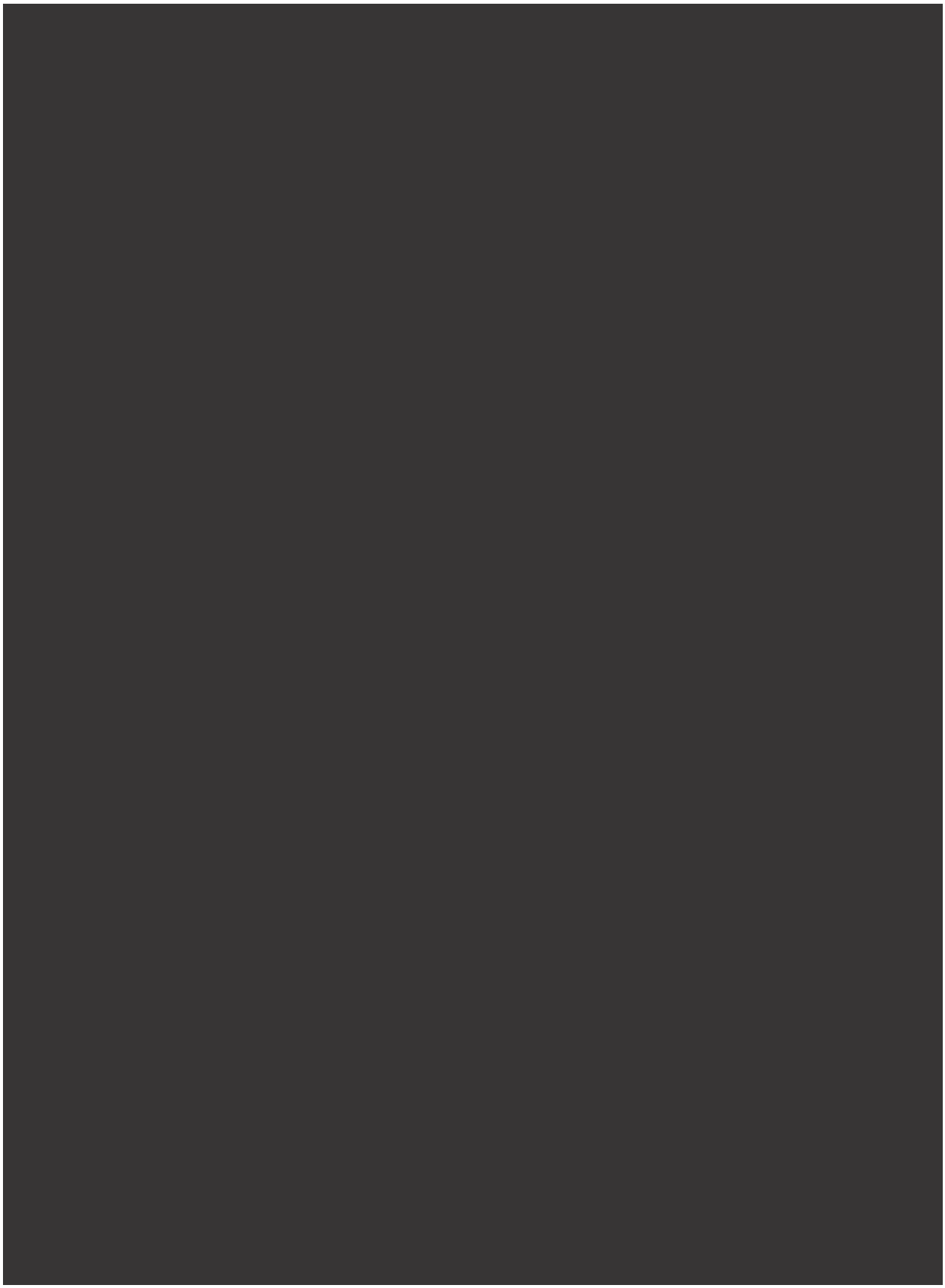
ES subscores will be provided via email by the independent central endoscopy vendor [redacted] for all eligibility and efficacy assessments, at all time points. The endoscopy procedure from screening (central read) will be used to determine the **baseline** (Week 0 [Day 1]) ES subscore component of the Mayo score. The ES subscores of the Mayo score will be modified so that the value 1 does not include friability.

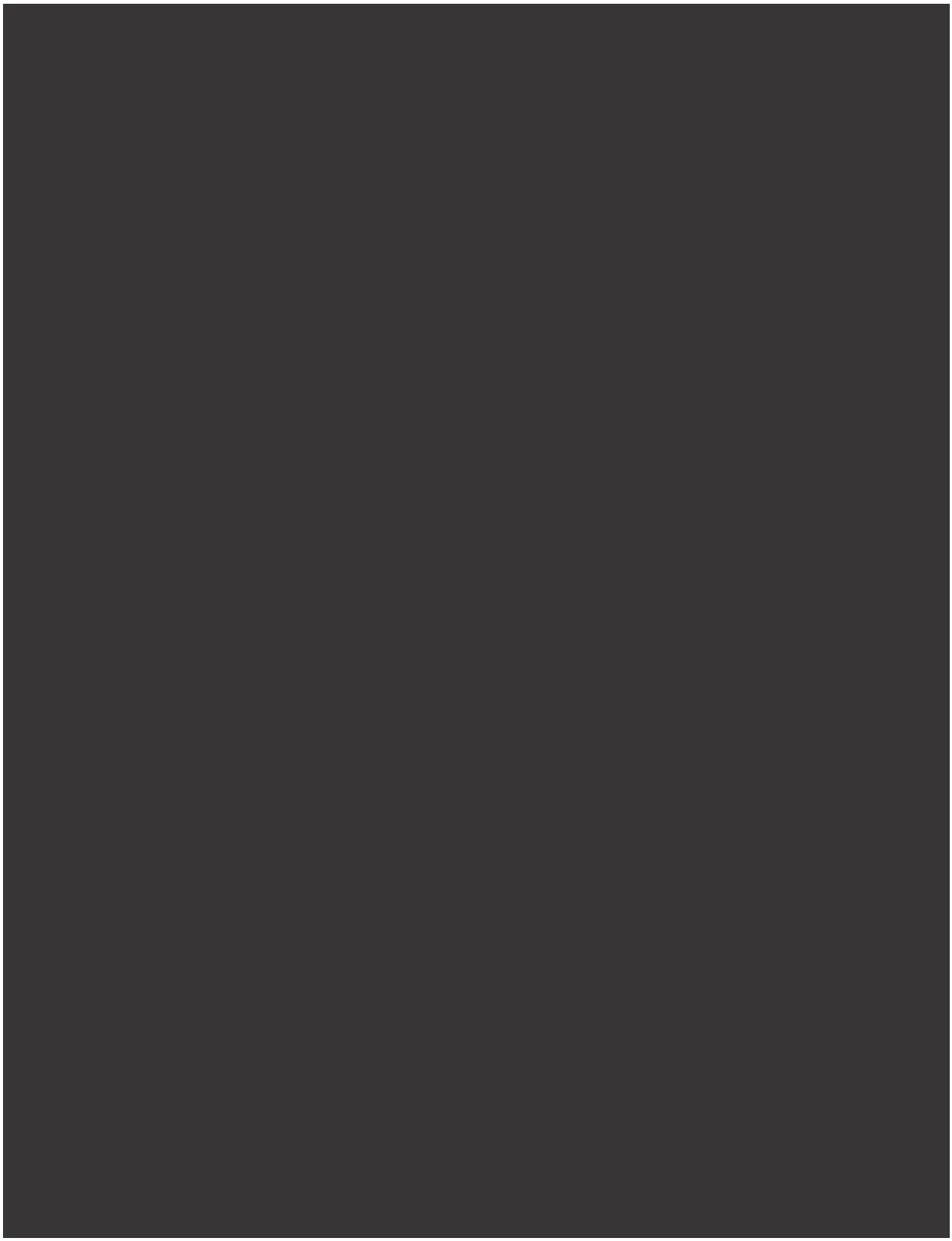
At Week 12 only: **Local** assessment of the endoscopy will be utilized to derive the ES component of the Mayo Score; this is used for determination of treatment assignment during the maintenance period (see Section 8.1.1 for details). The central read of the endoscopy will be used for efficacy analysis at all time points.

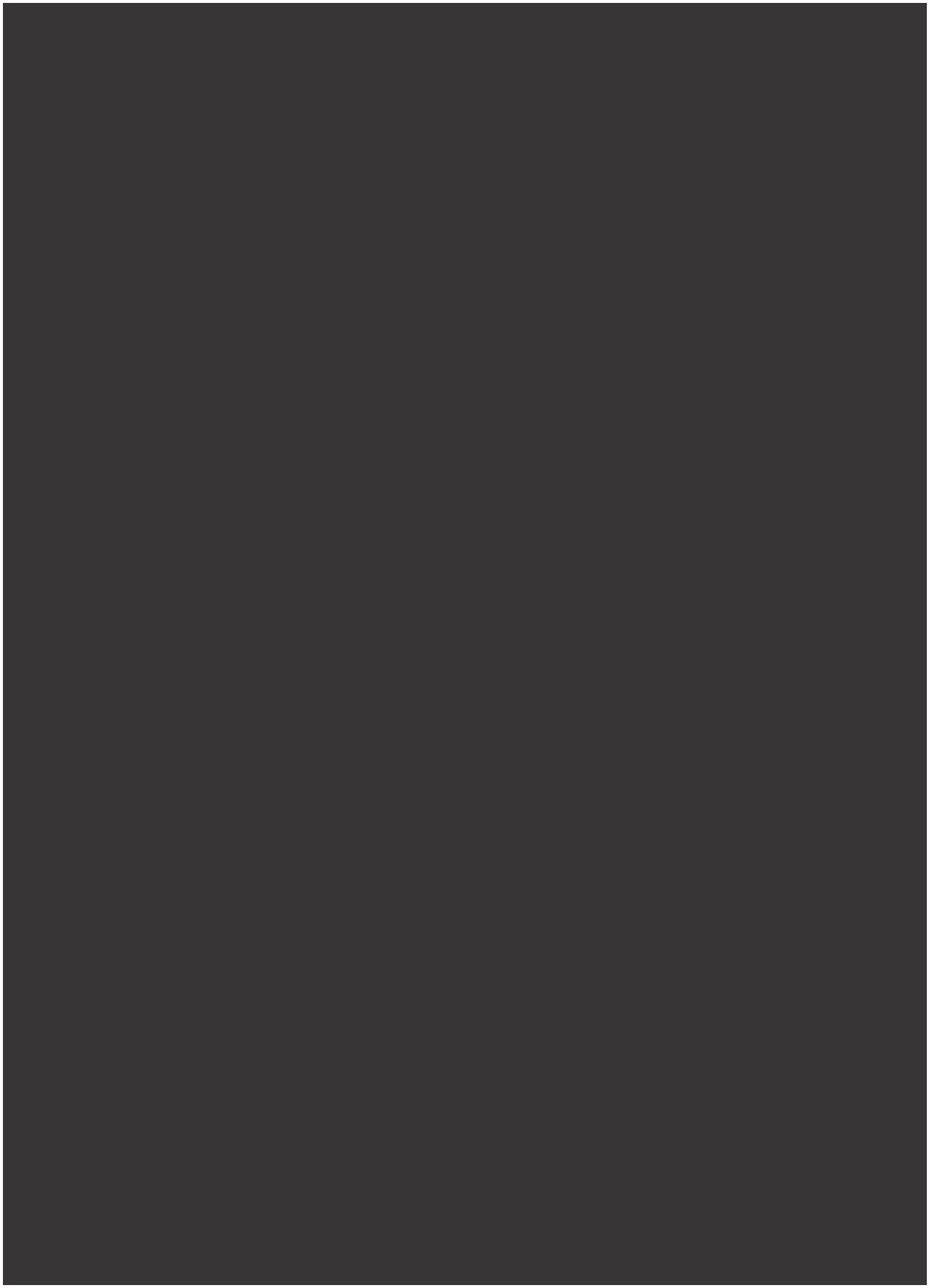


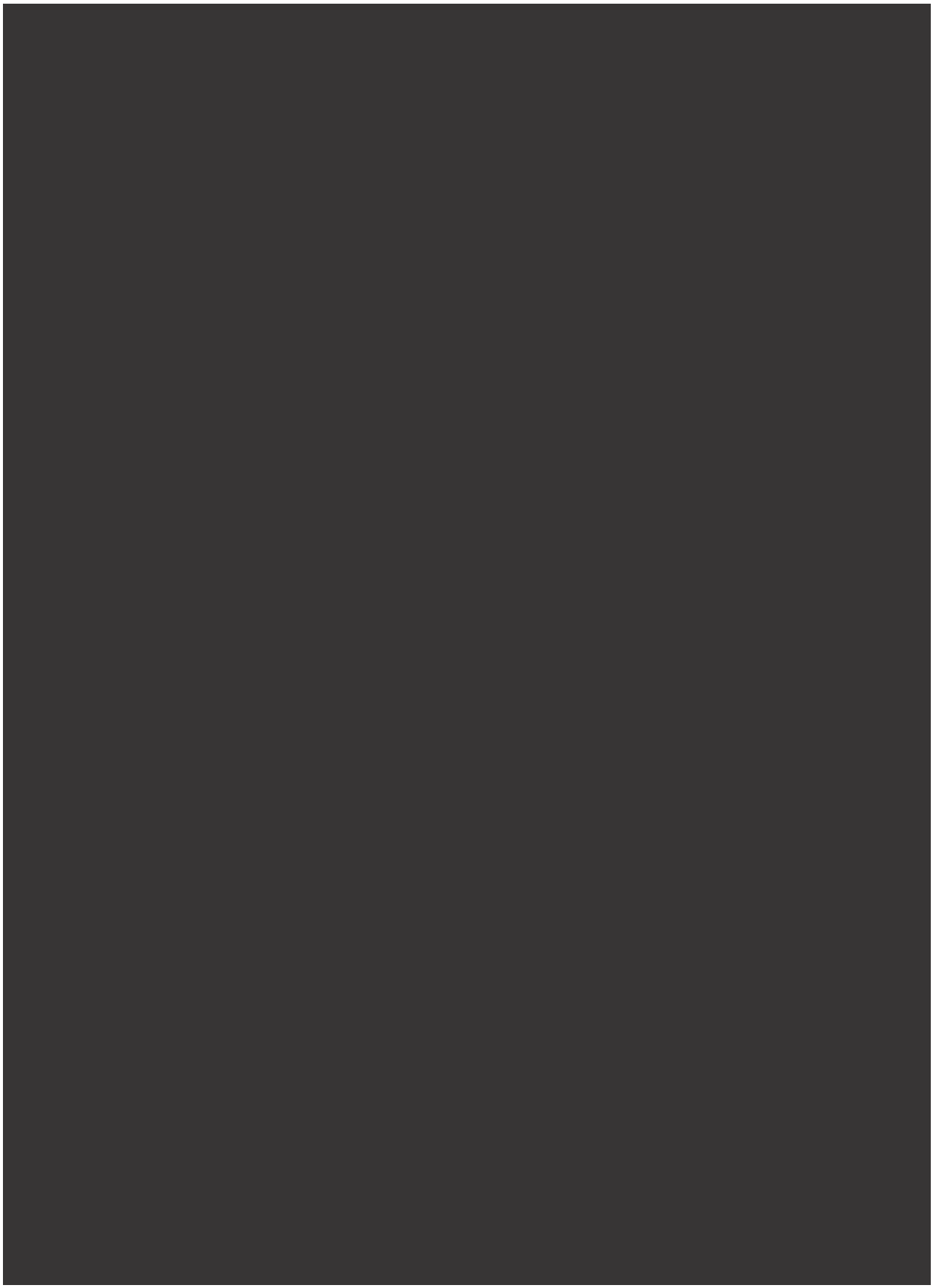


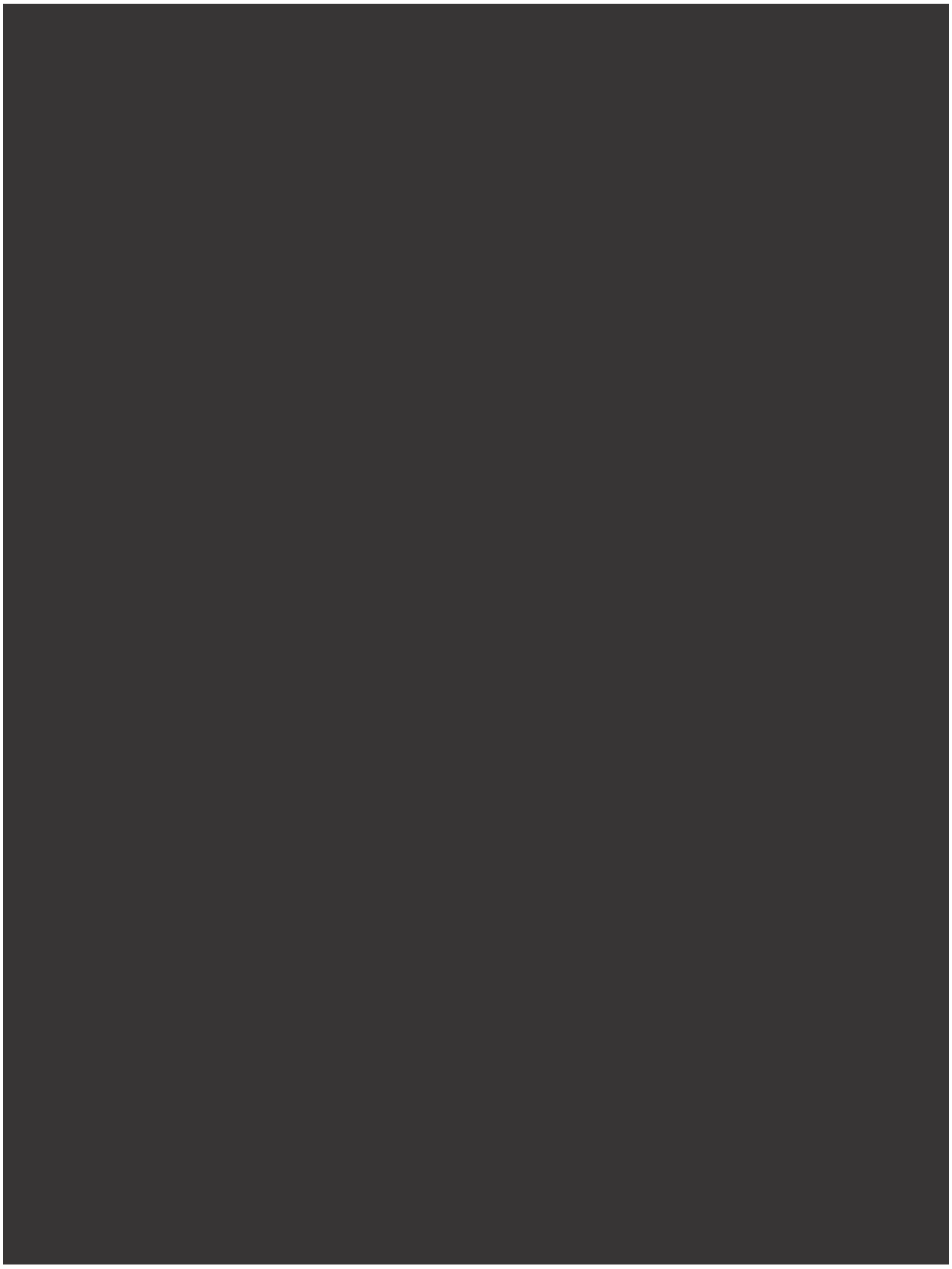


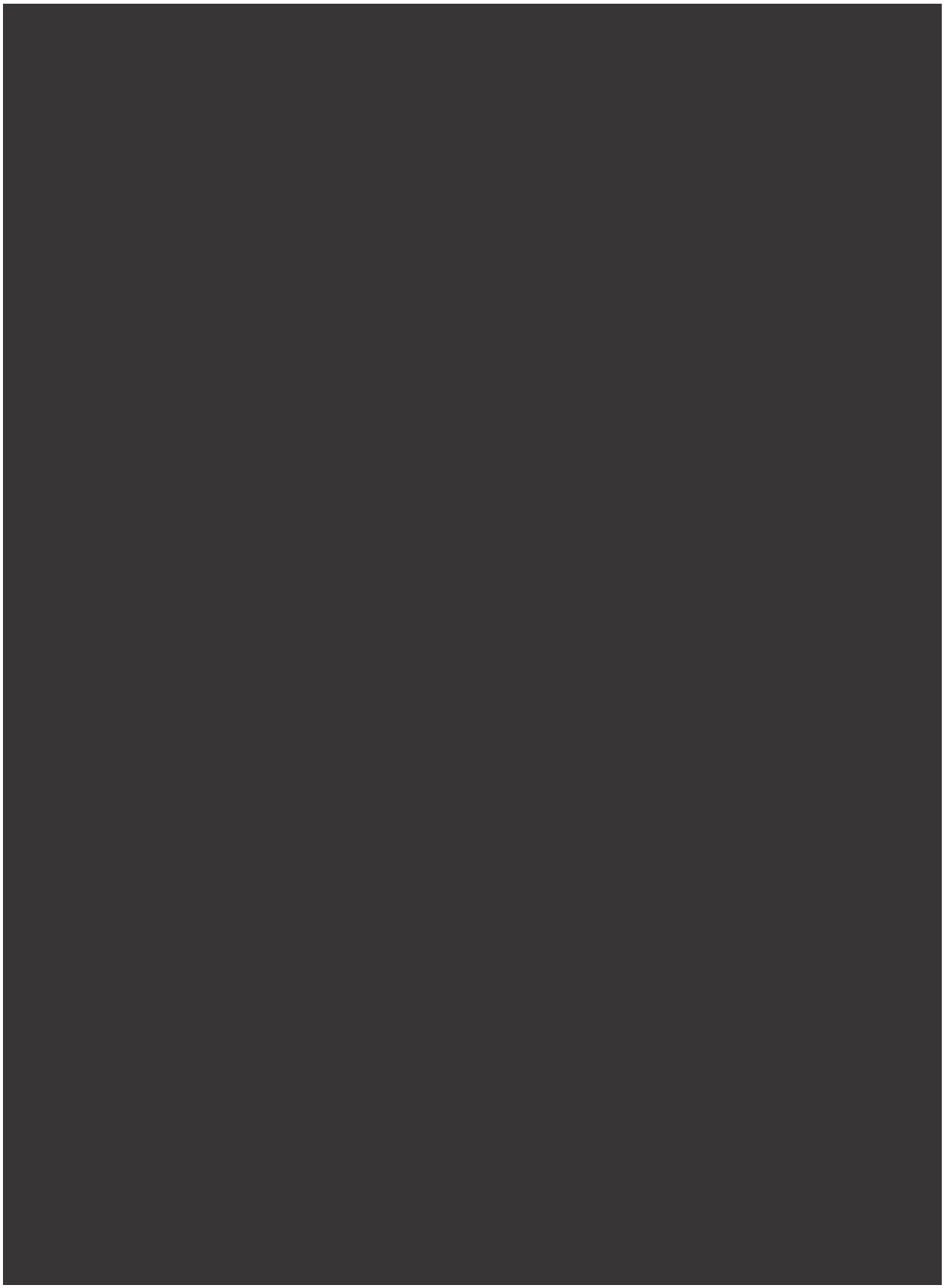


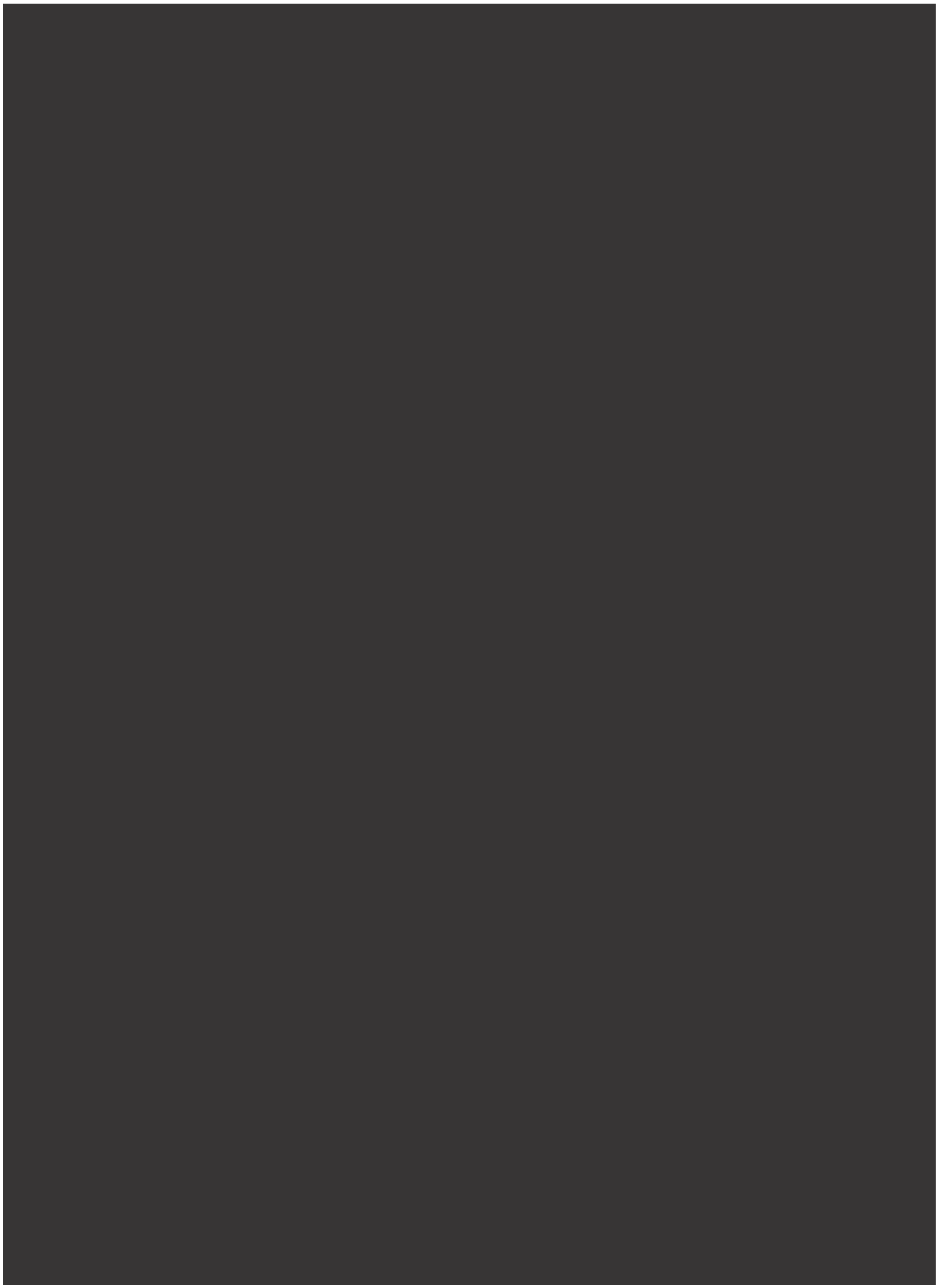


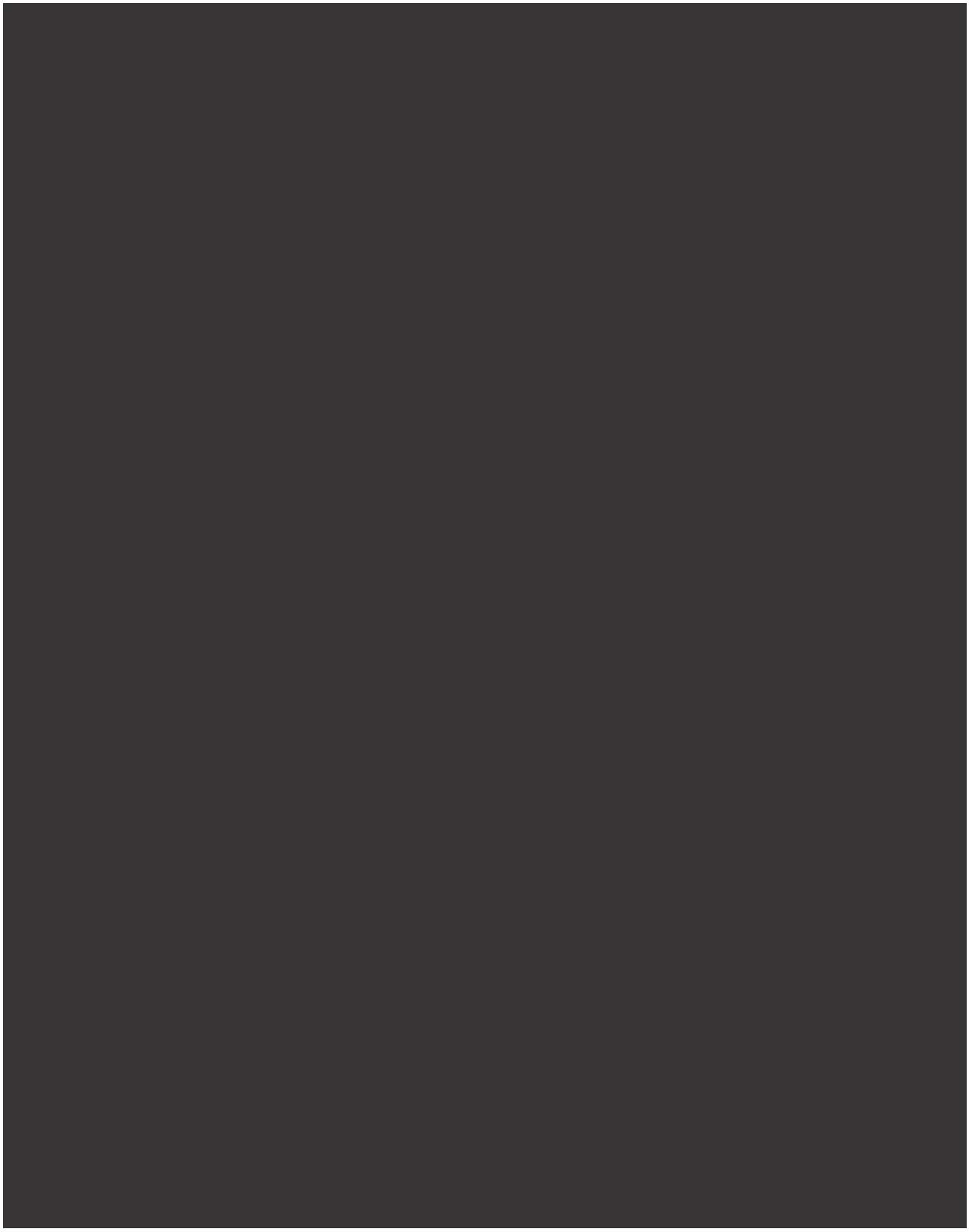


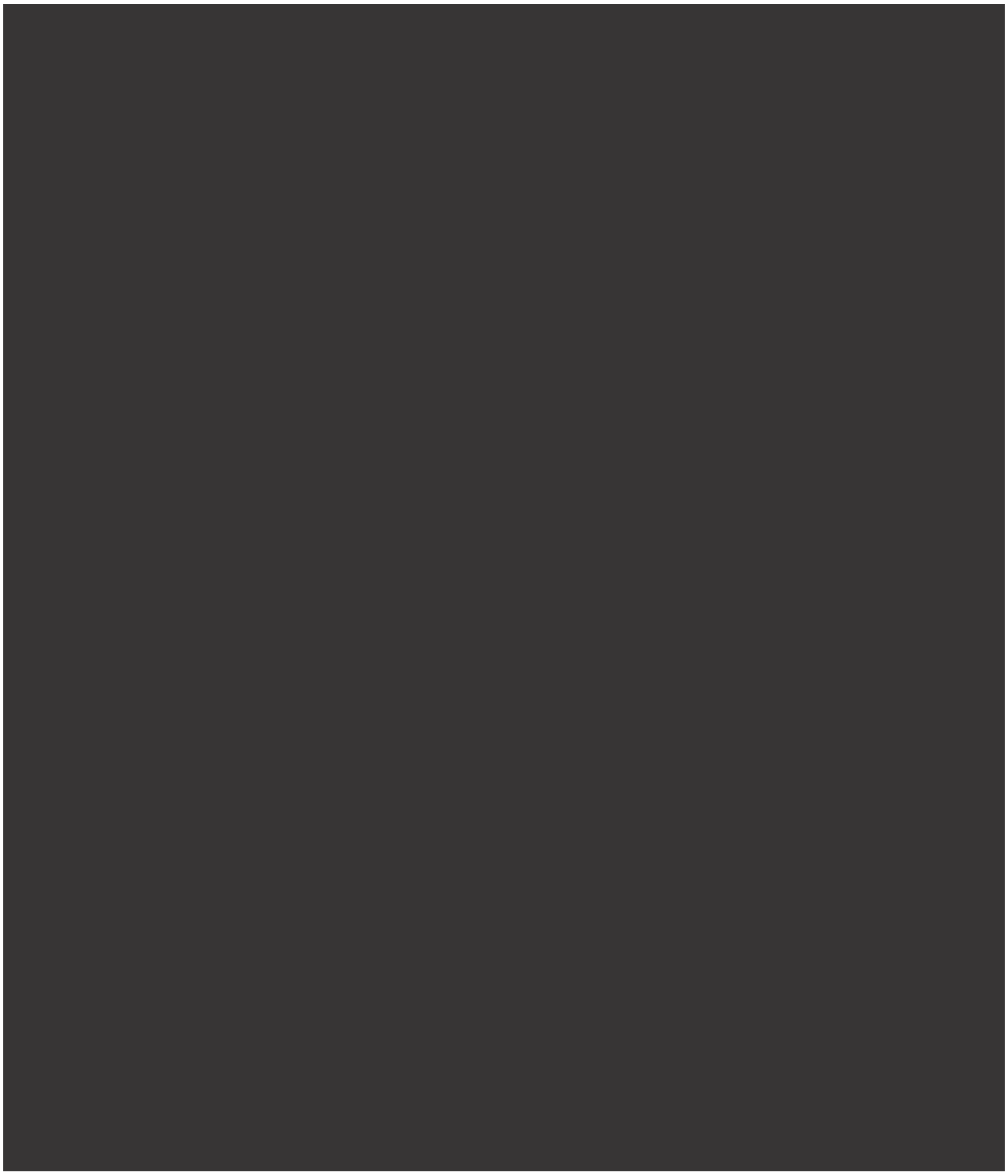


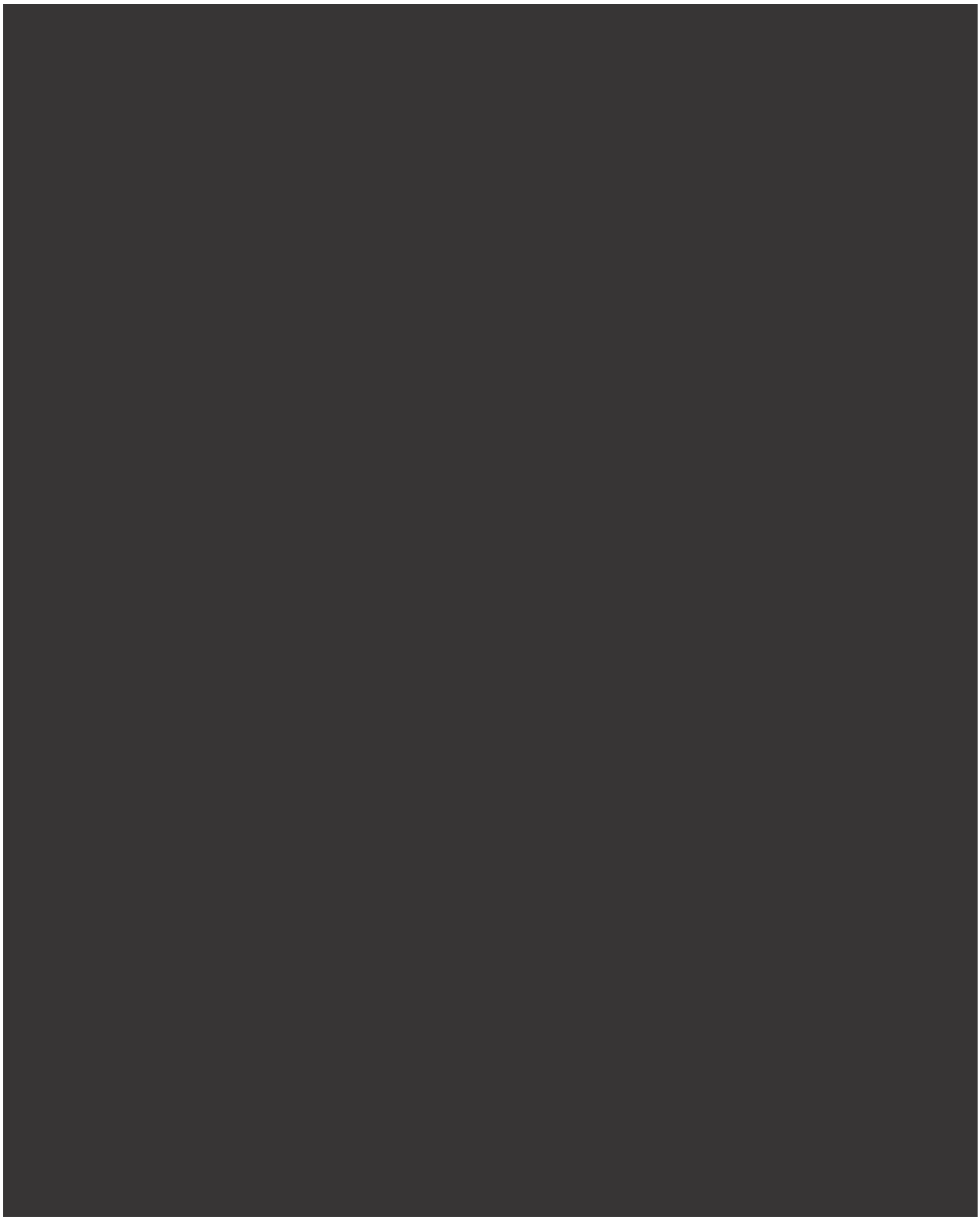


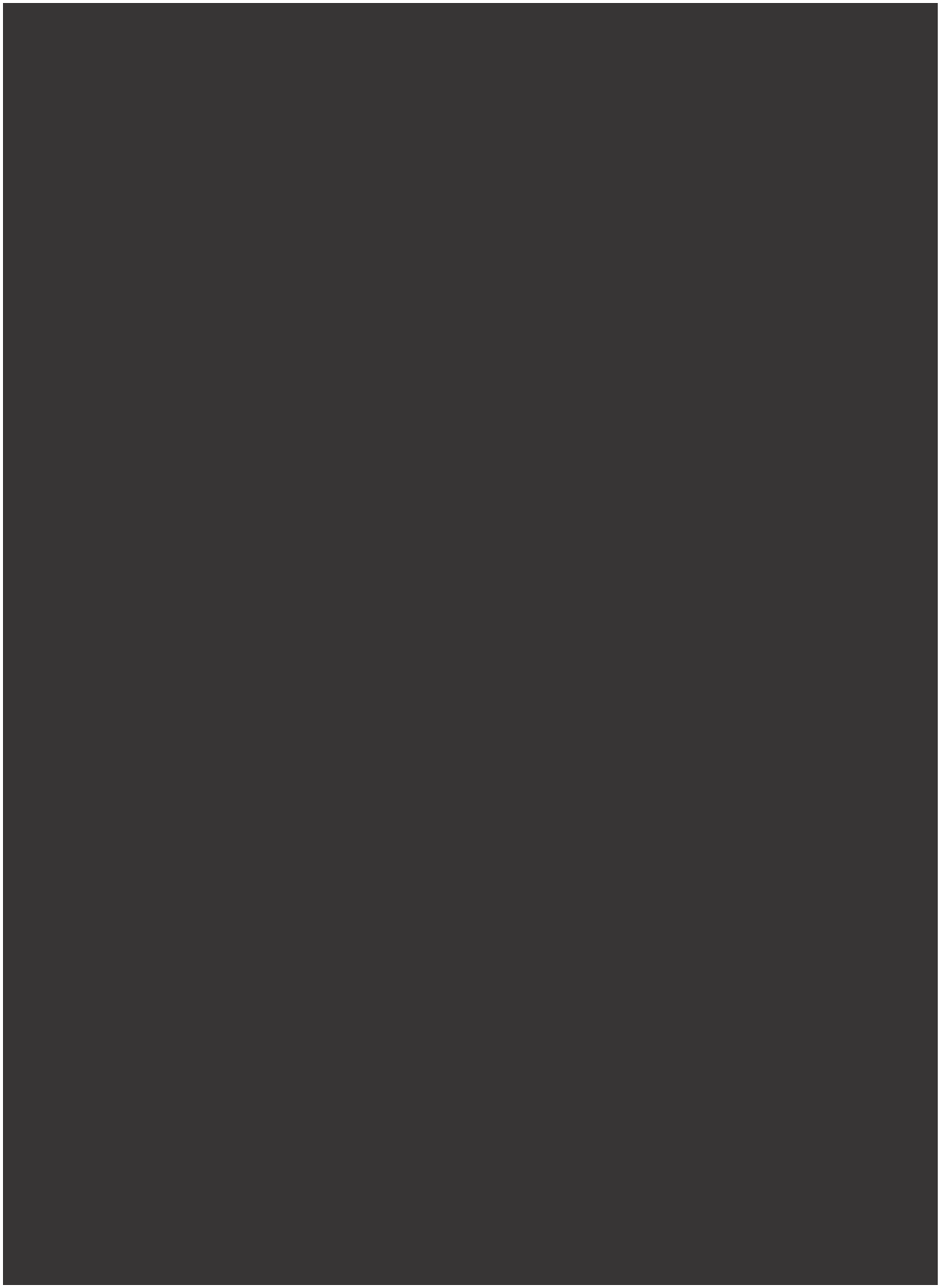












APPENDIX 19 COVID-19 VACCINES

If a subject has received a specific COVID-19 vaccination, the type of vaccine received should be recorded on the concomitant medication page, if given during the study, or the past history page, if given prior to enrollment.

- Administration of a live vaccine is prohibited 90 days prior to the randomization visit; during the induction period, maintenance period, or OLE; or within 2 months after the last dose of IP.
- Administration of a non-live vaccine is allowed during the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 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 COVID-19 vaccine).
- For COVID-19 vaccines requiring more than one 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 participant at risk. Ideally, adverse events attributable to a vaccine should have resolved prior to enrollment.

Please contact the medical monitor with any questions related to COVID-19 vaccines.