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 Crohn's Disease

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CLINICAL PROTOCOL IM011023

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

Protocol Amendment No.: 05

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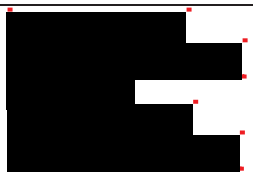
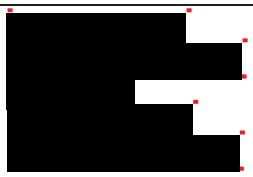
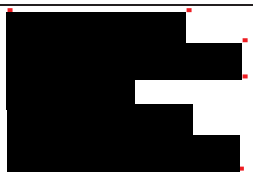
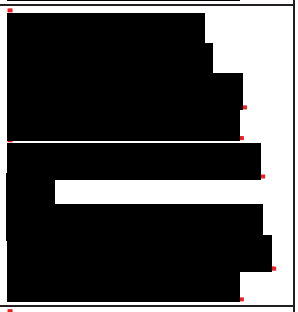
DOCUMENT HISTORY

Document	Date of Issue	Summary of Changes	Approvers
Amendment 05 (Global Amendment 34 v6.0[a]) (im011023-protamend05)	02-Sep-2022	Includes the following modifications: • Added diary selection rules for Week 0 of CDAI/PRO2 calculation • Updated efficacy analyses to reflect updated planned statistical analyses • Clarification of assessments and timing for Week 104 visit • [redacted] • Elucidation of treatment failure rules • Added open-label 6 mg BID BMS-986165 arm to the Selection and Timing of Dose table • Applied minor editorial changes to enhance the clarity of the protocol and update address information	[redacted]
Administrative Letter 07	15-Oct-2021	Corrected numbering in inclusion/exclusion criteria.	[redacted]
Amendment 01 Netherlands Revised Protocol 33[a] Netherlands-specific (im011023-protamend01-nl)	27-Sep-2021	Netherlands-specific protocol amendment incorporating modification to Inclusion Criteria 2, Type of Subject and Target Disease Characteristics.	[redacted]
Amendment 05 China Revised Protocol 32[a] China-specific (im011023-protamend05-cn)	27-Sep-2021	China-specific protocol amendment incorporating modifications implemented in Global Protocol Amendment 04, v5.0, and the following additional China-specific changes: [redacted] • *C. difficile* toxin screening procedures specific to mainland China sites, as previously described in Administrative Letter 05 (20-Jan-2021), were added in APPENDIX 20	[redacted]

Document	Date of Issue	Summary of Changes	Approvers
Amendment 01 Belgium Revised Protocol 31[a] Belgium-specific (im011023-protamend01-be)	08-Sep-2021	Belgium-specific protocol amendment clarifying contraceptive requirements for male subjects in Belgium.	
Administrative Letter 06	02-Sep-2021	Clarifies a study endpoint that was incorrectly duplicated in both the secondary and exploratory endpoint sections.	
Amendment 05 Japan Revised Protocol 30[a] Japan-specific (im011023-protamend05-jp)	01-Sep-2021	Japan-specific protocol amendment incorporating modifications implemented in Global Protocol Amendment 04, v5.0.	
Amendment 03 Portugal Revised Protocol 29[a] Portugal-specific (im011023-protamend03-pt)	27-Aug-2021	Portugal-specific protocol amendment incorporating modifications implemented in Global Protocol Amendment 04, v5.0.	
Amendment 02 France Revised Protocol 28[a] France-specific (im011023-protamend02-fr)	27-Aug-2021	France-specific protocol amendment incorporating modifications implemented in Global Protocol Amendment 04, v5.0.	
Amendment 03 South Korea and Taiwan Revised Protocol 27[a] South Korea and Taiwan-specific (im011023-protamend03-kr-tw)	27-Aug-2021	South Korea and Taiwan-specific protocol amendment incorporating modifications implemented in Global Protocol Amendment 04, v5.0.	
Amendment 05 Italy Revised Protocol 26[a] Italy-specific (im011023-protamend05-it)	27-Aug-2021	Italy-specific protocol amendment incorporating modifications implemented in Global Protocol Amendment 04, v5.0.	

Document	Date of Issue	Summary of Changes	Approvers
Amendment 04 Germany Revised Protocol 25[a] Germany-specific (im011023-protamend04-de)	27-Aug-2021	Germany-specific protocol amendment incorporating modifications implemented in Global Protocol Amendment 04, v5.0.	[redacted]
Amendment 04 (Global Amendment 24 v5.0[a]) (im011023-protamend04)	06-Aug-2021	Includes the following modifications: • Added information, instructions, and measures to be taken related to SARS-CoV-2 infection. • Reconfigured secondary and exploratory endpoints in response to expert consensus on treatment targets in IBD. • [redacted] • Removed exclusion criterion that prohibited the participation of subjects who had previously experienced inadequate response or loss of response to ustekinumab. • Clarified multiple other inclusion and exclusion criteria. • Updated vendor information • Added efficacy and safety findings from recent BMS-986165 studies • Removed fasting requirement at screening. • Clarified procedures for *C. difficile* testing, endoscopies, unblinding for Week 12 analysis, hematocrit analysis, potential future analyses, and subjects with liver abnormalities and potential DILI AEs. • [redacted] • Clarified that subjects who need rescue treatment must discontinue study treatment during the OLE. • Updated language throughout protocol to reflect current BMS procedures, policies, and guidelines.	[redacted]
Revised Protocol 23 IM011023 Revised Protocol 01d Italy Specific[a]	08-Jan-2021	This country-specific revised protocol applies to all subjects enrolled in Italy.[redacted]	[redacted]

Document	Date of Issue	Summary of Changes	Approvers
Revised Protocol 22 IM011023 Revised Protocol 03a France Specific[a]	23-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 #2g, which allowed patients with only an inadequate response, loss of response, or intolerance to a standard course of oral aminosalicylates for induction therapy for at least 6 weeks to be included in the trial.	[redacted]
Revised Protocol 21 IM011023 Revised Protocol 01d China Specific[a]	23-Mar-2020	China-specific including the following modifications: • Chest imaging for tuberculosis screening was amended to allow for chest x-ray or computed tomography scan • A negative result for *C. difficile* by nucleic acid amplification test will only be required for rescreening if a validated assay is available. If a validated nucleic acid amplification test is not available, the subject must have negative testing for *C. difficile* toxin and *C. difficile* glutamate dehydrogenase in order to be rescreened. • Optional Therapeutic Drug Monitoring to allow washout periods to be waived for certain medications was removed.	[redacted]
Revised Protocol 20 Revised Protocol 01b Portugal Specific[a]	12-Mar-2020	Portugal-specific incorporating changes from Global Protocol v3.0 (25-Jun-2019) and Global Protocol v4.0 (20-Aug-2019).	[redacted]
Revised Protocol 19 FINAL APPROVED (Portugal) v2.0	19-Nov-2019	[redacted]	[redacted]
Amendment 18 FINAL APPROVED (Japan) v4.0	23-Sep-2019	Japan-specific incorporating Global Protocol, v4.0.	[redacted]

Document	Date of Issue	Summary of Changes	Approvers
Amendment 17 FINAL APPROVED (China) v4.0	30-Sep-2019	China specific incorporating Global Protocol, v4.0.	
Amendment 16 FINAL APPROVED (Italy) v4.0	20-Sep-2019	Italy-specific incorporating Global Protocol, v4.0.	
Amendment 15 FINAL APPROVED (Germany) v4.0	27-Aug-2019	Germany-specific incorporating Global Protocol, v4.0.	
Amendment 14 FINAL APPROVED (South Korea and Taiwan) v4.0	27-Aug-2019	South Korea and Taiwan-specific incorporating Global Protocol, v4.0.	
Amendment 13 FINAL APPROVED (Japan) v3.0	23-Aug-2019	Japan-specific incorporating Global Protocol, v3.0.	
Amendment 12[b] Global (Global Revision 03	20-Aug-2019	Includes the following modifications: • Clarification of the number of subject diary days required to calculate the CDAI	

Document	Date of Issue	Summary of Changes	Approvers
FINAL APPROVED v4.0[a])		• Alignment in protocol text and Appendix 7 of washout times for specific treatments • Clarification of rescreening requirements for subjects positive for *C. difficile*	[redacted]
Amendment 11[b] FINAL APPROVED (China) v3.0	01-Aug-2019	China-specific Amendment incorporating Global Protocol, v3.0. Additional modifications include: [redacted]	[redacted]
Amendment 10[b] FINAL APPROVED (South Korea/Taiwan) v3.0	26-Jul-2019	South Korea/Taiwan specific incorporating Global Protocol Amendment, v3.0. [redacted]	[redacted]
Amendment 9[b] FINAL APPROVED (Germany) v3.0	24-Jul-2019	Germany specific incorporating Global Protocol Amendment, v3.0.	[redacted]
Amendment 8[b] FINAL APPROVED (Italy) v3.0	24-Jul-2019	Italy specific incorporating Global Protocol Amendment, v3.0.	[redacted]
Amendment 7[b] Global	25-Jun-2019	Includes the following modifications: • Change of co-primary endpoint (clinical remission) definition	[redacted]

Document	Date of Issue	Summary of Changes	Approvers
(Global Revision 02 FINAL APPROVED v3.0[a])		• Removal of 12 mg QD treatment arm • Addition of 52-week open-label extension period • Clarification of clinical response, loss of response, and treatment failure definitions • [redacted] • Revision of the Schedule of Activities [redacted] to provide clarity • Update of Multiplicity Adjustment Section (10.4.6) • Update of wording in various appendices to be consistent across studies of BMS-986165 • Minor grammatical and typographic corrections	[redacted]
Amendment 6[b] Germany (Amendment 4 FINAL APPROVED v2.3[a])	04-Dec-2018	Germany specific	[redacted]
Amendment 5[b] Italy (Amendment 3 FINAL APPROVED v2.2[a])	29-Oct-2018	Italy specific	[redacted]
Amendment 4[b] China (Amendment 2 FINAL APPROVED v2.1[a])	12-Oct-2018	China specific	[redacted]
Amendment 3[b]	27-Aug-2018	Japan specific	[redacted]

Document	Date of Issue	Summary of Changes	Approvers
Japan specific (Japan Protocol Amendment 2[a])			
Amendment 2[b] Japan specific (Japan Protocol Amendment 1[a])	17-Jul-2018	Japan specific	[redacted]
Global Revision 01 FINAL APPROVED v2.0	24-May-2018	[redacted]	[redacted]
Original protocol FINAL APPROVED, v1.0	14-Feb-2018 & 27-Mar-2018 (updated)	Not applicable	[redacted]

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

[b] Protocol Amendment numbering has been updated to reflect total amendment count.

OVERALL RATIONALE FOR GLOBAL PROTOCOL AMENDMENT 05

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

- Added diary selection rules for Week 0 of CDAI/PRO2 calculation
- [redacted]
- Updated efficacy analyses language to reflect updated planned statistical analyses

The amendment will be implemented after the Investigator receives all appropriate regulatory 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 amendment is provided in the summary of key changes table, as shown below.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 05

Section Number & Title	Description of Change	Brief Rationale
Title page	Changed the Europe/East Asia/Pacific Medical Monitor's address and BMS Japan headquarters address	To ensure investigators have correct study contact information
2 Schedule of Activities, Table 4	Lengthened visit window of Week 104 from ± 3 days to ± 7 days	To decrease subject burden and align with updated endoscopy recommendations
2 Schedule of Activities, Table 4 9.2 Laboratory Assessments 9.5.3 Clinical Safety Laboratory Assessment	Clarified that a local lab can be used to analyze hematocrit at Week 104, in addition to Week 2 through Week 52	To ensure prompt CDAI score calculation at Week 104 [redacted]
2 Schedule of Activities, Table 4 9.6.1 Sampling Schedule, Table 7	[redacted]	[redacted]
2 Schedule of Activities, Table 4	[redacted]	[redacted]

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
3.2.1 Scientific Rationale for Study Design 5.1 Overall Design, Figure 1 5.1.3.2 Week 26 7.1 Treatments Administered	Clarified study procedures for subjects who do not achieve a clinical response by Week 12	To ensure Week 12 nonresponders are switched into the open-label BMS-986165 treatment group and reassessed for clinical response at Week 26 (compared to Week 0)
4.3 Exploratory	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
5.3 End of Study Definition	[redacted]	[redacted]
6.1 Inclusion Criteria	Fixed numbering of Inclusion Criterion 2 subcriteria to be alphabetical “a” through “g,” in place of previous erroneous numbering (a, b, c, b, d, e, f)	To incorporate changes from Administrative Letter 07 (dated 15-Oct-2021)
6.5.1 Retesting During the Screening Period; Rescreening	Clarified that previously randomized subjects are not eligible for rescreening, even if they did not receive a dose of study treatment	To clarify rescreening procedures for a subgroup of participants
7.1 Treatments Administered, [redacted]	[redacted]	[redacted]
9.1 Efficacy Assessments	Added diary selection rules for Week 0 of CDAI/PRO2 calculation	To align with SAP and site training materials
10.4 Efficacy Analyses	Updated efficacy analyses language to reflect updated planned statistical analyses	To align with the latest updates to the SAP (August 2022 version)

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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 Crohn's Disease

Study Phase: 2

Background:

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. 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 interferon receptor. This results in the activation of STAT-dependent transcription and functional responses specific for these cytokines. 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 and JAK3 (eg, IL-2, IL-6, IL-7, IL-15) 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 Crohn's disease (CD), ulcerative colitis, psoriasis, psoriatic arthritis, systemic lupus erythematosus (SLE) and spondyloarthritides.

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. Inhibition of TYK2 is expected to provide therapeutic benefit for patients with CD for multiple reasons: 1) IL-12 and IL-23 have been implicated in pathogenesis of CD; 2) Biologic agents targeting IL-23p19 and IL-12/23p40 cytokines have been shown to be efficacious in CD, and ustekinumab targeting IL-12/23p40 has been approved for the treatment of CD; and 3) BMS-986165 has been shown to be efficacious in psoriasis, an IL-23-mediated disease, in a recent Phase 2 study.

Overview of Study Design:

IM011023 is a Phase 2 randomized, double-blind, placebo-controlled clinical study designed to assess the safety and efficacy of BMS-986165 compared to placebo in subjects with moderately to severely active CD.

Approximately 240 subjects will be randomized in this study. After a 28-day Screening Period, eligible subjects will be randomized in a 3:3:2 ratio to one of three study arms: (i) BMS-986165 6 mg twice daily (BID) by mouth (PO); n≈90, (ii) BMS-986165 3 mg BID PO; n≈90, or (iii) matched placebo; n≈60. [redacted]

This study has a 12-week double-blind Induction Period, a 40-week double-blind Maintenance Period, and a 52-week Open-label Extension (OLE) Period, leading to a total of up to 104 weeks of exposure to investigational product (IP). The primary efficacy assessment occurs at Week 12. The co-primary endpoints are defined as achieving clinical remission (defined as Crohn's Disease Activity Index [CDAI] of < 150) and achieving endoscopic response (≥ 50% improvement from baseline in the Simple Endoscopic Score for Crohn's Disease [SES-CD]), on a population basis, at Week 12.

This study has a treat-through design in order to explore sustained clinical benefit and safety in the Maintenance Period. Subjects who achieve clinical response (a reduction from baseline in the CDAI score of ≥ 100 points or a total CDAI score < 150) at Week 12 (Day 85), are eligible to enter the Maintenance Period and to continue on the same double-blind treatment regimen that they received in the Induction Period for up to an additional 40 weeks, up to Week 52. Subjects with a loss of response (LOR; an increase in the CDAI score of ≥ 100 points compared to Week 12 and a total CDAI score of ≥ 220 points) at any time from Week 13 through Week 52 are eligible to enter an open-label BMS-986165 6 mg BID PO arm through Week 52.

Subjects who do not achieve clinical response at Week 12 and who have an appropriate safety profile are eligible to enter an open-label BMS-986165 6 mg BID PO arm, in which clinical response is again assessed at Week 26 (compared to Week 0). Subjects in this open-label study arm who achieve clinical response at Week 26 (compared to Week 0) may continue in this arm through Week 52. Subjects in this open-label study arm who do not achieve clinical response at Week 26 (compared to Week 0) will be considered treatment failures and must permanently discontinue IP and enter the Post-treatment Follow-up Period. Throughout the study, subjects who permanently discontinue IP prior to Week 52 must enter the Post-treatment Follow-up Period.

Subjects who continue to derive a clinical benefit from IP at Week 52, as judged by the investigator, are eligible to enter the OLE Period. The OLE Period lasts 52 weeks, to Week 104.

Overview of Scientific Rationale:

The scientific rationale for the study is summarized above and further detailed in Section 3 and the Investigator Brochure (IB). This Phase 2 randomized, double-blind clinical trial is designed to assess the safety and efficacy of BMS-986165 in patients with moderately to severely active CD.

[redacted]

[redacted]

[redacted]

The eligibility criteria are designed to ensure that subjects have moderately to severely active CD at baseline and to minimize the risk for serious infections that may be associated with immune modulating therapies.

[redacted]

[redacted]

A [redacted] benefit/risk assessment are provided in [redacted] Section 3.2.3, [redacted]

Study Population:

The study population includes male and female subjects, 18 to 75 years old (inclusive), with a documented diagnosis of CD for at least 3 months prior to screening. The diagnosis must be confirmed with source document evidence of a colonoscopy with ileal intubation (ileo-colonoscopy) and histopathology showing features consistent with CD. Subjects with ileal, colonic, or ileocolonic disease distribution are eligible to participate in the study. Subjects with perianal fistulizing disease are eligible to participate in the study, provided they meet the other inclusion/exclusion criteria, eg, subjects with a current abscess or suspected abscess are excluded.

Subjects must have an inadequate response, LOR, or intolerance to a standard treatment course of either conventional therapy (eg, 5-ASAs, corticosteroids, immunomodulators) or biologic therapy (eg, infliximab, adalimumab, certolizumab pegol, vedolizumab, natalizumab, or ustekinumab) for CD.

A subject will be considered enrolled only when the informed consent form (ICF) is signed. Subjects must have clinical and endoscopic evidence of moderately to severely active CD, as evidenced by the following minimum disease activity criteria, assessed during the Screening Period:

(i) A CDAI score of 220 to 450 (see Section 9.1 and APPENDIX 10)

(ii) An average daily score for AP ≥ 2 OR average daily number of very soft (loose) or liquid (watery) stools (Bristol Stool Scale [BSS] Type 6 or 7 only; [redacted] ≥ 4 on the PRO2 (see Section 9.1 and [redacted])

(iii) Evidence of active inflammation in at least 1 of the 5 ileocolonic segments (based on central reading) with total SES-CD ≥ 6, or SES-CD ≥ 4 if only isolated ileitis is present on baseline endoscopy (other inclusion criteria are listed Section 6.1)

Subjects will be excluded if they present with severe or fulminant colitis that is likely to require surgery or hospitalization; a diagnosis of alternative forms of colitis other than CD; a stoma, gastric or ileoanal pouch; a previous proctocolectomy or total colectomy; symptomatic, stenosing disease that is likely to confound efficacy assessment (eg, symptomatic CD-related stricture); an abscess or suspected abscess; pouchitis; short bowel syndrome; or a history of bowel perforation. In addition, subjects with colonic or ileal strictures that are not passable via colonoscope that the endoscopist normally uses in clinical practice, or strictures in the ileum or ileocecal valve that are fibrotic in nature, will be excluded. Other exclusion criteria are listed in Section 6.2.

Objectives and Endpoints:

Key study definitions are provided below.

Clinical remission	CDAI score < 150
Clinical response	A reduction from baseline in the CDAI score of ≥ 100 points or a total CDAI score < 150
Endoscopic response	≥ 50% improvement from baseline in the SES-CD
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PRO2 remission	Average daily score for abdominal pain ≤ 1 and average number of very soft (loose) or liquid (watery) stools (BSS Type 6 or 7 only) ≤ 3 on the PRO2, and both not worse than baseline.
[redacted]	[redacted]
[redacted]	[redacted]

BSS = Bristol Stool Scale; CD = Crohn's Disease; CDAI = Crohn's Disease Activity Index; [redacted]; PRO2 = patient (or subject) reported outcome based on the stool frequency and abdominal pain components of the CDAI; SES-CD = Simple Endoscopic Score for Crohn's Disease

[redacted]

Primary Efficacy Objectives and Endpoints:

- Objective: To assess the effect of BMS-986165 on clinical remission and endoscopic response at the end of the Induction Period (Week 12 [Day 85])
- Co-primary endpoints:
  - Proportion of subjects achieving clinical remission at Week 12, *and*
  - Proportion of subjects achieving endoscopic response at Week 12, both at a population level.

Secondary Efficacy Objectives and Endpoints:

- To assess the effect of BMS-986165 on clinical response at the end of the Induction Period
  - Endpoint: Proportion of subjects who achieve a clinical response at Week 12
- To assess the effect of BMS-986165 on PRO2 remission at the end of the Induction Period
  - Endpoint: Proportion of subjects who achieve PRO2 remission at Week 12
- To assess the effect of BMS-986165 on gut mucosal disease activity by endoscopy at the end of the Induction Period
  - Endpoint: Change from baseline in SES-CD at Week 12

The exploratory objectives and endpoints are summarized in Section 4.3.

Overall Design:

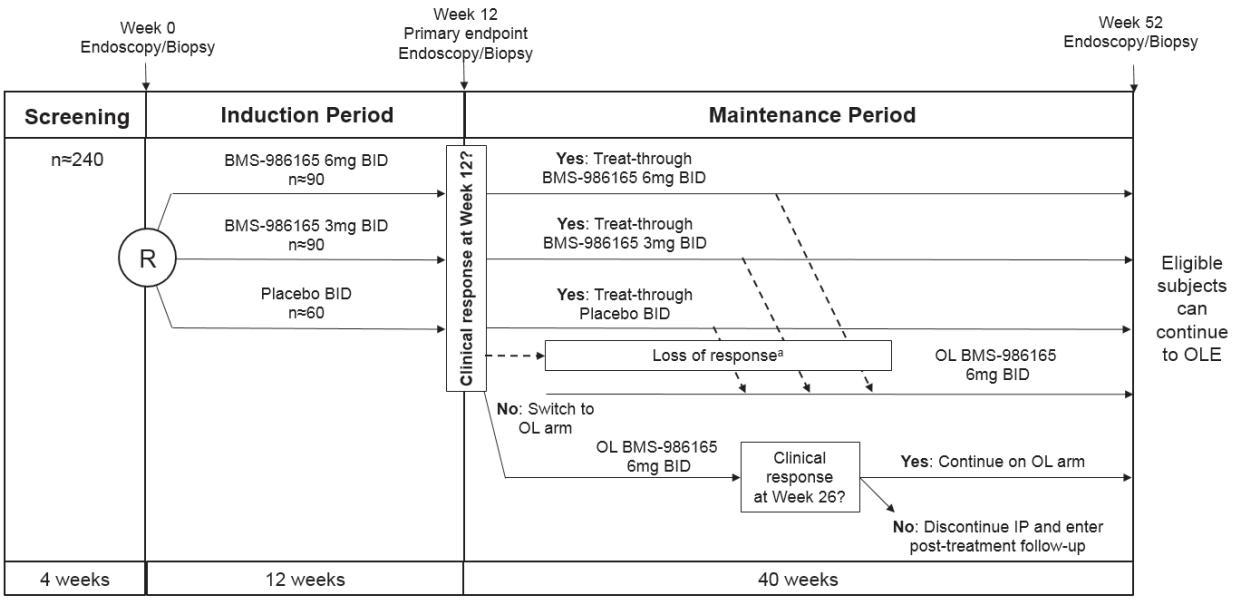
The IM011023 study is designed as follows:

- A randomized, double-blind, placebo-controlled, multicenter study
- Consists of 5 periods:
  - Screening Period: up to 4 weeks (28 days)
  - Induction Period: 12 weeks (84 days)
  - Maintenance Period: 40 weeks (280 days)
  - Open-label Extension Period: 52 weeks (364 days)
  - Post-treatment Follow-up Period: 4 weeks (28 days)
- On Day 1 of the Induction Period, subjects who have completed screening and met all eligibility criteria will be randomized in a 3:3:2 ratio using interactive response technology (IRT) to receive oral BMS986165 6 mg BID PO, BMS-986165 3 mg BID PO, or matched placebo BID PO, respectively, as described below in Treatments Arms and Durations. [redacted]
- Endoscopic (ileocolonoscopy) evaluations and collection of ileal and/or colonic tissue biopsies will be performed during the Screening Period, at the end of the Induction Period (Week 12), [redacted] Endoscopy should also be performed at Early Termination (ET) visits that occur at least 4 weeks after the most recent endoscopy. Endoscopy is required at ET visits that occur between Week 4 and Week 12. [redacted]
- Physical examinations, vital sign measurements, 12-lead electrocardiogram (ECG), and clinical laboratory evaluations will be performed at selected times throughout the study.

- The study blind will be maintained during the study [redacted]
- Clinical, laboratory, and endoscopic evidence of disease activity will be assessed. Endoscopic videos will be scored by blinded, external central readers.
- Progression from the Induction Period to the Maintenance Period, and from the Induction to or during the Maintenance Period to the Open-label Treatment Arms, and from the Maintenance Period to the OLE Period is contingent on an appropriate safety profile in each individual subject.
- A Data Monitoring Committee (DMC) will assess safety data (Section 5.1.5).
- The primary efficacy analysis will be performed after all subjects have completed Week 12 (Day 85) efficacy assessments (or permanently discontinued study treatment prior to Week 12).

The study design schematic is presented in Figure 1 and Figure 2.

Figure 1 Study Design Schematic: Induction and Maintenance Periods



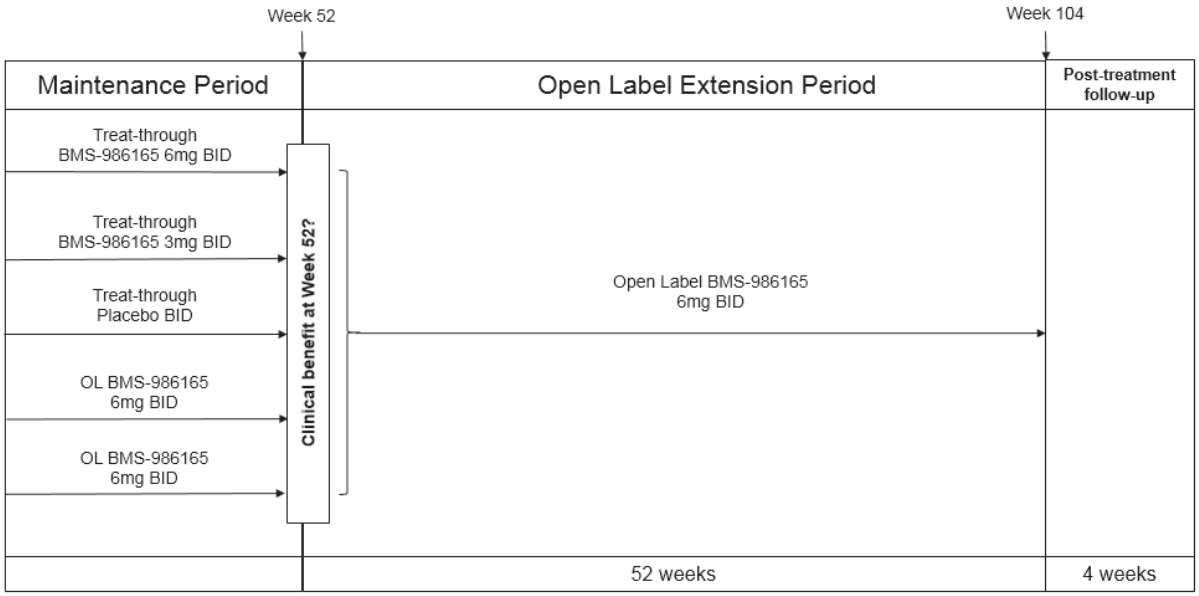
BID = twice daily; IP = investigational product; OL = open-label; R = randomization

[a] Subjects who achieve clinical response at Week 12 can enter the OL "loss of response" arm **at any time** from Week 13 through Week 52. Loss of response is defined as an increase in the CDAI score of ≥ 100 points compared to Week 12, and a total CDAI score of ≥ 220.

NOTE: This study has a treat-through design. At Week 12, subjects who achieve clinical response (defined as a reduction from baseline in the CDAI score of ≥ 100 points or a total CDAI score < 150) are eligible to continue to the Maintenance Period, where they will continue to receive the double-blind treatment regimen that they received in the Induction Period. Subjects who have loss of response in these arms may be eligible to enter the loss of response arm, where they will receive open-label BMS-986165 6 mg BID PO through Week 52. Subjects who do not achieve clinical response at Week 12 and who have an appropriate safety profile are eligible to enter an open-label treatment arm, in which they will receive open-label BMS-986165 6 mg BID PO during the Maintenance Period. Subjects in this arm must have clinical response assessed again at Week 26 (compared to Week 0). Subjects in this arm who do not achieve

clinical response at Week 26 (compared to Week 0) will be considered treatment failures and must permanently discontinue IP and enter the Post-treatment Follow-up Period. Subjects in this arm who do achieve clinical response at Week 26 may continue IP through Week 52.

Figure 2 Study Design Schematic: OLE



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

Subjects who were randomized when earlier versions of the protocol (Protocol v1.0 [27-Mar-2018] or Protocol v2.0 [24-May-2018]) were in effect will continue on their currently assigned double-blind study treatment. These subjects will complete all study procedures and assessments outlined in the current version of the protocol.

Number of Subjects:

Approximately 240 subjects will be randomized in a 3:3:2 ratio to receive BMS-986165 6 mg BID, BMS-986165 3 mg BID, or placebo BID, resulting in approximately 90 subjects per BMS-986165 dose arm and 60 subjects in the placebo arm during the Induction Period.

Treatment Arms and Duration:

The total duration of study participation will be up to approximately 112 weeks (784 days) in 5 periods including up to a 4-week (28-day) Screening Period, a 12-week (84-day) Induction Period, a 40-week (280 day) Maintenance Period, a 52-week (364-day) OLE Period, and a 4-week (28-day) Post-treatment Follow-up Period. The total exposure to IP in this study will be up to 104 weeks.

In all treatment groups, subjects will take their randomly assigned treatment twice daily as oral capsules.

Screening Period (up to 28 days duration):

The purpose of the Screening Period is to determine if a subject meets the enrollment criteria for this clinical trial. The suggested order of screening investigations is as follows:

(i) Screening visit in order to sign the ICF and then obtain a medical history, vital signs and physical examination, screening blood tests, chest x-ray, ECG, etc, give the subject the electronic study diary and train on the diary, and schedule the screening ileocolonoscopy and Week 0 visit. Sites should consider the turnaround time for the centrally read endoscopy result when scheduling the ileocolonoscopy and Week 0 visits.

(ii) The subject will then record up to 14 days of daily diary data at home, in order to facilitate CDAI and PRO2 calculation. The minimum daily diary requirements for CDAI/PRO2 calculation are outlined in Section 9.1. In order to ensure that a subject can be successfully randomized, sites should consider periodically confirming that subjects are successfully entering and uploading daily diary data. See Section 9.1, APPENDIX 10, and [redacted] for more details.

(iii) Sites should check the results of screening investigations to confirm that a subject remains potentially eligible for inclusion before a subject commences bowel preparation for the screening ileocolonoscopy.

(iv) The screening ileocolonoscopy will be performed. Subjects should be randomized within 14 days of the screening ileocolonoscopy.

Induction Period (Weeks 0 through 12):

During the Induction Period, subjects will take twice daily oral doses of the IP over 12 weeks [redacted] For each dose level, capsules are taken once in the morning and once in the evening. Subjects will be randomized to 1 of the 3 following treatments:

- BMS986165 6 mg BID [redacted]
- BMS986165 3 mg BID [redacted]
- Placebo [redacted]

Video ileocolonoscopic examination and collection of ileal and/or colonic tissue biopsies should be performed within a window of 7 days prior to the Week 12 visit. The CDAI/PRO2 scores for determination of clinical response/remission status will be calculated as described in Section 9.1. In order to avoid missing data, sites should consider periodically confirming that subjects are successfully entering and uploading daily diary data prior to Week 12.

[redacted]

(i). Subjects Who Demonstrate Clinical Response at Week 12

At Week 12 (Day 85), subjects who achieve a clinical response (as defined above) and who have an appropriate safety profile are eligible to continue to receive the same blinded study regimen (BMS-986165 6 mg BID or 3 mg BID or placebo BID) during the Maintenance Period. Blinded study treatment will continue until these subjects have completed Week 52 (Day 365), or have LOR (Section 5.1.3.3), or if they permanently discontinue IP prior to Week 52 for another reason.

Subjects who achieve a clinical response at Week 12 and subsequently have an LOR during the Maintenance Period and who have an appropriate safety profile are eligible to switch to open-label treatment with BMS 6 mg BID. Alternatively, they can be permanently discontinued from treatment based on subject and/or investigator preference and enter the Post-treatment Follow-up Period.

(ii). Subjects With No Clinical Response at Week 12

Subjects who do not achieve a clinical response at Week 12 and who have an appropriate safety profile are eligible to switch to open-label BMS-986165 treatment at the highest dose (6 mg BID), regardless of the initial treatment regimen received during the Induction Period.

Subjects who do not achieve protocol-defined clinical response at Week 12 and are switched to the open-label BMS-986165 6 mg BID arm, as well as those who are currently receiving open-label BMS-986165 12 mg QD prior to implementation of Protocol v3.0, must be assessed for clinical response at Week 26. If clinical response at Week 26 (compared to Week 0) is achieved, and subjects have an appropriate safety profile, these subjects are eligible to continue on the open-label treatment for the remaining duration of the Maintenance Period. Subjects in this open-label study arm who do not achieve clinical response at Week 26 (compared to Week 0) will be considered treatment failures and must permanently discontinue IP and enter the Post-treatment Follow-up Period. Note: These subjects may also be discontinued at any time before Week 26 based on the clinical judgment of the investigator.

(iii). Subjects Randomized to 12 mg QD Arm in Protocol v1.0 or Protocol v2.0

Subjects who were randomized when Protocol v1.0 (27-Mar-2018) or Protocol v2.0 (24-May-2018) was in effect will continue on their currently assigned double-blind study treatment. Subjects who were randomized to BMS-986165 12 mg QD prior to the current protocol, and who have not yet reached Week 12 who then achieve clinical response at Week 12, with an appropriate safety profile, are eligible to continue on blinded 12 mg QD study treatment. Subjects from this cohort who do not achieve clinical response at Week 12 who have an appropriate safety profile are eligible to switch to open-label BMS-986165 6 mg BID for the Maintenance Period, and they will be managed as described above.

Open-label Extension Period (Week 52 through Week 104)

Subjects who complete per protocol assessments at Week 52 who have an appropriate safety profile and who also continue to derive a clinical benefit from IP at that time in the opinion of the investigator, are eligible to enter the OLE Period. The OLE Period lasts 52 weeks, from Week 52 through Week 104. The final study endoscopy should be performed within a window of 7 days prior to the Week 104 visit.

[redacted]

Post-treatment Follow-up Period:

Subjects who permanently discontinue IP prior to Week 52 will enter a 28-day Post-treatment Follow-up Period. Subjects will be instructed to report to the investigative site any adverse events (AEs) or serious adverse events (SAEs) experienced during this 28-day period. [redacted]

Study Treatment for IM011023		
Medication	**Potency**	**IP/Non-IP**
BMS-986165	3 mg	IP
Placebo	Not applicable	IP

IP = investigational product

2 SCHEDULE OF ACTIVITIES

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 OLE Period.

Table 1: Screening Procedural Outline (IM011023)

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.
Crohn's disease history	X	
Subject input data into the subject diary	X	APPENDIX 8
Endoscopy (ileocolonoscopy)	X	After bowel cleansing, video ileocolonoscopic examination must be performed within Day -28 and Day -1 of the Screening Period and should be scheduled as close as possible to the Week 0 visit. The Week 0 visit should occur within 14 days of the screening endoscopy. 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. At this examination, endoscopic collection of ileal and/or colonic tissue biopsies will be performed.
SES-CD	X	The SES-CD score is centrally read from the screening endoscopy and the central read must be reviewed to confirm eligibility prior to randomization. Local reads will not be used for study eligibility. Study sites should consider turnaround time for central reads to ensure results are obtained before the Week 0 visit. Results from central endoscopy review are final. Definitions of SES-CD are provided in APPENDIX 12.
[redacted]	[redacted]	[redacted]

Table 1: Screening Procedural Outline (IM011023)

Procedure	Screening Visit Day -28 to -1	Notes
[redacted]	[redacted]	[redacted]
Confirm washout of prohibited medication and dose stabilization of allowed medication (if applicable)	X	Prohibited medications are described in Section 7.7.1. Note: The washout periods for specific immunomodulatory and biologic agents required before a subject can be randomized, as 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 7.7.2. [redacted]
Smoking history	X	Record as packs per day multiplied by years of tobacco use (ie, pack-years).
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 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 antigen test. PCR testing is preferred (Section 9.10). Subjects may receive SARS-CoV-2 testing prior to the screening colonoscopy procedure.[a] If negative, this testing will satisfy the requirement for study eligibility.
Monitor for SAEs and SARS-CoV-2 related AEs	X	SAEs and all AEs related to SARS-CoV-2 infection should be collected from time of signing of ICF; nonserious AEs are collected starting with the first dose.

Table 1: Screening Procedural Outline (IM011023)

Procedure	Screening Visit Day -28 to -1	Notes
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, and coagulation	X	Blood and urine samples; (must be repeated as necessary and verified to ensure that subjects meet study inclusion criteria and no exclusion criteria if performed more than 28 days prior to randomization).
Serology	X	Hepatitis B Virus (HBV): HBsAg, HBsAb, anti-HBc (with reflex to HBV DNA if positive). Hepatitis C Virus (HCV): Anti-HCV (if positive or indeterminate, HCV RNA testing will be performed using a separate blood draw). 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 Section 9.5.2)
Urine pregnancy test	X	WOCBP only; 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.
Urinalysis	X	
Follicle-stimulating hormone	X	Postmenopausal women only to confirm status (APPENDIX 5)
Stool culture (performed locally)	X	If subjects are positive for enteric pathogens (not including flora that are considered commensal within a study region), they 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* testing (performed centrally)	X	See APPENDIX 20. If subjects are positive for *C. difficile*, they can be rescreened as described in Section 6.5.1.
Therapeutic Drug Monitoring (TDM)	X	Optional test for subjects who recently received infliximab, adalimumab, certolizumab pegol, 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

Table 1: Screening Procedural Outline (IM011023)

Procedure	Screening Visit Day -28 to -1	Notes
		for subjects who have an undetectable drug level for that specific medication on TDM testing at screening or prior to screening.
Diary Training		
Subject diary training	X	Along with diary input training, a paper copy of the Bristol Stool Scale (BSS) will be provided to subjects to assist with determining daily documentation of the number of very soft (loose) or liquid (watery) stools (BSS Type 6 and 7) [redacted] The subject daily diary information should be reviewed during the Screening Period to ensure that subjects are successfully entering and uploading diary data. If there are gaps in this process, subjects should be reached during the Screening Period to understand the gaps and to offer re-training.

AE = adverse event; anti-HBc = hepatitis B core antibody; anti-HCV = hepatitis C virus antibody; BSS = Bristol Stool Scale; CDAI = Crohn's Disease Activity Index; *C. difficile* = *Clostridium difficile*; [redacted]; [redacted]; ECG = electrocardiogram; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV-1 and -2 = human immunodeficiency virus -1 and -2; ICF = informed consent form; IHC = immunohistochemistry; IRT = interactive response technology; [redacted]; PCR = polymerase chain reaction; [redacted]; [redacted]; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SES-CD = Simple Endoscopic Score for Crohn's Disease; TDM = Therapeutic Drug Monitoring; WOCBP = women of childbearing potential

[a] Refer to: Sultan S, Siddique SM, Altayar O, et al. AGA Institute rapid review and recommendations on the role of pre-procedure SARS-CoV-2 testing and endoscopy. Gastroenterology 2020;159(5):1935-48.e5.

Table 2: Induction Period On-Treatment Procedural Outline Up to Week 12 (Day 85) (IM011023)

Procedure/Visit Weeks (Days)	**0 (1)**	**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 6.1 and 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 Section 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	
Safety Assessments						
Physical examination	X				X	General, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdominal, extremities, neurologic, skin, musculoskeletal.
Vital signs	X	X	X	X	X	See note in the Screening Period procedures (Table 1).
Electrocardiogram					X	ECGs should be recorded after the subject has been supine for at least 5 minutes.
Concomitant medication use	X	X	X	X	X	
Monitor AEs	X	X	X	X	X	AEs must be collected from the time of the first dose of the study drug through the date of the follow-up or last visit. Monitoring for AEs will occur at every study visit.
Monitor SAEs and SARS-CoV-2 related AEs	X	X	X	X	X	All SAEs and all AEs related to SARS-CoV-2 infection should be collected from the date of subject's written consent until 30 days after the final dose of the study drug or subject's participation in the study if the last scheduled visit occurs at a later time. Monitoring for SAEs will occur at every study visit.
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2: Induction Period On-Treatment Procedural Outline Up to Week 12 (Day 85) (IM011023)

Procedure/Visit Weeks (Days)	**0 (1)**	**2 (15)**	**4 (29)**	**8 (57)**	**12 (85)**	**Notes**
Visit Window (± n days)	**0**	**3**	**3**	**3**	**3**	
Laboratory Tests						
Hematology, chemistry, and coagulation	X	X	X	X	X	
HBV DNA			X	X	X	To be performed only in subjects with the following HBV serology at screening: HBsAg negative, anti-HBc positive, HBV DNA undetectable (APPENDIX 9)
Hematocrit	X*	X	X	X	X	* For CDAI calculation at Week 0, hematocrit obtained during screening will be used. For the purpose of prompt CDAI score calculation at Weeks 2, 4, 8, and 12, the hematocrit may be performed by a local laboratory.
Serum Igs	X		X		X	IgM, IgE, IgA, and IgG
TBNK panel	X		X		X	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Fasting lipid panel	X				X	Subjects are required to fast for ≥ 10 hours prior to the collection of specimens for the fasting lipid panel.
Fasting glucose	X				X	Subjects are required to fast for ≥ 10 hours prior to the collection of specimens for the fasting glucose evaluation.
Urine pregnancy test	X	X	X	X	X	WOCBP only; 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]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2: Induction Period On-Treatment Procedural Outline Up to Week 12 (Day 85) (IM011023)

Procedure/Visit Weeks (Days)	0 (1)	2 (15)	4 (29)	8 (57)	12 (85)	Notes
Visit Window (± n days)	**0**	**3**	**3**	**3**	**3**	
[redacted]	[redacted]	[redacted]				[redacted]
[redacted]	[redacted]				[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]				[redacted]	[redacted]
[redacted]	[redacted]				[redacted]	[redacted]
Efficacy Assessments						
Weight	X	X	X	X	X	Required for CDAI assessment
Review subject diary	X	X	X	X	X	Prior to each scheduled visit at which CDAI/PRO2 is to be calculated, ascertain whether an adequate number of days of diary entries have been made. If adequate entries have not been made, the site should contact the subject to reschedule the visit (or endoscopy, if applicable), and the subject should be counseled about proper study procedures. See Section 9.1 and APPENDIX 8.
CDAI	X[a]	X	X	X	X	[a] Calculation of CDAI eligibility criterion (220 to 450). Diary data and Hct obtained during the Screening Period will be used to calculate the baseline CDAI. See Section 9.1 and APPENDIX 10.
PRO2	X	X	X	X	X	See Section 9.1 and [redacted]
Endoscopy (ileocolonoscopy)					X*	After bowel cleansing, video ileocolonoscopic examination should be performed within a window of 7 days prior to the Week 12 (Day 85) visit. * Endoscopy is required for ET subjects between Weeks 4 and 12.
SES-CD					X	

Table 2: Induction Period On-Treatment Procedural Outline Up to Week 12 (Day 85) (IM011023)

Procedure/Visit Weeks (Days)	0 (1)	2 (15)	4 (29)	8 (57)	12 (85)	Notes
Visit Window (± n days)	0	3	3	3	3	
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

AE = adverse event; anti-HBc = hepatitis B core antibody; CDAI = Crohn's Disease Activity Index; [redacted] DNA = deoxyribonucleic acid; ECG = electrocardiogram; eCRF = electronic case report form; ET = early termination; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; Hct = hematocrit; [redacted]; IBD = inflammatory bowel disease; [redacted]; Ig = immunoglobulin; IgA = immunoglobulin A; IgE = immunoglobulin E; IgG = immunoglobulin G; IgM = immunoglobulin M; IHC = immunohistochemistry; IP = investigational product; [redacted]; [redacted]; [redacted]; [redacted]; PO = by mouth; PRO2 = patient (or subject) reported outcome based on the stool frequency and abdominal pain components of the CDAI; [redacted]

[redacted]; [redacted]; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SES-CD = Simple Endoscopic Score for Crohn's Disease; [redacted]; TBNK = T cells, B cells, and natural killer cells; [redacted]; WOCBP = women of childbearing potential.

Table 3: Maintenance Period On-Treatment Procedural Outline (IM011023)

Procedure/Visit Weeks (Days)	16 (113)	22 (155)	26 (183)	36 (253)	44 (309)	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
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. 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 in previous 2 rows.
Review study treatment compliance	X	X	X	X	X	X	
Safety Assessments							
Physical examination	X	X	X	X	X	X	General, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdominal, extremities, neurologic, skin, musculoskeletal
Vital signs	X	X	X	X	X	X	See notes in the Screening Period procedures (Table 1).
Electrocardiograms						X	ECGs should be recorded after the subject has been supine for at least 5 minutes.
Concomitant medication use	X	X	X	X	X	X	
Monitor for AEs	X	X	X	X	X	X	AE reporting begins at the time of the first dose of blinded study treatment.
Monitor for SAEs and SARS-CoV-2 related AEs	X	X	X	X	X	X	SAEs and all AEs related to SARS-CoV-2 infection should be collected from begins at the time of signing of the ICF.
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 3: Maintenance Period On-Treatment Procedural Outline (IM011023)

Procedure/Visit Weeks (Days)	**16 (113)**	**22 (155)**	**26 (183)**	**36 (253)**	**44 (309)**	**52 (365)**	**Notes**
Visit window (± n days)	**3**	**3**	**3**	**3**	**3**	**3**	
Laboratory Tests							See notes in the Screening Period procedures (Table 1) and Section 9.5.3.
Hematology, chemistry, 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, anti-HBc positive, HBV DNA undetectable (APPENDIX 9)
HBV DNA (Week 12 responder arms, with subsequent LOR and entry to the open-label LOR arm)	See note					X	For subjects with HBsAg negative, anti-HBc positive, HBV DNA undetectable serology at screening. Subjects who have a clinical response at Week 12 and who subsequently have a LOR and enter the open-label LOR study arm: Obtain HBV DNA at the following 3 study visits, and thereafter according to the schedule for the Week 12 responder arm (above). (APPENDIX 9)
HBV DNA (Week 12 non-responder arm)	X	X	X	X		X	For subjects with the following HBV serology at screening: HBsAg negative, anti-HBc positive, HBV DNA undetectable (APPENDIX 9)
Hematocrit	X	X	X	X	X	X	For the purpose of prompt CDAI score calculation at Weeks 16, 22, 26, 36, 44, and 52, the hematocrit may be performed by a local laboratory. If the result cannot be obtained before the end of the visit, the subject should return the following day for calculation of the CDAI.
Serum Igs	X		X	X	X	X	IgM, IgE, IgA, and IgG
TBNK panel			X			X	
[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
Fasting lipid panel			X	X		X	Subjects are required to fast for at least 10 hours prior to the collection of specimens for the fasting lipid panel.

Table 3: Maintenance Period On-Treatment Procedural Outline (IM011023)

Procedure/Visit Weeks (Days)	16 (113)	22 (155)	26 (183)	36 (253)	44 (309)	52 (365)	Notes
Visit window (± n days)	**3**	**3**	**3**	**3**	**3**	**3**	
Fasting glucose			X	X		X	Subjects are required to fast for at least 10 hours prior to the collection of specimens for the fasting glucose panel.
Urine pregnancy test	X	X	X	X	X	X	WOCBP only. 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]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
Efficacy Assessments							
Weight	X	X	X	X	X	X	Required for CDAI assessment

Table 3: Maintenance Period On-Treatment Procedural Outline (IM011023)

Procedure/Visit Weeks (Days)	16 (113)	22 (155)	26 (183)	36 (253)	44 (309)	52 (365)	Notes
Visit window (± n days)	**3**	**3**	**3**	**3**	**3**	**3**	
Review subject diary	X	X	X	X	X	X	Prior to each scheduled visit at which CDAI/PRO2 is to be calculated, ascertain whether an adequate number of days of diary entries have been made. If adequate entries have not been made, the site should contact the subject to reschedule the visit (or endoscopy, if applicable), and the subject should be counseled about proper study procedures. See Section 9.1 and APPENDIX 8.
CDAI	X	X	X	X	X	X	See Section 9.1 and APPENDIX 10.
PRO2	X	X	X	X	X	X	See Section 9.1 and [redacted].
Endoscopy (ileocolonoscopy)						X*	After bowel cleansing, video ileocolonoscopic examination should be performed within a window of 7 days prior to the Week 52 (Day 365) visit. At this examination endoscopic (ileocolonoscopy) collection of ileal and/or colonic tissue biopsies will be performed. * Endoscopy is recommended for ET subjects between Weeks 16 and 52
SES-CD						X	The SES-CD is centrally read from a video of the ileocolonoscopy and the result will be provided to sites (APPENDIX 12).
[redacted]						[redacted]	[redacted]
[redacted]						[redacted]	[redacted]

Table 3: Maintenance Period On-Treatment Procedural Outline (IM011023)

Procedure/Visit Weeks (Days)	16 (113)	22 (155)	26 (183)	36 (253)	44 (309)	52 (365)	Notes
Visit window (± n days)	3	3	3	3	3	3	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						[redacted]	[redacted]
[redacted]			[redacted]			[redacted]	[redacted]
[redacted]						[redacted]	[redacted]
[redacted]						[redacted]	[redacted]
[redacted]						[redacted]	[redacted]
[redacted]						[redacted]	[redacted]

AE = adverse event; anti-HBc = hepatitis B core antibody; CDAI = Crohn's Disease Activity Index; [redacted] DNA = deoxyribonucleic acid; ECG = electrocardiogram; eCRF = electronic case report form; ET = early termination; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; [redacted] IBD = inflammatory bowel disease; [redacted]; ICF = informed consent form; Ig = immunoglobulin; IgA = immunoglobulin A; IgE = immunoglobulin E; IgG = immunoglobulin G; IgM = immunoglobulin M; [redacted]; IP = investigational product; LOR = loss of response; [redacted] OL = open-label; OLE = open-label extension; [redacted]; PRO2 = patient (or subject) reported outcome based on the stool frequency and abdominal pain components of the CDAI; [redacted]; RNA = ribonucleic acid; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SES-CD = Simple Endoscopic Score for Crohn's Disease; [redacted]; 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 point, [redacted].

Table 4: Open-label Extension Period On-Treatment Procedural Outline (IM011023)

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[b]	Notes
Visit Window (± n days)	**3**	**3**	**3**	**3**	**3**	**7**			
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	
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
Vital signs	X	X	X	X	X	X	X	X	See notes in the Screening Period procedures (Table 1).
Electrocardiograms			X			X			ECGs should be recorded after the subject has been supine for at least 5 minutes.
Concomitant medication use	X	X	X	X	X	X	X	X	
Monitor for AEs	X	X	X	X	X	X	X	X	
Monitor for SAEs and SARS-CoV-2 related AEs	X	X	X	X	X	X	X	X	SAEs and all AEs related to SARS-CoV-2 infection should be collected from begins at the time of signing of the ICF.
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			

Table 4: Open-label Extension Period On-Treatment Procedural Outline (IM011023)

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[b]	Notes
Visit Window (± n days)	**3**	**3**	**3**	**3**	**3**	**7**			
Laboratory Tests									See [redacted] Section 9.5.3.
Hematology, chemistry, and coagulation	X	X	X	X	X	X	X		
Hematocrit	X	X	X	X	X	X	X		[redacted]
HBV DNA	X	X	X	X	X	X			For subjects with the following HBV serology at screening: HBsAg negative, anti-HBc positive, HBV DNA undetectable (APPENDIX 9)
Serum Igs				X		X			IgM, IgE, IgA, and IgG
TBNK panel				X		X			
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]			
Fasting lipid panel			X	X		X			Subjects are required to fast for at least 10 hours prior to the collection of specimens for the fasting lipid panel.
Fasting glucose			X	X		X			Subjects are required to fast for at least 10 hours prior to the collection of specimens for the fasting glucose panel.
Urine pregnancy test	X	X	X	X	X	X	X		WOCBP only. If the urine pregnancy test is positive, a serum pregnancy test should be done for confirmation prior to

Table 4: Open-label Extension Period On-Treatment Procedural Outline (IM011023)

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[b]	Notes
Visit Window (± n days)	**3**	**3**	**3**	**3**	**3**	**7**			
									discontinuing the subject. Study treatment should not be administered until the results of the confirmatory test are known.
Pharmacokinetic									
Efficacy Assessments									
Weight	X	X	X	X	X	X			Required for CDAI assessment
Review subject diary	X	X	X	X	X	X			
CDAI	X	X	X	X	X	X			See Section 9.1 and APPENDIX 10.
PRO2	X	X	X	X	X	X			See Section 9.1 and

Table 4: Open-label Extension Period On-Treatment Procedural Outline (IM011023)

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[b]	Notes
Visit Window (± n days)	**3**	**3**	**3**	**3**	**3**	**7**			
Endoscopy (ileocolonoscopy)						X*			After bowel cleansing, video ileocolonoscopic examination should be performed within a window of 7 days prior to the Week 104 (Day 729) visit. [redacted]. At this examination endoscopic (ileocolonoscopy) collection of ileal and/or colonic tissue biopsies will be performed. * Endoscopy is recommended for early termination subjects between Weeks 56 and 104
SES-CD						X			The SES-CD is centrally read.
[redacted]						[redacted]			[redacted]

Table 4: Open-label Extension Period On-Treatment Procedural Outline (IM011023)

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[b]	Notes
Visit Window (± n days)	3	3	3	3	3	7			
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									

Table 4: Open-label Extension Period On-Treatment Procedural Outline (IM011023)

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[b]	Notes
Visit Window (± n days)	3	3	3	3	3	7			
[redacted]	[redacted]		[redacted]			[redacted]			[redacted]

AE = adverse event; anti-HBc = hepatitis B core antibody; CDAI = Crohn's Disease Activity Index; [redacted]; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ET = early termination; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; [redacted]; IBD = inflammatory bowel disease; [redacted]; Ig = immunoglobulin; IgA = immunoglobulin A; IgE = immunoglobulin E; IgG = immunoglobulin G; IgM = immunoglobulin M; IHC = immunohistochemistry; LTE = long-term extension; [redacted]; PRO2 = patient (or subject) reported outcome based on the stool frequency and abdominal pain components of the CDAI; [redacted]; ; [redacted] SAE = serious adverse eventSARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SES-CD = Simple Endoscopic Score for Crohn's Disease; [redacted]; TBNK = T cells, B cells, and natural killer cells; [redacted]; WOCBP = women of childbearing potential

[redacted]

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

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 point, [redacted]

3 INTRODUCTION

3.1 Background

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. 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.[1,2,3] 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 Crohn's disease (CD), ulcerative colitis, psoriasis, psoriatic arthritis, systemic lupus erythematosus (SLE) and spondyloarthritides.

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. Inhibition of TYK2 is expected to provide therapeutic benefit for patients with CD for multiple reasons: 1) IL-12 and IL-23 have been implicated in pathogenesis of CD;[4] 2) Biologic agents targeting IL-23p19 and IL-12/23p40 cytokines have been shown to be efficacious in CD, and ustekinumab targeting IL-12/23p40 has been approved for the treatment of CD; and 3) BMS-986165 has been shown to be efficacious in psoriasis, an IL-23-mediated disease, in a recent Phase 2 study.[5]

IM011023 is a Phase 2 randomized, double-blind placebo-controlled study designed to assess the safety and efficacy of BMS-986165 compared to placebo in subjects with moderately to severely active CD. Approximately 240 subjects will be randomized in this study. After a 28-day Screening Period, eligible subjects will be randomized in a 3:3:2 ratio to one of three study arms: (i) BMS-986165 6 mg twice daily (BID) by mouth (PO); n≈90, (ii) BMS-986165 3 mg BID PO; n≈90, or (iii) matched placebo; n≈60. [redacted] 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 3 mg BID or

placebo BID) that they received during the Induction Period. Open-label study arms are available for subjects who do not achieve a clinical response at Week 12, and for subjects in the treat-through study arms who have a loss of response (LOR) to blinded treatment between Week 13 and Week 52. The Open-label Extension (OLE) Period lasts from Week 52 through Week 104 and is available to subjects who complete per protocol assessments at Week 52 and who continue to derive clinical benefit from investigational product (IP) at that time.

[redacted]

3.1.1 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).

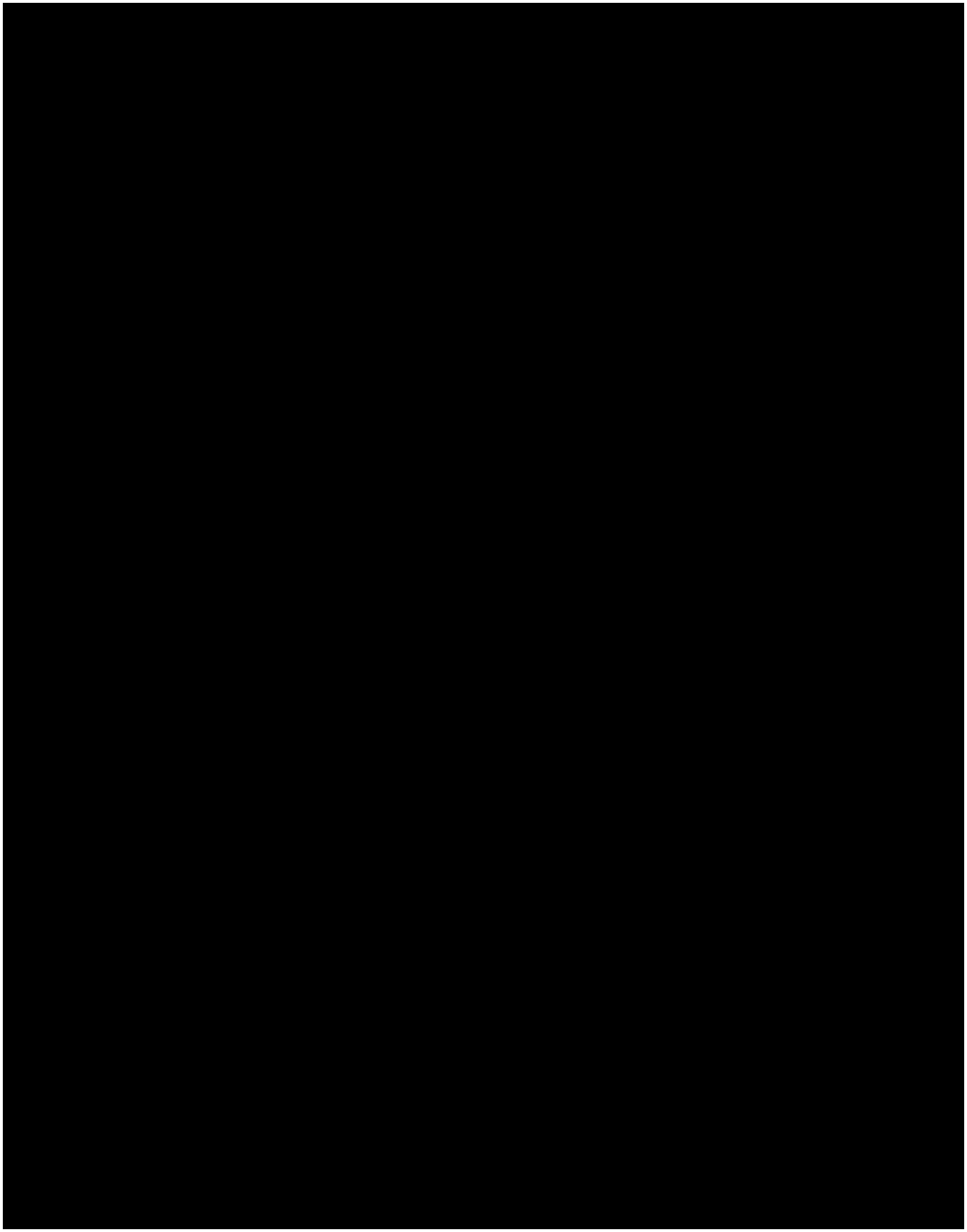
In repeat-dose (≤ 3 months) oral toxicity studies in monkeys, BMS-986165 was well tolerated at all doses (0.5, 1.5, or 5 mg/kg/day for 1 month; 0.75, 1.5, or 5 mg/kg/day for 3 months). All doses were associated with on-target PD effects. Exposures to BMS-986165 increased approximately dose proportionally, 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.

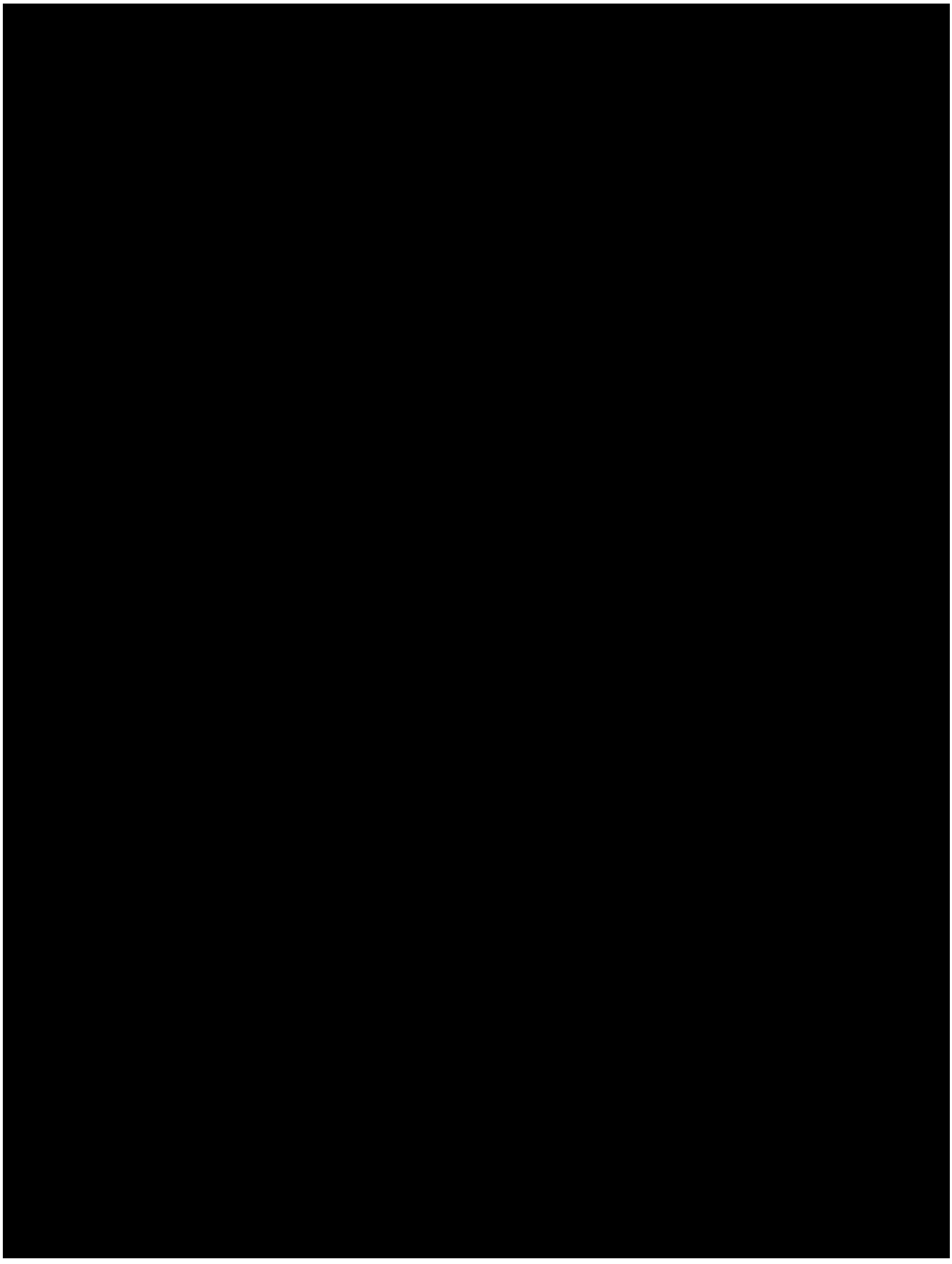
In the 9-month monkey toxicity study (doses of 0, 1, 3, or 10 mg/kg/day; the 10-mg/kg dose was changed to 5 mg/kg due to observed toxicity) with 2-month postdose recovery period, the principal BMS-986165-related findings at all doses included generally dose-dependent skin changes, which were likely infectious 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 towards reversibility during the 2-month post-dose recovery.

BMS-986165 was not genotoxic or phototoxic. There was no evidence of teratogenicity or effects on development up to the highest administered doses of 75 mg/kg/day in the rat (AUC[0-24h] 126 µg•h/mL; 147-fold AUC multiple) or 10 mg/kg/day in the rabbit (AUC[0-24h] 43.2 µg•h/mL; 50-fold AUC multiple). BMS-986165 had no effects on male rat reproductive parameters (mating, fertility, and sperm morphology), or early embryonic development of the litters sired by treated males up to 50 mg/kg/day (AUC[0-24h] 117 µg•h/mL; 137-fold AUC multiple). In a female rat fertility study (preliminary results), there were no BMS-986165-related effects on mating and fertility parameters up to 50 mg/kg/day, and the maternal and reproductive NOAEL were considered to be 50 mg/kg/day (AUC[0-24h] 81.1 µg•h/mL; 95-fold AUC multiple).

In summary, 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 towards recovery, and are clinically monitorable and manageable.

[redacted]





[redacted]

3.2 Study Rationale

3.2.1 Scientific Rationale for Study Design

IM011023 is a Phase 2 randomized, double-blind, placebo-controlled clinical study designed to assess the safety and efficacy of BMS-986165 compared to placebo in subjects with moderately to severely active CD.

Approximately 240 subjects will be randomized in this study. After a 28-day Screening Period, eligible subjects will be randomized in a 3:3:2 ratio to one of three study arms: (i) BMS-986165 6 mg BID by mouth (PO); n≈90, (ii) BMS-986165 3 mg BID PO; n≈90, or (iii) matched placebo; n≈60. [redacted]

This study has a 12-week Induction Period, a 40-week Maintenance Period, and a 52-week OLE Period leading to a total of up to 104 weeks of exposure to IP. The primary efficacy assessment occurs at Week 12. The co-primary endpoints are defined as achieving clinical remission (defined as Crohn's Disease Activity Index [CDAI] of < 150) and achieving endoscopic response (≥ 50% improvement from baseline in the Simple Endoscopic Score for Crohn's Disease [SES-CD]), on a population basis, at Week 12. This study is powered for the primary endpoint at Week 12.

This study has a treat-through design in order to explore sustained clinical benefit and safety in the Maintenance Period. Subjects who achieve clinical response (a reduction from baseline in the CDAI score of ≥ 100 points or a total CDAI score < 150) at Week 12 (Day 85), are eligible to enter the Maintenance Period and to continue on the same, double-blind treatment regimen that they received in the Induction Period, for up to an additional 40 weeks, up to Week 52. Subjects with LOR (an increase in the CDAI score of ≥ 100 points compared to Week 12, and a total CDAI score of ≥ 220 points, at any time from Week 13 through Week 52) in the Maintenance Period are eligible to enter an open-label BMS-986165 6 mg BID PO arm through Week 52.

Subjects who do not achieve clinical response at Week 12 and who have an appropriate safety profile are eligible to enter an open-label BMS-986165 6 mg BID PO arm, in which clinical response is again assessed at Week 26 (compared to Week 0). This study arm is designed to explore the potential benefit of ongoing treatment with BMS-986165 in subjects who do not achieve clinical response by that time. This may include subjects who received either BMS-986165 or placebo in the Induction Period. Subjects who achieve clinical response at Week 26 (compared to Week 0) may continue in this arm through Week 52. Subjects who do not achieve clinical response at Week 26 (compared to Week 0) will be considered treatment failures and must permanently discontinue IP and enter the Post-treatment Follow-up Period.

Subjects who complete per protocol assessments at Week 52 and who continue to derive clinical benefit from IP, in the opinion of the investigator, are eligible to enter the OLE Period, which lasts up to Week 104. This period explores safety and efficacy of BMS-986165 beyond Week 52.

Throughout the study, subjects who permanently discontinue IP prior to Week 104 must enter the Post-treatment Follow-up Period.

[redacted]

Taken together, these data provide a scientific rationale for studying BMS-986165 in CD. [redacted]

[redacted]

Clinical disease activity is assessed in this study using the CDAI.[10] CDAI is a composite instrument that includes patient-reported abdominal pain (AP), stool frequency (SF), general well-being, presence of complications of CD, hematocrit, body weight, presence of a CD-related abdominal mass, and the use of antidiarrheal medication. CDAI has been widely used in registrational clinical trial programs, but does have certain limitations eg, (i) the AP and SF components are weighted, (ii) the CDAI incorporates items that are not patient-reported outcomes (PROs), (iii) the CDAI does not include an assessment of mucosal inflammation, and (iv) the CDAI does not correlate well with endoscopic findings.[10,11] In order to address these limitations, a PRO2 (patient-reported outcome based on the stool frequency and abdominal pain components of the CDAI) instrument that includes unweighted AP and SF will be evaluated during the study, and mucosal inflammation will also be assessed by endoscopy [redacted].[12] Thus, in addition to classical definitions of CDAI response and remission, this study will also examine PRO2-based endpoints, endoscopic response and remission, [redacted]

[redacted]

[redacted]

[redacted]

3.2.3 Benefit/Risk Assessment

[redacted]These data suggest that subjects with CD are likely to derive clinical benefit after treatment with BMS-986165.

As discussed in Section 3.1, and detailed in the Investigator's Brochure, the safety and tolerability of BMS-986165 at multiple doses, including 6 mg BID, have been investigated in normal healthy volunteer studies, Phase 2 and Phase 3 clinical studies in psoriasis, and a Phase 2 clinical study in psoriatic arthritis. Overall, in the Phase 1 studies, BMS-986165 was generally well tolerated. In the Phase 2 study in psoriasis (IM011011), BMS-986165 was generally safe and well tolerated. In two Phase 3 clinical studies in psoriasis (IM011046 and IM011047), BMS-986165 6 mg QD PO was superior to placebo and apremilast in achieving the coprimary endpoints of PASI 75 and static Physician's Global Assessment (sPGA) 0/1 responses at Week 16. In a recent Phase 2 clinical study in psoriatic arthritis (IM011084), BMS-986165 12 mg QD and 6 mg QD demonstrated significantly greater American College of Rheumatology 20 (ACR20) responses at Week 16 compared with placebo. The IL-23/T_H17 axis has been implicated as an important immune pathway in the pathogenesis of psoriasis, psoriatic arthritis, and CD. Taken together, these data indicate an overall favorable benefit-risk assessment for evaluating BMS-986165 as an oral treatment for patients with CD.

The proposed dosing regimens reflect implementation of appropriate safety margins and are within the range of doses tested in the FIH study and within exposure margins based on comparisons of systemic exposure and body surface area with toxicology findings.

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

BMS-986165 was safe when investigated in clinical 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 acne-like skin lesions particularly after multiple doses of 24 mg/day (12 mg BID). Importantly, all the 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. Due to these findings, the highest proposed dose for the Phase 2 study IM011023 in subjects with CD will be 6 mg BID. In case of the occurrence of skin-related events, subjects may receive treatment as per standard practice according to investigator's discretion and followed until resolution.

[redacted] At the maximum concentrations expected in this study (in portal vein or systemic circulation, as appropriate), the potential for DDIs involving 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 the metabolism of the fraction metabolized. 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 co-medications that are BCRP substrates, such as rosuvastatin, was also expected to be low. Based on data from IM011015 DDI study with rosuvastatin, 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.

The reproductive toxicology studies for BMS-986165 are complete and detailed in the IB. Briefly, BMS-986165 is not genotoxic. BMS-986165 was neither teratogenic nor fetotoxic up to the highest evaluated dose of 50 mg/kg/day, and there was no evidence of teratogenicity or effects on development in reproductive and developmental toxicity studies in rats and/or rabbits. These findings support the contraception requirements for this study.

In addition, a completed thorough QT_c study has excluded a clinically meaningful effect on QT interval at doses of up to 36 mg (a supratherapeutic dose).

Taken together, these data suggest that BMS-986165 may be beneficial, safe and well tolerated in patients with active CD. In addition, there is no evidence for clinically significant DDIs at the concentrations expected in this study, or clinically meaningful effects on electrocardiogram (ECG) parameters. The reproductive risk potential has not been comprehensively evaluated in humans.

BMS-986165 is an immunomodulatory IP and a potential immunosuppressant. [redacted]

The global coronavirus disease 2019 (COVID-19) pandemic has been identified as a potential risk to clinical study 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 subjects taking BMS-986165 is unknown. The individual benefit-risk considerations regarding COVID-19 infection remains the responsibility of the investigator. 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 9.10). Testing for SARS-CoV-2 to inform decisions on subject care during the study, should follow local standard of care and clinical practice. Potential subjects with recent COVID-19 infection will be excluded until their symptoms have completely resolved for 30 days prior to receiving first dose of IP. The protocol provides guidance to investigators on temporary discontinuation of IP in the case of suspected or proven COVID-19 infection. The protocol also provides guidance on restarting IP following recovery from a COVID-19 infection, which must be confirmed by a negative diagnostic test for SARS-CoV-2 (Section 8.2.1).

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 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 serious adverse events [SAEs]) must be reported from the time of consent (Section 9.3.2).

[redacted] Nevertheless, BMS-986165 is a potential immunosuppressant, and in line with standard practice for immunosuppressant IPs, this study has been designed with eligibility criteria that minimize the risk that a subject with malignancy will be enrolled. Subjects with a clinical picture that is

suspicious for malignancy are excluded from participation. Subjects are not allowed to enter the study with unresected colonic adenomas or unresected colonic dysplasia. Standard-of-care screening for colorectal neoplasia and surveillance for dysplasia can be incorporated into the baseline endoscopy in this study, and into subsequent annual study endoscopies.

Subjects in IBD clinical studies may experience an increase in disease activity (ie, disease exacerbation or a "flare") during their participation. Investigator recognition of treatment futility or a requirement for efficacious treatment outside of the study is important in the management of CD patients. Subjects may remain on permitted background standard of care therapy regardless of whether they are randomized to one of the active treatment or placebo arms. At the investigator's discretion, rescue therapy can be initiated, or dosing of study medication can be discontinued at any time during the study. The protocol provides guidance to investigators on the level of disease activity that constitutes a LOR to IP in the maintenance period. The protocol also requires that subjects who do not achieve a clinical response at Week 12 and at Week 26 must permanently discontinue IP and enter the Post-treatment Follow-up Period. These design elements are intended to assist investigators in the recognition and management of treatment failure within the study.

In addition to a comprehensive monitoring of safety with oversight by the investigators, medical monitors from both Bristol-Myers Squibb (BMS) and the partner organization, Pharmaceutical Research Associates (PRA), and the BMS Safety Physician, the safety of subjects will also be monitored by an independent Data Monitoring Committee (DMC).

Taken together, the study design, including eligibility criteria, clinical assessments at study visits, study investigations such as safety bloods and endoscopies, and guidance for investigators on the recognition and/or management of AEs (including potential infections and disease exacerbation) mitigate expected risks and facilitate the detection and management of reasonably anticipated AEs in this study.

In summary, existing preclinical data and clinical experience in healthy subjects in combination with the design and doses selected for the proposed Phase 2 study indicate an overall favorable benefit-risk assessment of investigating BMS-986165 as an oral treatment for subjects with CD. Additional detailed information on the known and expected benefits and risks and reasonably anticipated AEs of BMS-986165 is provided in the IB.

4 OBJECTIVES AND ENDPOINTS

Key study definitions are provided below.

Clinical remission	CDAI < 150
Clinical response	A reduction from baseline in the CDAI score of ≥ 100 points or a total CDAI score < 150
Endoscopic response	≥ 50% improvement from baseline in the SES-CD
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PRO2 remission	Average daily score for abdominal pain ≤ 1 and average number of very soft (loose) or liquid (watery) stools (BSS Type 6 or 7 only) ≤ 3 on the PRO2 and both not worse than baseline
[redacted]	[redacted]
[redacted]	[redacted]

BSS = Bristol Stool Scale; CD = Crohn's Disease; CDAI = Crohn's Disease Activity Index; [redacted]; PRO2 = patient (or subject) reported outcome based on the stool frequency and abdominal pain components of the CDAI; SES-CD = Simple Endoscopic Score for Crohn's Disease.

[redacted].

Safety endpoints and primary, secondary, and exploratory efficacy endpoints are specified below. Additional endpoints may be specified in the statistical analysis plan (SAP).

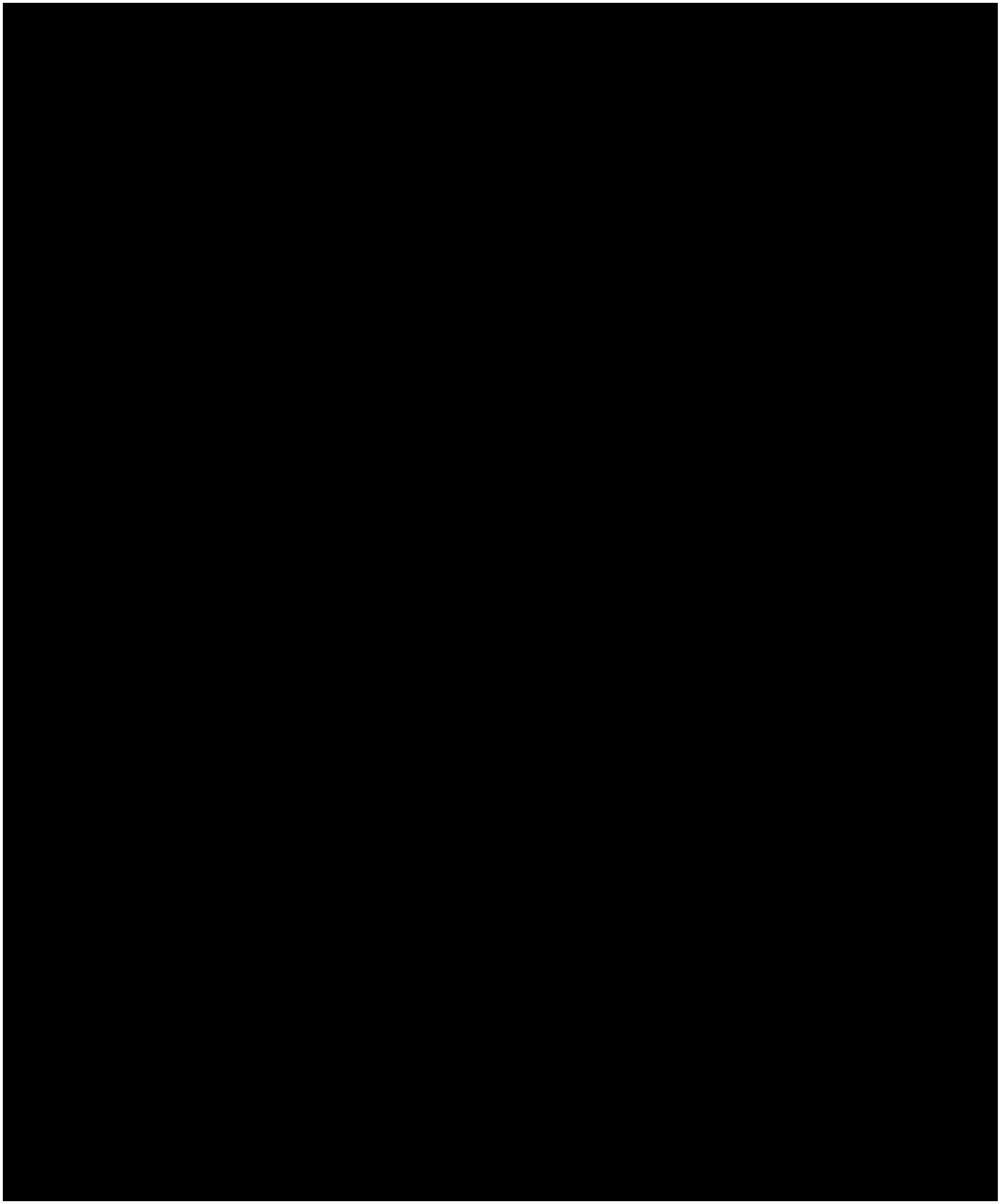
4.1 Primary Efficacy

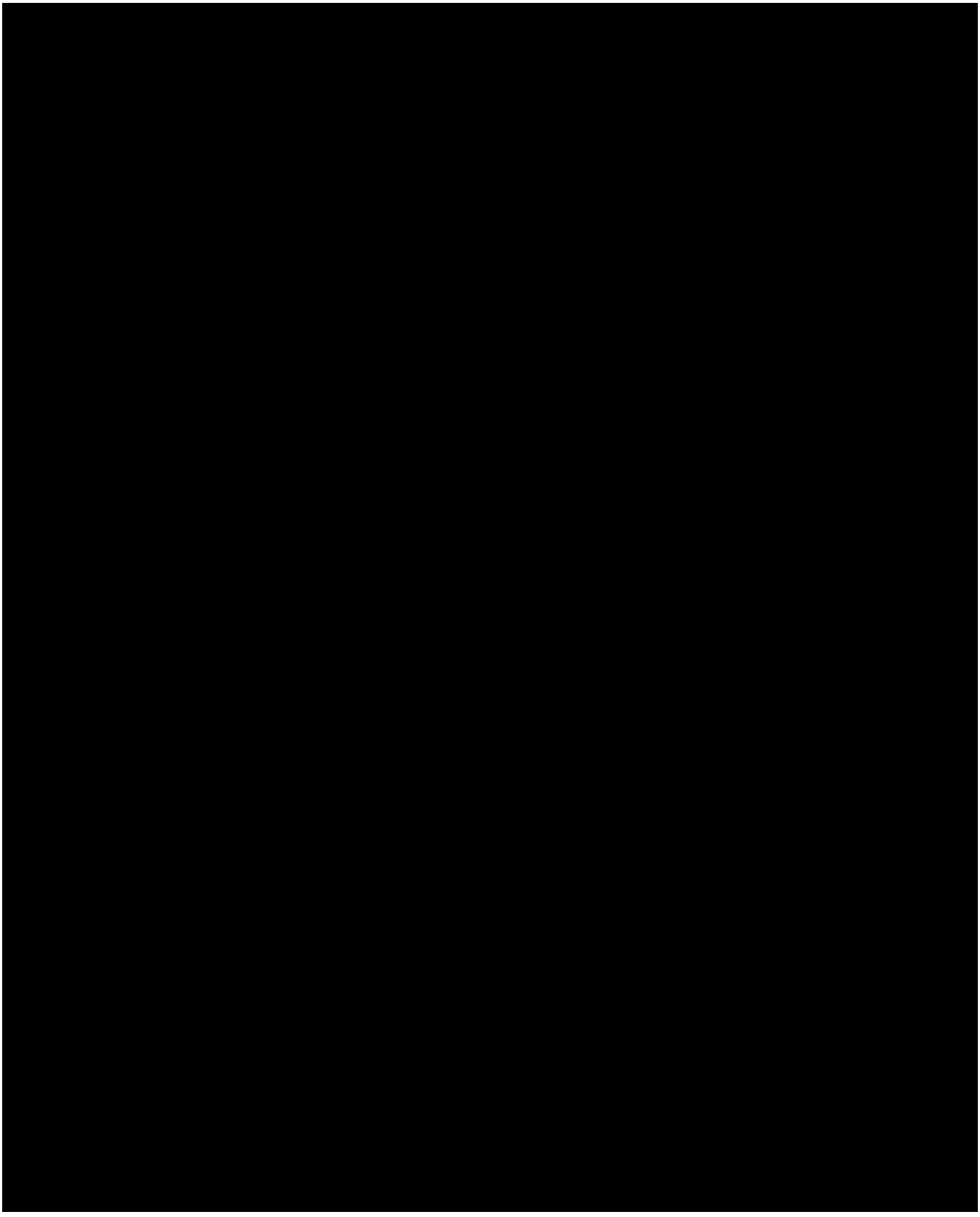
- Objective: To assess the effect of BMS-986165 on clinical remission and endoscopic response at the end of the Induction Period (Week 12 [Day 85])
  - Co-primary endpoints:
    - Proportion of subjects achieving clinical remission at Week 12, and
    - Proportion of subjects achieving endoscopic response at Week 12, both at a population level.

4.2 Secondary Efficacy

- Objective: To assess the effect of BMS-986165 on clinical response at the end of the Induction Period
  - Endpoint: Proportion of subjects who achieve a clinical response at Week 12
- Objective: To assess the effect of BMS-986165 on PRO2 remission at the end of the Induction Period
  - Endpoint: Proportion of subjects who achieve PRO2 remission at Week 12
- Objective: To assess the effect of BMS-986165 on gut mucosal disease activity by endoscopy at the end of the Induction Period
  - Endpoint: Change from baseline in SES-CD at Week 12

[redacted]





[redacted]

4.4 Safety

- Objective: To assess the safety and tolerability of BMS-986165
  - Endpoint: Number and proportion of subjects experiencing AEs, SAEs, and abnormalities in laboratory testing, physical examination, vital signs, and ECGs

5 STUDY DESIGN

5.1 Overall Design

This is a dose-ranging, randomized, placebo-controlled, double-blind, multicenter clinical trial that is designed to evaluate the safety and efficacy of 2 dosing regimens of BMS-986165 in subjects with moderately to severely active CD. The primary objective is to assess the effect of BMS-986165 on the co-primary endpoints of clinical remission (CDAI < 150) and endoscopic response (≥ 50% improvement from baseline in the SES-CD), on a population basis, at the end of the Induction Period (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)
- OLE Period: 52 weeks (364 days; Section 5.1.4)
- Post-treatment Follow-up Period: 4 weeks (28 days; Section 5.1.4.1)

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 (ileocolonoscopy) evaluations and collection of ileal and/or colonic tissue biopsies will be performed during the Screening Period, at the end of the Induction Period (Week 12), and at the end of the Maintenance Period (Week 52) and OLE Period (Week 104). Ileocolonoscopy will also be performed at Early Termination (ET) visits that occur at least 4 weeks after the most recent per protocol endoscopy. These are 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 Weeks 56 and 104 (OLE Period). Endoscopic procedures will be video-recorded and scored for disease activity by a blinded central reader. [redacted]

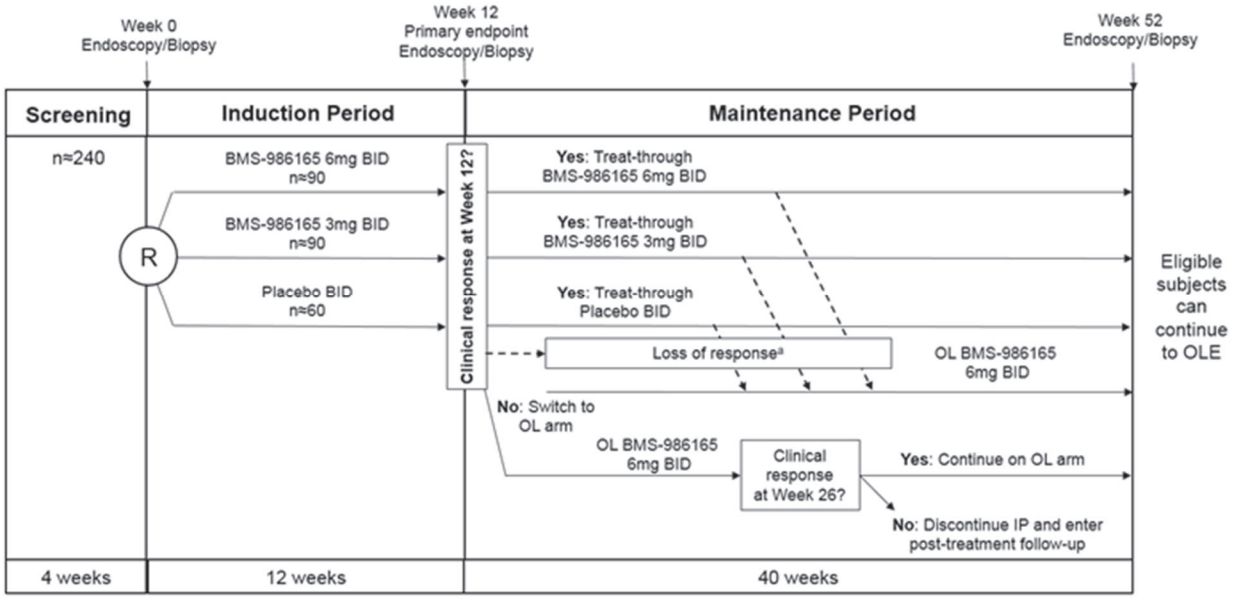
Physical examinations, vital sign measurements, 12-lead ECG, and clinical laboratory evaluations will be performed at selected times throughout the dosing interval, as indicated in the Schedule of Activities (Section 2). Subjects will be closely monitored for AEs throughout the study. [redacted] (Table 2, Table 3, and Table 4).

A DMC will be instituted to monitor subject safety during the study (Section 5.1.5).

The study design schematic is presented in Figure 1 and Figure 2.

Subjects who were randomized when Protocol v1.0 (27-Mar-2018) or Protocol v2.0 (24-May-2018) were in effect will continue on their currently assigned double-blind study treatment. These subjects will complete all study procedures and assessments outlined in the current version of the protocol.

Figure 1: Study Design Schematic: Induction and Maintenance Periods

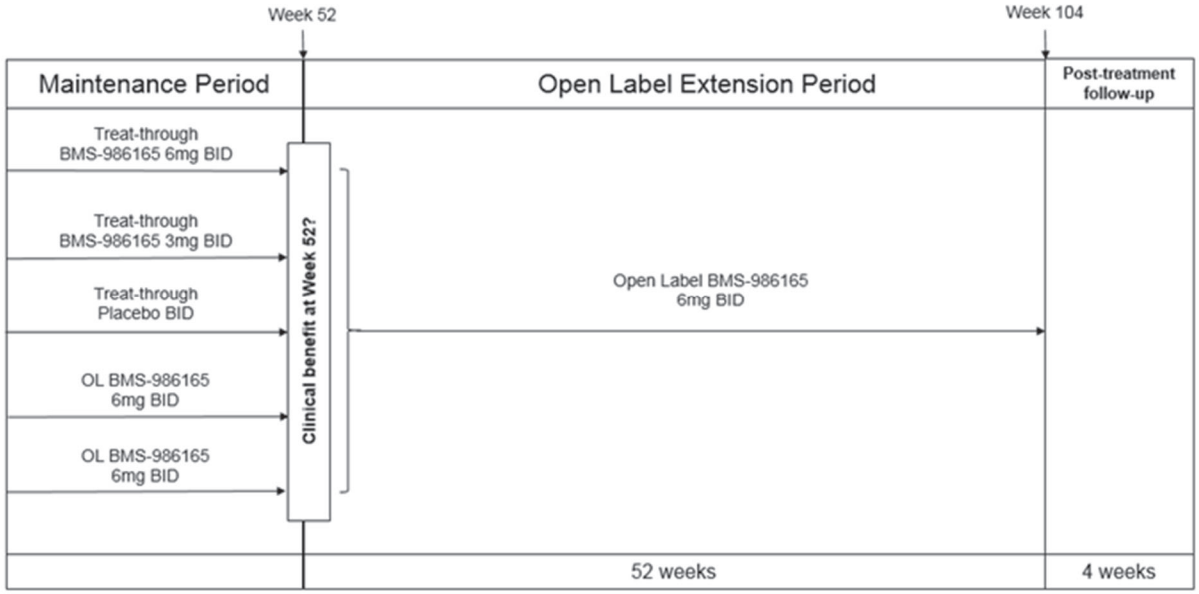


BID = twice daily; IP = investigational product; OL = open-label; R = randomization

[a] Subjects who achieve clinical response at Week 12 can enter the OL "loss of response" arm **at any time** from Week 13 through Week 52. Loss of response is defined as an increase in the CDAI score of ≥ 100 points compared to Week 12, and a total CDAI score of ≥ 220.

NOTE: This study has a treat-through design. At Week 12, subjects who achieve clinical response (defined as a reduction from baseline in the CDAI score of ≥ 100 points or a total CDAI score < 150) are eligible to continue to the Maintenance Period, where they will continue to receive the double-blind treatment regimen that they received in the Induction Period. Subjects who have loss of response in these arms may be eligible to enter the loss of response arm, where they will receive open-label BMS-986165 6 mg BID PO through Week 52. Subjects who do not achieve clinical response at Week 12 and who have an appropriate safety profile are eligible to enter an open-label treatment arm, in which they will receive open-label BMS-986165 6 mg BID PO during the Maintenance Period. Subjects in this arm must have clinical response assessed again at Week 26 (compared to Week 0). Subjects in this arm who do not achieve clinical response at Week 26 (compared to Week 0) will be considered treatment failures and must permanently discontinue IP and enter the Post-treatment Follow-up Period. Subjects in this arm who do achieve clinical response at Week 26 may continue IP through Week 52.

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



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

5.1.1 Screening Period

Once subjects sign the ICF, they are considered "enrolled" in the study and they enter the Screening Period. During the Screening Period, subjects will complete the study procedures outlined in the Schedule of Activities to determine if they meet eligibility criteria (Section 6).

In order to be eligible for the study, a subject must meet minimum disease activity criteria outlined in the inclusion criteria (Section 6.1), assessed by CDAI, PRO2, and SES-CD.

Subjects are expected to complete a daily diary throughout the Screening Period. AP and SF data recorded in the daily diary contributes to disease activity assessment during screening and throughout the study. The minimum daily diary requirements for CDAI/PRO2 calculations are outlined in Section 9.1. In order to ensure that a subject can be successfully randomized, sites should consider periodically confirming that subjects are successfully entering and uploading daily diary data (see Section 9.1, APPENDIX 10, and [redacted].

Screening endoscopy is performed in order to determine if a subject has active intestinal inflammation (assessed by centrally read SES-CD), [redacted] For screening and throughout the study, endoscopy should ideally be performed on a different day than the office visit, in order to avoid potentially confounding effects of bowel preparation, the endoscopy procedure, or sedation on clinical assessments, especially patient-reported outcome data.

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 should be randomized within 14 calendar days of the endoscopy.

Consequently, 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 ileocolonoscopy and Week 0 visit. Sites should consider the turnaround time for the centrally read endoscopy result when scheduling the ileocolonoscopy and Week 0 visits.

ii. The study diary requirements for the calculation of CDAI/PRO2 are outlined in Section 9.1. In order to ensure that a CDAI score can be determined, sites should consider periodically confirming that subjects are successfully entering and uploading daily diary data.

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 ileocolonoscopy.

iv. Once the screening ileocolonoscopy is performed, subjects should be randomized within 14 days.

In order to be eligible for randomization, subjects must have had an inadequate response, LOR, or intolerance to a standard treatment course of 1 or more of the following medications, as outlined in Inclusion Criterion 2)g):

i. Oral 5-ASAs, oral corticosteroids, intravenous (IV) corticosteroids, or immunomodulators, and/or

ii. Infliximab, adalimumab, certolizumab pegol, vedolizumab, ustekinumab, or natalizumab.

[redacted] The prior medication failure or intolerance used to qualify a subject for Inclusion Criterion 2)g) must be recorded in source documents.

The medications outlined in APPENDIX 7 are subject to a washout period prior to the day of randomization (Week 0). These medications include immunomodulators (eg, methotrexate [MTX], 5-azathioprine [AZA], 6-mercaptopurine [6-MP]) and biologic medications (eg, infliximab, adalimumab, certolizumab pegol, vedolizumab, natalizumab, and ustekinumab). In order to be eligible for randomization, subjects taking the medications listed in APPENDIX 7 must discontinue those medications prior to randomization and comply with washout periods listed in APPENDIX 7.

Some subjects will require adequate washout of biologics in order to be eligible for randomization. Therapeutic drug monitoring (TDM) assays that test for drug levels of these biologic medications are 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 for 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) certolizumab pegol, (iv) vedolizumab (if received > 14 weeks of vedolizumab therapy), or (v) ustekinumab (if received > 12 weeks of ustekinumab therapy). If a TDM assay is used to waive the washout period for any of the 5 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.

Corticosteroids (prednisone ≤ 20 mg QD PO or equivalent [redacted] or ileal-release budesonide ≤ 9 mg QD PO [eg, Entocort® EC]), 5-ASAs, probiotics, and CD-related antibiotics are allowed, subject to dose stabilization rules outlined in Section 6.3.

Selected subjects with complicated CD may be eligible to participate in this study. Subjects with perianal fistulizing disease are eligible to participate in the study, provided they meet the other inclusion/exclusion criteria, eg, perianal abscess should be carefully excluded during the Screening Period. In addition, certain subjects with asymptomatic stenosing disease may be eligible to participate in this study. However, subjects whose symptoms are primarily attributable to CD-related strictures are excluded, as obstructive symptoms or overflow diarrhea caused by a CD-related stricture are unlikely to respond to anti-inflammatory treatment and these may confound efficacy assessment. Malignancy should be carefully excluded in subjects with CD-related colonic strictures.

5.1.2 Induction Period

On Day 1 of the Induction Period, subjects who have completed the screening procedures and met the inclusion/exclusion criteria will be randomized in a 3:3:2 ratio to receive oral BMS-986165 6 mg BID or 3 mg BID or placebo BID, respectively, [redacted]

Video ileocolonoscopic examination and collection of ileal and/or colonic tissue biopsies should be performed within a window of 7 days prior to the Week 12 visit. Note: This requirement will

also apply to subjects who terminate early and have received study treatment for at least 4 weeks. The study diary requirements for the calculation of CDAI/PRO2 are outlined in Section 9.1.

Clinical response will be assessed at Week 12 (Section 5.1.3) to determine whether subjects will continue on the initially assigned double-blind dose or be offered the opportunity to switch to open-label BMS-986165 6 mg BID for the Maintenance Period. Subjects who were randomized prior to the implementation of Protocol v3.0 who have not yet reached Week 12 will likewise be offered the opportunity to switch to open-label BMS-986165 6 mg BID for the Maintenance Period, if they do not achieve a clinical response at Week 12.

If, in the opinion of the investigator, a subject requires rescue therapy for CD during the Induction Period, the subject must permanently discontinue study treatment, complete an ET Visit and enter the Post-treatment Follow-up Period. Examples of rescue therapies that are prohibited in this study include prednisone > 20 mg QD PO (or equivalent), intramuscular (IM) or IV corticosteroids, and biologic therapies that are approved for the treatment of CD in at least 1 country ([redacted] and Section 7.7.1). 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.

5.1.3 Maintenance Period

There will be a seamless transition between the Induction Period and Maintenance Period.

The Maintenance Period will last up to 40 weeks (52 weeks total).

Subjects who require prohibited rescue treatment for CD (see [redacted] Section 7.7.1) during the Maintenance Period must permanently discontinue study treatment, complete an ET Visit, and enter the Post-treatment Follow-up Period. An exit endoscopy is recommended for all subjects who undergo an ET Visit between Weeks 16 and 52. This 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 are eligible to enter the Maintenance Period and continue to receive the same blinded study regimen that they received in the Induction Period. Blinded study treatment will continue until the subject completes Week 52, experiences LOR (Section 5.1.3.3), 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 at the highest dose (6 mg BID PO), regardless of the initial treatment regimen received during the Induction Period. Subjects who were randomized prior to the implementation of Protocol v3.0 who have not yet reached Week 12 will likewise be offered the opportunity to switch to open-label BMS-986165 6 mg BID for the Maintenance Period, if they had not achieved a clinical response at Week 12.

Study treatment may be adjusted by the Sponsor should any emerging safety/tolerability issues be identified by the investigators, Sponsor, and/or DMC. Entrance of a subject to the Maintenance

Period or to an open-label study arm is conditional on an appropriate safety profile. Any safety concerns should be discussed with the medical monitor.

5.1.3.2 Week 26 (Day 183)

Subjects who do not achieve a clinical response at Week 12 and who have an appropriate safety profile are eligible to switch to open-label BMS-986165 treatment at the highest dose (6 mg BID), regardless of the initial treatment regimen received during the Induction Period.

Subjects who do not achieve protocol-defined clinical response at Week 12 and are switched to the open-label BMS-986165 6 mg BID study arm, as well as those who are currently receiving open-label BMS-986165 12 mg QD prior to implementation of Protocol v3.0, must be assessed for clinical response at Week 26. If clinical response at Week 26 (compared to Week 0) is achieved, and subjects have an appropriate safety profile, these subjects are eligible to continue on the open-label treatment for the remaining duration of the Maintenance Period.

Subjects in the open-label study arm who do not achieve clinical response at Week 26 (compared to Week 0) will be considered treatment failures and must permanently discontinue IP and enter the Post-treatment Follow-up Period. Note: These subjects may also be discontinued at any time before Week 26 based on the clinical judgment of the investigator.

5.1.3.3 Week 12 Responders: Loss of Response in the Maintenance Period

Subjects who achieve clinical response at Week 12 and continue on blinded study treatment will be judged to have LOR if they experience a worsening of clinical disease activity between Weeks 13 and 52, as defined below:

- ≥ 100 point increase in CDAI score, compared with CDAI score at Week 12, *and*
- Total CDAI score ≥ 220

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

5.1.3.4 Week 12 Non-responders: Loss of Response after Week 26 in the Open-label Arm

Subjects who do not achieve clinical response at Week 12 and who have an appropriate safety profile are eligible to enter the open-label BMS-986165 6 mg BID PO arm. Subjects in that arm who achieve clinical response at Week 26 will be judged to have LOR if they experience a worsening of clinical disease activity between Weeks 27 and 52, defined as:

- ≥ 100 point increase in CDAI score compared to Week 26, *and*
- Total CDAI score ≥ 220

A subject in this open-label treatment arm with LOR after Week 26 will be considered a treatment failure, must permanently discontinue study treatment, and must complete the appropriate per protocol procedures.

5.1.3.5 Week 52 (Day 365)

Video ileocolonoscopic examination and collection of ileal and/or colonic tissue biopsies should be performed within a window of 7 days prior to the Week 52 visit. The study diary requirements for the calculation of CDAI/PRO2 are outlined in Section 9.1.

5.1.4 Open-label Extension Period

Subjects who continue to derive a clinical benefit from IP at Week 52, as judged by the investigator, are eligible to enter the OLE Period. The OLE 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. The final ileocolonoscopy will occur within a window of 7 days prior to the Week 104 visit. The study diary requirements for the calculation of CDAI/PRO2 are outlined in Section 9.1.

Subjects who require prohibited rescue treatment for CD (see [redacted] and Section 7.7.1) during the OLE Period must permanently discontinue study treatment, complete an ET Visit, and enter the Post-treatment Follow-up Period. An exit endoscopy is recommended for all subjects who undergo an ET Visit between Week 56 and Week 104. This is not required for ET Visits within 4 weeks of the Week 52 endoscopy.

[redacted]

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, will enter a 4-week Post-treatment Follow-up Period. Subjects will be encouraged to report to the investigative site any SAEs or AEs experienced during the 28-day Follow-up Period. [redacted]

[redacted]

[redacted]

[redacted]

5.1.5 Data Monitoring Committee and Other External Committees

An external DMC will be used in this study to perform safety monitoring by blinded 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. 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.

[redacted]

5.2 Number of Subjects

Approximately 240 subjects will be randomized in a 3:3:2 ratio to receive BMS-986165 at 6 mg BID or 3 mg BID or placebo BID, respectively, during the Induction Period. Sample size considerations are described in Section 10.1.

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 visit or 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 SAEs). [redacted]

6 STUDY POPULATION

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 valid. It is imperative that subjects fully meet all eligibility criteria.

All screening and randomization evaluations must be completed and reviewed 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 the criteria in Section 6.1 and Section 6.2. To be randomized into the study on Day 1, subjects must meet the criteria in Section 6.3.

6.1 Inclusion 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 per Global Revised Protocol v3.0

b) Not applicable per Global Revised Protocol v3.0

c) Not applicable per Global Revised Protocol v3.0

d) Not applicable per Global Revised Protocol v3.0

e) Documented diagnosis of CD for at least 3 months prior to screening, including ileal, colonic, or ileo-colonic disease distribution, confirmed by:

- Source: Medical records with report of a colonoscopy with ileal intubation (ileocolonoscopy), which shows features consistent with CD, as determined by the procedure performing physician, AND
- Source: Medical record documentation of a histopathology report showing features consistent with CD, 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 CD before proceeding to randomization. The screening endoscopy must show features consistent with CD.

f) Must have active moderate to severe CD, as defined by:

- CDAI score of 220 to 450 AND
- PRO2: Average daily score for abdominal pain ≥ 2 OR average daily number of very soft (loose) or liquid (watery) stools (BSS Type 6 or 7 only; [redacted] ≥ 4, (see Section 9.1), AND
- Evidence of active inflammation in at least 1 of the 5 ileocolonic segments (based on central reading) with total SES-CD ≥ 6 or SES-CD ≥ 4 if only isolated ileitis is present on baseline endoscopy

g) Must have had an inadequate response, LOR, or intolerance to a standard treatment course of 1 or more of the following medications as below:

- Oral 5-ASAs: (eg, mesalamine, sulfasalazine, olsalazine, balsalazine) at or above the approved label dose (or per local standard of care) for induction therapy for at least 6 weeks
- Oral corticosteroids: Prednisone ≥ 40 mg/day or equivalent for 2 weeks, or 2 failed attempts to taper oral corticosteroids below prednisone or equivalent 10 mg daily, or a relapse within 3 months of discontinuing corticosteroids
- Intravenous (IV) corticosteroids: hydrocortisone ≥ 400 mg/day or equivalent for at least 1 week
- Immunomodulators: AZA ≥ 1.5 mg/kg/day, 6-MP ≥ 0.75 mg/kg/day, MTX ≥ 15 mg/week, or as per Institutional Practice/Country-approved label or guideline, for at least 12 weeks. At institutions that utilize thiopurine levels in clinical practice: AZA or 6-MP prescribed for at least 12 weeks with at least 1 demonstration of therapeutic thiopurine metabolite levels. Note: subjects with defined NUDT15 or TPMT mutations who experience intolerance to thiopurines at lower doses than those listed above may be eligible for this study. This should be discussed with the medical monitor on a case-by-case basis.
- Biologics: (eg, infliximab, adalimumab, certolizumab pegol, vedolizumab, natalizumab, ustekinumab) [redacted] Subjects can be included if treatment with a biologic was stopped due to primary or secondary nonresponse, or were intolerant to treatment, [redacted].

3) Age and Reproductive Status

a) Men and women aged 18 to 75 years inclusive at the time of screening

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

c) Women must not be breastfeeding

d) Not applicable per Global Revised Protocol v3.0

e) Not applicable per Global Revised Protocol v3.0

f) Not applicable per Global Revised Protocol v3.0

g) Not applicable per Global Revised Protocol v3.0

h) 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.

i) Not applicable per Global Revised Protocol v3.0

j) Not applicable per Global Revised Protocol v5.0

k) Investigators shall counsel WOCBP and men who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of methods of contraception (APPENDIX 5).

l) Male subjects should maintain their usual practice with regards to contraception (if any). However, no specific additional contraceptive measures are required.

m) WOCBP must agree to at least an acceptable, less than highly effective means of contraception (see APPENDIX 5) for the duration of treatment with study treatment(s) (BMS-986165 or placebo).

6.2 Exclusion Criteria

1) Target Population

a) Severe or fulminant colitis that is likely to require surgery or hospitalization

b) Presence of a diagnosis of alternative forms of colitis (infectious, inflammatory including ulcerative colitis, malignant, toxic, indeterminate, etc) other than CD

c) Not applicable per Global Revised Protocol v3.0

d) History of intra-abdominal abscess within the last 60 days

i) Previous intra-abdominal abscess that has been drained and successfully treated with a local standard course of antimicrobial therapy is permitted (the course must be completed at least 60 days prior to Day 1)

e) History of diverticulitis within the last 60 days

i) Previous diverticulitis that has been successfully treated with a local standard course of antimicrobial therapy is permitted. (the course must be completed at least 60 days prior to Day 1)

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

g) Current colonic dysplasia or past colonic dysplasia that has not been definitively treated

h) History of infectious (bacterial, viral, fungal, parasitic, etc.) colitis within past 30 days; must be fully treated to rescreen

i) Use of therapeutic enema or suppository, other than required for ileocolonoscopy, within 7 days prior to screening or during the Screening Period

j) Not applicable per Global Revised Protocol v3.0

k) Not applicable per Global Revised Protocol v3.0

l) Previous exposure to BMS-986165 in any study

m) Not applicable per Global Revised Protocol v.5.0

n) Not applicable per Global Revised Protocol v3.0

o) Not applicable per Global Revised Protocol v.5.0

p) Prior treatment with specific lymphocyte-depleting agents, such as alemtuzumab and rituximab, are prohibited within 12 months prior to the first dose of study treatment during the Induction Period.

q) Receipt of either lymphocyte apheresis or selective monocyte, granulocyte apheresis (eg, Cellsorba™) is prohibited within 12 months prior to the first dose of study treatment during the Induction Period.

r) Previous treatment with investigational agents within 4 weeks or 5 half-lives (whichever is longer) prior to the first dose of study treatment during the Induction Period. Subjects treated with investigational agents 4 to 12 weeks prior to the first dose of study treatment must be discussed with the medical monitor.

s) Previous stem cell transplantation, (except local stem cell therapy to treat perianal fistulae (eg, Alofisel® [darvadstrocel]). Please discuss on a case by case basis with the medical monitor.

t) Presence of a stoma, gastric or ileoanal pouch, previous proctocolectomy or total colectomy, or symptomatic, stenosing disease that is likely to confound efficacy assessment (eg, symptomatic CD-related stricture), abscess or suspected abscess, pouchitis, short bowel syndrome, or history of bowel perforation. In addition, subjects with colonic or ileal strictures that are not passable via colonoscope that the endoscopist normally uses in clinical practice, or strictures in the ileum or ileocecal valve that are fibrotic in nature, will be excluded.

2) Other 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, 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 within the last 30 days before the first dose of study treatment, or any surgery planned during the course of the study

d) Not applicable per Global Revised Protocol v3.0

e) 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

f) Significant blood loss (> 500 mL) or blood transfusion within 4 weeks of study treatment administration

g) Inability to tolerate oral medication

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

i) Not applicable per Global Revised Protocol v3.0

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

k) Potential subjects with the following characteristics will be excluded from the study:

- History of any kind of bowel resection within 6 months or any other intra-abdominal surgery within 3 months prior to baseline
- History of any surgical procedure requiring general anesthesia, other than required for ileocolonoscopy, within 30 days prior to the first dose of study treatment, or is planning to undergo surgery during the study period
- 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
- Currently on any therapy for chronic infection (eg, pneumocystis, cytomegalovirus, herpes simplex, herpes zoster, invasive bacterial or fungal infections, or atypical mycobacteria)
- History of congenital or acquired immunodeficiency

- 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.
  - In the case of prior SARS-CoV-2 infection, symptoms must have completely resolved 4 weeks prior to screening and based on investigator assessment in consultation with the medical monitor, there are no sequelae that would place the subject at a higher risk of receiving BMS-986165. See Section 9.10 for additional information regarding retesting subjects who have had prior SARS-CoV-2 infection.
- 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)
- 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)
- 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
- 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
- Administration of a live vaccine within 90 days before the first dose of study treatment administration. Heat-killed, or otherwise inactivated, protein or subunit vaccines (eg, 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 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.
- Current or recent (within 3 months before the first dose) gastrointestinal disease, including gastrointestinal surgery, that could impact the absorption of study treatment, or current or recent (within 6 months before the first dose) gastrointestinal resections

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

3) Prior/Concomitant Therapy

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

b) Not applicable per Global Revised Protocol v3.0

c) Not applicable per Global Revised Protocol v3.0

d) Not applicable per Global Revised Protocol v.5.0

e) Inadequate response or LOR to medications that target the same pathway as BMS-986165 such as anti-12/23p40 antibodies (eg, 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 have not had a treatment failure (ie, an inadequate response or LOR) 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.

4) Physical and Laboratory Test Findings

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

b) Not applicable per Global Revised Protocol v3.0

c) Not applicable per Global Revised Protocol v3.0

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

e) 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 (Subjects with total bilirubin > 2× ULN who have a confirmed diagnosis of Gilbert's syndrome are not excluded from this study but must be discussed with the BMS medical monitor/designee.)
- Alkaline phosphatase > 2.5× ULN
- Serum creatinine > 2× ULN
- Hemoglobin level < 9 g/dL
- Absolute white blood cell count < 3000/mm^3
- Absolute lymphocyte count < 500/mm^3
- Neutrophil count < 1000/mm^3
- Platelet count < 100,000/mm^3

f) 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

g) Not applicable per Global Revised Protocol v3.0

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

i) 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 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.

j) Evidence of, or positive test for, hepatitis B virus (HBV) at screening as defined per APPENDIX 9

k) Evidence of, or positive for, hepatitis C virus (HCV) at screening. A positive test for HCV is defined as:
   i) Positive for HCV antibody (anti-HCV) AND
   ii) Positive via a confirmatory test for HCV (eg, detectable HCV RNA, HCV polymerase chain reaction)

l) 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

m) Not applicable per Global Revised Protocol v.5.0

n) Stool positive for *Clostridium difficile* (*C. difficile*) at screening visit; for full screening procedures, refer to APPENDIX 20. Subjects who test positive may be rescreened 30 days after completion of an institutional standard of care course of antibiotics and subsequent negative testing for *C. difficile*. For further clarification, contact the medical monitor.

5) Allergies and Adverse Drug Reaction

a) History of any significant drug allergy (such as anaphylaxis or hepatotoxicity)

6) Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated. If applicable to national or local legislation: history of being admitted to an institution under an administrative or court order

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

c) Inability to comply with the study protocol

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 Day 1 before randomization and the first dose:

1) The subject continues to satisfy all eligibility criteria.
2) If no previous confirmation of diagnosis is available or if previous diagnosis is not deemed conclusive, at time of baseline endoscopy, histology must be performed and read locally to confirm diagnosis of CD.
3) Previous therapy must follow the rules outlined below:
   a) 5-ASAs must be at stable doses for at least 2 weeks prior to the first dose of study treatment on Day 1 of the Induction Period.
   b) Probiotics must be at stable doses for at least 2 weeks prior to the first dose of study treatment on Day 1 of the Induction Period.
   c) CD-related antibiotics (ciprofloxacin, metronidazole, etc.) must be at stable doses for at least 2 weeks prior to the first dose of study treatment on Day 1 of the Induction Period.
   d) Corticosteroids:
      - Prednisone ≤ 20 mg QD PO (or equivalent) or ileal-release budesonide ≤ 9 mg QD PO (eg, Entocort® EC) must be stable for at least 2 weeks prior to randomization.
      - Use of IV corticosteroid is prohibited within 14 days prior to or during the Screening Period.
   e) Prior exposure to the immunomodulators 6-MP, AZA, and MTX is permitted, but these agents must be discontinued for at least 4 weeks prior to the first dose of study treatment on Day 1 of the Induction Period. Treatment with cyclosporine, mycophenolate mofetil, leflunomide, tacrolimus, JAK inhibitors, or IFN must be discontinued prior to the first dose of study treatment on Day 1 of the Induction Period as described in APPENDIX 7.
   f) The washout period for biologics is discussed in Section 5.1.1 and APPENDIX 7. The washout period for infliximab, adalimumab or certolizumab pegol may be waived for subjects with an undetectable drug level on a TDM assay performed in routine clinical practice, or in screening. The washout period for subjects who have received vedolizumab maintenance therapy for > 14 weeks or ustekinumab therapy for > 12 weeks may similarly be waived, if a TDM assay shows undetectable drug levels on a TDM assay.

6.4 Lifestyle Restrictions

No restrictions are required.

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 [Days 1 and 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 publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any SAEs.

The 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). Subjects who were screen-failed due to *C. difficile* infection must be adequately treated and subsequently test negative for *C. difficile*. The subject must be re-consented (ie, re-signing of the ICF), and rescreened (if outside the 28-day Screening Period window). Only 1 re-enrollment per subject is permissible.

6.5.1 Retesting During the Screening Period; Rescreening

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.

The study permits the rescreening (after the end of the initial 4-week Screening Period) of a subject who discontinues the study as a pretreatment failure (ie, the subject fails screening or randomization and has not been treated) or if they have experienced an infection with *C. difficile* and were adequately treated, and subsequently test negative for *C. difficile* (see APPENDIX 20). The subject must be re-consented and will be assigned a new identification number, and a full screening visit must be performed again.

A subject can only be rescreened 1 time (ie, if the subject fails 1 rescreening attempt, no additional rescreening is allowed). Duration of existing treatments and required discontinuation periods shall be considered relative to the given screening visit and/or randomization.

Subjects who were previously randomized in IM011023 are not eligible for rescreening, even if they did not receive a dose of study treatment.

If subjects test positive for *C. difficile* (see APPENDIX 20), they can be rescreened 30 days after completing a full course of standard treatment for *C. difficile* colitis and subsequently test negative for *C. difficile*.

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, marketed product, placebo, or medical device intended to be administered to a study subject according to the study randomization or treatment allocation.

Study treatment includes IP/investigational medicinal product (IMP) and consists of placebo and BMS-986165. Information about the pharmacology and previous experience with BMS-986165 is provided in Section 3.1.1 and Section 3.1.2.

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

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

[redacted]

7.1 Treatments Administered

During the Induction Period, subjects will take BMS-986165 6 mg BID or 3 mg BID or placebo BID over 12 weeks (Section 5.1.2). For each dose level of BMS-986165 or placebo, capsules are taken BID (ie, once in the morning and once in the evening). [redacted]

Study treatment for subjects with no response or who have lost response, and enter into the open-label portion of the study will be supplied with the 3 mg hard gelatin capsules. [redacted]

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 (a reduction from baseline in the CDAI score of ≥ 100 points or a total CDAI score < 150) at Week 12 may be eligible to enter the double-blind and placebo-controlled Maintenance Period. During the Maintenance Period, subjects will take the same blinded study treatment dose level (BMS-986165 6 mg BID or 3 mg BID or placebo BID) that was assigned during the Induction Period. Subjects who were randomized to the BMS-986165 12 mg QD PO study arm when Protocol v1.0 (27-Mar-2018) or Protocol v2.0 (24-May-2018) were in effect who have not yet reached Week 12 will continue to receive blinded BMS-986165 12 mg QD for the Maintenance Period if they achieve a clinical response at Week 12.

Clinical Non-Responders at Week 12: Subjects who do not achieve a clinical response at Week 12 and who have an appropriate safety profile are eligible to switch to the BMS-986165 6 mg BID PO in the open-label study arm, regardless of the initial treatment regimen received during the 12-week Induction Period. Subjects who were randomized prior to when Protocol v1.0 (27-Mar-2018) or Protocol v2.0 (24-May-2018) were in effect and are currently receiving open-label BMS-986165 12 mg QD will continue on that dose until discontinuation.

At Week 26 of the Maintenance Period, the investigator will check if these subjects have achieved a clinical response (compared to Week 0). Subjects who achieve a clinical response at Week 26 (compared to Week 0) will continue on open-label treatment at the highest dose level (6 mg BID), or continue 12 mg QD if they were already receiving it. Subjects who do not achieve a clinical response at Week 26 (compared to Week 0) will be considered treatment failures and must permanently discontinue [redacted]

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) for assignment of the subject identification number. This number will be unique across all sites. All enrolled subjects, including those not randomized or dosed, 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 identification number.

Eligible subjects will be centrally randomized using IRT to receive oral treatment during the Induction Period with BMS-986165 at 6 mg BID or 3 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 (Section 5.1).

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).

7.3 Blinding

7.3.1 Maintaining the Blind

Blinded treatment assignments will be managed using IRT.

All capsules (BMS-986165 3 mg and placebo) have an identical matching placebo capsule in order to maintain the blind. [redacted] Investigative site staff, Sponsor and designee personnel, and subjects and their families will remain blinded to treatment assignments.

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

The DMC may review unblinded data summaries and listings, at their request (see Section 5.1.5). DMC processes and procedures will be outlined in the DMC Charter.

Designated staff of Bristol-Myers Squibb Company may be unblinded (obtain the randomization codes) prior to database lock to facilitate the bioanalytical analysis of [redacted] and immunogenicity. A bioanalytical scientist in the Bioanalytical Sciences department of Bristol-Myers Squibb Research & Development (or a designee in the external central bioanalytical laboratory) will be unblinded to (may obtain) the randomized treatment assignments in order to minimize bioanalytical analysis of samples.

7.3.2 Circumstances for Unblinding

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

Before breaking the blind of an individual subject's treatment, the investigator should determine that the unblinded information is necessary (ie, determine if 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 in order to discuss subject safety and whether the subject should remain in the study. 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).

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.

7.3.3 Unblinding for Week 12 Analysis

An unblinded analysis of data through Week 12 will be performed after all subjects complete their Week 12 efficacy assessments or have discontinued prior to Week 12. A select group of BMS personnel who are not involved in the conduct of the study will review the unblinded results to write a clinical study report. Following the Week 12 analysis until the end of the study, the investigators, subjects, and clinical study team members who directly cooperate with the site staff will continue to remain blinded to the initial treatment assignment. Details of maintaining the blind

following the unblinded analysis will be finalized in the SAP prior to the Week 12 database lock. A final analysis will be performed after all subjects complete the Week 104 visit or discontinue prior to the Week 104 visit, and a clinical study report will be written.

7.4 Dosage Modification and/or Interruption

There is no provision for dose modification of study treatment. [redacted]. Modification of other background CD therapies or dose regimens is not permitted during study participation. [redacted] 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 properly stored and administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Guidance and information for the final disposition of unused study treatments are provided in APPENDIX 2 and the Study Reference Manual.

7.6 Treatment Compliance

Study treatment compliance will be periodically monitored using standard drug accountability procedures (comparing the number of capsules 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) of study treatment must be recorded on the eCRF.

Other than existing treatment for CD (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 clinical events.

7.7.1 Prohibited and/or Restricted Treatments

Restrictions and prohibitions on prior and concomitant medications are as follows:

1) Prior exposure to BMS-986165 is prohibited.
2) [redacted].
3) Nonsteroidal anti-inflammatory drugs (NSAIDs) may be used on an as-needed basis during the study for indications other than CD-related pain (eg, headache), but use is not recommended. Assessment of AP is a component of the CDAI and PRO2 instruments, and NSAIDs are likely to confound the assessment of efficacy in this study, ie, by improving or exacerbating AP related to CD.
4) Prior treatment with specific lymphocyte-depleting agents, such as alemtuzumab, rituximab, are prohibited within 12 months prior to the first dose of study treatment during the Induction Period.
5) Not applicable per Global Revised Protocol v5.0
6) Receipt of either lymphocyte apheresis or selective monocyte, granulocyte apheresis (eg, Cellsorba™) is prohibited.
7) Required washout periods for individual immunomodulatory and biologic drugs are provided in APPENDIX 7.
8) Live vaccines are prohibited 90 days prior to randomization, during the Induction Period or Maintenance Period, or within the 2 months after the last dose. Heat-killed, or otherwise inactivated, 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 on study. The effectiveness of vaccination in subjects receiving BMS-986165 has not been studied. Similarly, the effectiveness of vaccination in subjects who will shortly receive BMS-986165 (eg, subjects in the screening period) has not been studied.
9) For COVID-19 vaccine information, refer to APPENDIX 19.

10) Exposure to any investigational drug within 4 weeks or 5 half-lives (whichever is longer) before the first dose of study treatment is prohibited (Exclusion Criterion 1)r); Section 6.2).

7.7.2 Existing Therapies for Crohn's Disease

Use of concomitant 5-ASAs, probiotics, antibiotics to treat luminal CD, and corticosteroids (prednisone ≤ 20 mg/day or equivalent, or ileal-release budesonide ≤ 9 mg/day [eg, Entocort® EC]) is permitted. All subjects will continue their existing CD treatment(s) during the study as follows (if the treatment complies with the eligibility criteria; Section 6), unless dose modification or discontinuation is required for subject safety reasons:

- 5-ASAs must be at stable doses for at least 2 weeks prior to the first dose of study treatment on Day 1 of the Induction Period and must be maintained at stable doses during the Induction Period.
- CD-related antibiotics (eg, ciprofloxacin, metronidazole, etc.) must be at stable doses for at least 2 weeks prior to the first dose of study treatment on Day 1 of the Induction Period and must be maintained at stable doses during the Induction Period.

If subjects were previously prescribed any of the above medications, they must have been discontinued for ≥ 4 weeks prior to the randomization visit.

- Probiotics must be at stable doses for at least 2 weeks prior to the first dose of study treatment on Day 1 of the Induction Period and must be maintained at stable doses during the Induction Period. During the Maintenance Period, a dose decrease is permitted if due to probiotics-related toxicity.
- Corticosteroids
  - Prednisone ≤ 20 mg QD PO (or equivalent) or ileal-release budesonide ≤ 9 mg QD PO (eg, Entocort® EC) must be stable for at least 2 weeks prior to randomization, with dose stabilization during the Induction Period. [redacted]
  - Use of IV corticosteroid is prohibited within 14 days prior to or during the Screening Period and throughout the duration of the Induction Period and Maintenance Period.

Immunomodulators and biologics must be discontinued prior to the first dose of study treatment as outlined below and are prohibited during the study:

- Prior exposure to the immunomodulators 6-MP, AZA, and MTX is permitted, but these agents must be discontinued for at least 4 weeks prior to the first dose of study treatment on Day 1 of the Induction Period. Treatment with cyclosporine, mycophenolate mofetil, leflunomide, tacrolimus, or JAK inhibitors must be discontinued prior to the first dose of study treatment on Day 1 of the Induction Period as described in APPENDIX 7.
- The washout period for biologics is discussed in Section 5.1.1 and APPENDIX 7. The washout period for infliximab, adalimumab or certolizumab pegol may be waived for subjects with an undetectable drug level on a TDM assay performed in routine clinical practice, or in screening.

The washout period for subjects who have received vedolizumab maintenance therapy for > 14 weeks or ustekinumab therapy for > 12 weeks may similarly be waived, if a TDM assay shows undetectable drug levels.

7.8 Treatment After the End of the Study

[redacted]

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 or other reasons, including but not limited to, lack of efficacy and/or failure to meet study objectives; b) development of BMS-986165 for the treatment of CD and/or the development of the compound is terminated for other reasons, including but not limited to lack of efficacy and/or failure to meet 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 requests 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 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.
- Subject meets the following criteria for laboratory abnormalities in 2 sequential laboratory measurements taken 3 to 5 days apart (2 additional days are permitted to allow for local logistics):
  - Absolute neutrophil count < 0.75×10^9/L (< 750/mm^3)
  - Absolute lymphocyte count < 0.5×10^9/L (< 500/mm^3)
  - Hemoglobin < 8.0 g/dL or a decrease of > 30% from baseline
  - Platelet count < 75×10^9/L (< 75,000/mm^3)
  - An increase in serum creatinine > 50% over the average of screening and baseline values AND an absolute increase in serum creatinine > 0.5 mg/dL (> 44.2 µmol/L)
  - Creatine kinase (CK) elevations > 10 times the ULN, unless the causality is known not to be medically serious (eg, exercise-induced)

- Subjects who develop a significant infection during the study, defined as any infection (viral, bacterial, or fungal) requiring parenteral antimicrobial therapy, or meeting the SAE criteria
- Termination of the study by BMS or a specific dose arm (for subjects receiving that dose) by BMS. Subjects enrolled prior to Protocol v3.0 and who may have been randomized to blinded BMS-986165 12 mg QD treatment do not need to be discontinued.
- Loss of ability to freely provide consent through imprisonment or involuntary 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
- [redacted]
- Subject meets any of the following criteria for liver-related laboratory abnormalities. If these abnormalities are identified, repeat testing should occur within 48 to 72 hours and these results should be discussed with the BMS medical monitor/designee. Additional recommendations on the recognition and investigation of potential drug-induced liver injury (DILI) are given in Section 9.3.8.
  - ALT or AST > 8× ULN on a single occasion
  - ALT or AST > 5× ULN for more than 2 weeks
  - ALT or AST > 3× ULN and total bilirubin > 2× ULN or international normalized ratio (INR) > 1.5
- ALT or AST > 3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)
- Any other serious or severe AE or intercurrent illness, that, in the opinion of the investigator and after consultation with the medical monitor or designee, indicates that continued participation in the study is not in the best interest of the subject. If study treatment is discontinued due to an AE, the AE eCRF must be completed to show that the AE caused discontinuation

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

In the case of pregnancy, the investigator must immediately notify the BMS medical monitor or designee of this event. In the event a female subject becomes pregnant during a clinical trial, the study treatment must be discontinued immediately. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please call the BMS medical monitor within 24 hours of awareness of the pregnancy.

All subjects who discontinue BMS-986165 should comply with protocol-specified follow-up procedures as outlined in Section 2. The only exception to this requirement is when a subject withdraws consent for all study procedures including posttreatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). Replacement of subjects is not permitted.

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.

8.2 Discontinuation from the Study

Subjects who request to discontinue study treatment (possible circumstances are listed in Section 8.1) will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a 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 IP 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 9.10).
- 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 9.10.

8.3 Discontinuation of the Study/Study Stopping Rules

There will be a DMC to provide oversight of the safety in this trial as outlined in Section 5.1.5 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 the Sponsor study team 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 in the event that either of the following occur:
- 2 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 underlying or intercurrent medical condition or concomitant medication)
- 2 or more subjects are discontinued due to the same laboratory parameter abnormality as defined by the criteria in Section 8.1

8.4 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, in order 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.

8.5 Replacement of Subjects

Subject replacement is not permitted.

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 the ICF may be used for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the time frame 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, 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 CD and related health conditions. The study data may also be used to help understand the biology of CD and related health conditions, study test performance in people with CD, 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' CD activity during the study (see schedule in Section 2):

- CDAI[10,15,16] (APPENDIX 10) and PRO2[12] ([redacted]: The CDAI and PRO2 scores will be calculated using 7 days of subject diary entries. CDAI also includes additional components, as outlined in APPENDIX 10. The following rules apply to the calculation of CDAI and PRO2 scores:

  For Week 0, if there are < 14 days between the endoscopy date and the visit date, the bowel preparation day will serve as the diary reference point; if there are ≥ 14 days between the endoscopy date and the visit date, the Week 0 visit date will serve as the diary reference point.

  – The collection window for subject diary data used for the calculation of CDAI and PRO2 scores for a study visit (other than Week 0) should be a maximum of 14 days prior to the day of the study visit. For study visits that include endoscopy, the final day of diary collection is the day before the subject starts bowel preparation for ileocolonoscopy.
  – CDAI/PRO2 calculation will be performed using the 7 latest days of diary entry in the collection window. These days do not have to be consecutive. At least 4 of those 7 days of diary data must be collected in the final 7 days of the collection window. If either of these criteria are not met, the CDAI/PRO2 score will be counted as "missing."

- If the requirements outlined above are not met, CDAI/PRO2 cannot be calculated for that study visit. If this occurs prior to the Week 0 visit, the subject cannot meet Inclusion Criterion 2)f), cannot be randomized, and must be screen-failed.
- Prior to each scheduled visit at which CDAI/PRO2 is to be calculated, determine whether an adequate number of diary entries have been made. If adequate entries have not been made, the site should contact the subject to reschedule the visit (or endoscopy, if applicable), and the subject should be counseled about proper study procedures.

- SES-CD[17] (APPENDIX 12): The SES-CD assesses the size of mucosal ulcers, the ulcerated surface, the endoscopic extension, and the presence of stenosis. This blinded assessment will be carried out by Alimentiv Clinical Trials, and the results will be considered final for this study.
- [redacted]

- [redacted]

9.2 Laboratory Assessments

The following laboratory tests will be performed according to the Schedule of Activities in Section 2 to gather more information about CD activity: [redacted]; stool *C. difficile*; quantitative immunoglobulins (IgM, IgE, IgA, IgG); T, B, and natural killer (TBNK) cells; and hematocrit (ie, for CDAI). For the purpose of prompt CDAI score calculation from Week 2 through Week 52 and at Week 104, the hematocrit may be performed by a local laboratory.

9.3 Adverse Events

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 discontinue before completing the study.

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

[redacted]

9.3.1 Adverse Events of Interest

AEIs are AEs for a particular product or class of products that a Sponsor may wish to monitor carefully. AEIs 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 immunomodulation 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.

9.3.2 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 Appendix 1 of the IB should be used to determine expectedness of SAEs for expedited reporting.

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) [redacted]

The investigator must report any SAE that occurs after this time period and that is believed to be related to study treatment or protocol-specified procedure.

- 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.

9.3.3 Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of 1 or more AEs.

9.3.4 Follow-up of AEs and SAEs

- AEs should be followed to resolution or stabilization, or until they are reported as SAEs if they become serious (APPENDIX 3).
- Follow-up is also required for AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.

- All identified AEs must be recorded and described on the "adverse events" page of the eCRF. Completion of supplemental eCRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and AEIs (as defined in Section 9.3.1) 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 8.4.

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

9.3.5 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards 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/Independent Ethics Committee, if appropriate according to local requirements.

The 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 (CFR) 21, Parts 312 and 320. Suspected, unexpected, serious adverse reactions are a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.3.6 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the BMS medical monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in APPENDIX 3.

Pregnancy occurring in a female subject is a reason for discontinuation of study treatment (see Section 8.1). Protocol-required procedures for study discontinuation (except endoscopy) and follow-up should be performed on the subject.

Any pregnancy that occurs in a female partner of a male study subject should be reported to PRA Drug Safety. In order for 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.

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.

9.3.7 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the AE eCRF page or SAE Report Form electronic, as appropriate.

- Any laboratory test result that is clinically significant or meets the definition of an 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 PRA 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" is preferable to "low hemoglobin value").

9.3.8 Potential Drug-induced Liver Injury

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 (APPENDIX 3). The Sponsor will require follow-up testing when DILI is suspected (eg, HBV DNA, IgM anti-HEV, HEV RNA, IgM & IgG anti-HSV, etc).

Potential DILI is defined by presence of all of the following characteristics:

- Transaminase (ALT or AST) elevation > 3× ULN
- Total bilirubin > 2× ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
- No other immediately apparent possible causes of transaminase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, preexisting chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic

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

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

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

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

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 9.3 and APPENDIX 3 for reporting details). All subjects with clinically significant abnormalities in liver-related blood tests, or potential DILI, must be followed until all abnormalities return to normal or to the baseline state.

9.3.9 Other Safety Considerations

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

9.4 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.

9.5 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 9.5.1), TB screening (Section 9.5.2), vital signs, ECGs, concomitant medication use, laboratory tests (Section 9.5.3).

Planned time points for all safety assessments are listed in the Schedule of Activities.

9.5.1 Physical Examinations

Schedules for physical examinations are provided in 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. These body systems can include lymph nodes, liver, spleen, and breast at the discretion of the examiner. 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.

9.5.2 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 Exclusion Criterion 4)i) (Section 6.2). 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 PRA medical monitor. A negative IGRA performed within 6 months of the screening visit may be acceptable, provided a copy of the report is in the subject's source documentation, and the subject has no new risks for LTBI in the interim. 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.

9.5.3 Clinical Safety Laboratory Assessments

A central laboratory will perform assessments of safety laboratory assessments (except pregnancy tests) and provide reference ranges and laboratory reports. For the purpose of prompt CDAI score calculation from Week 2 through Week 52 and at Week 104, the hematocrit may be performed by a local laboratory. If the result cannot be obtained before the end of the visit, the subject should return the following day for calculation of the CDAI. 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 9.3.7). 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, fasting glucose, fasting lipids, total protein, albumin, sodium, potassium, chloride, calcium, phosphorus, magnesium, CK, creatinine clearance (screening only), and thyroid-stimulating hormone blood test (with reflex T3 and T4 testing)
- Coagulation: prothrombin time, INR, 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: anti-HCV, HCV RNA if anti-HCV is positive or indeterminate, HBsAb, HBsAg, anti-HBc, reflex to HBV DNA, HIV-1 and -2 antibody, and TB testing
- Quantitative serum immunoglobulins: IgG, IgE, IgA, and IgM
- TBNK
- [redacted]

In addition, urine pregnancy testing will be performed for WOCBP, and follicle-stimulating hormone (FSH) will be measured to confirm postmenopausal status (as applicable; at screening only).

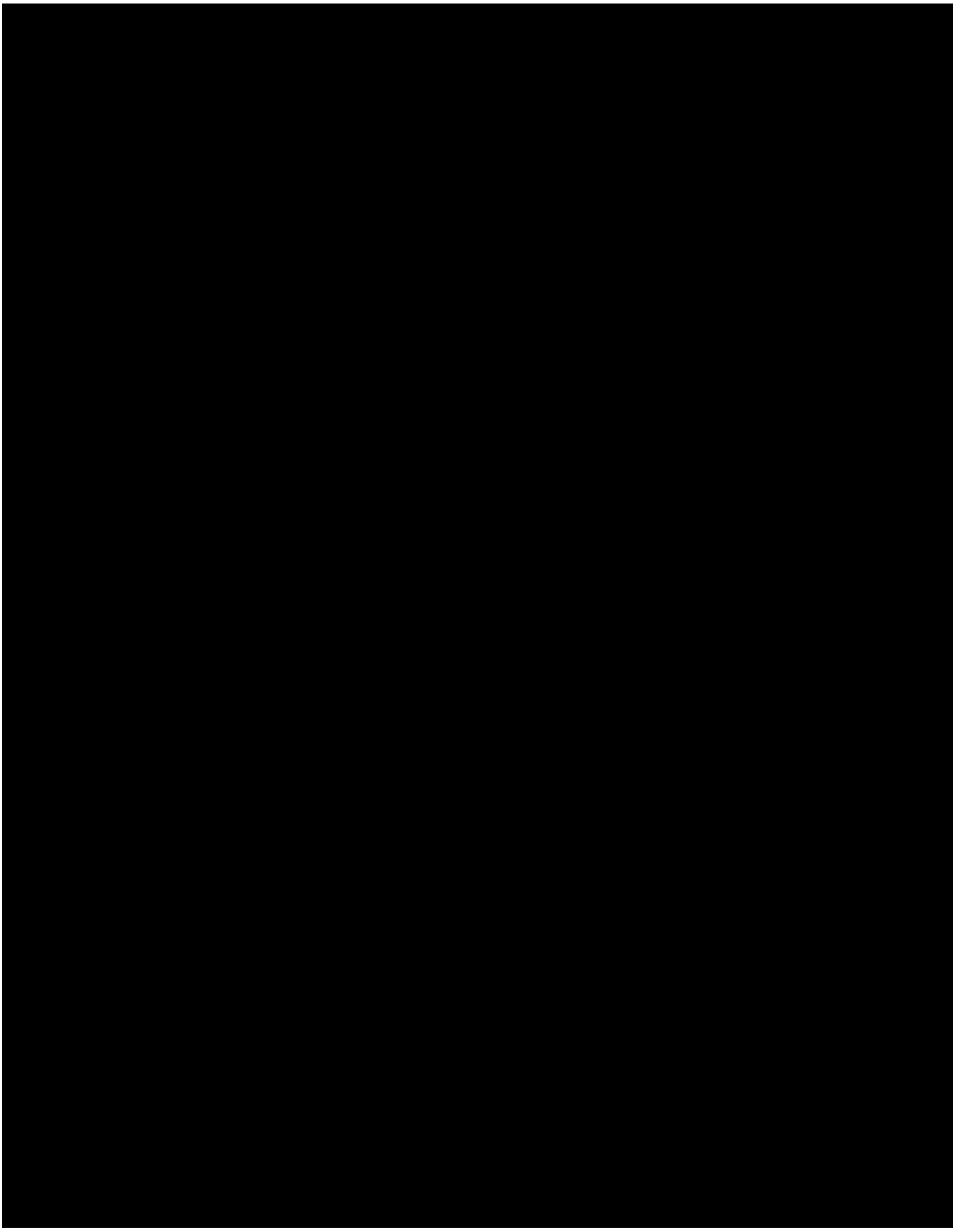
9.5.4 Imaging Safety Assessment

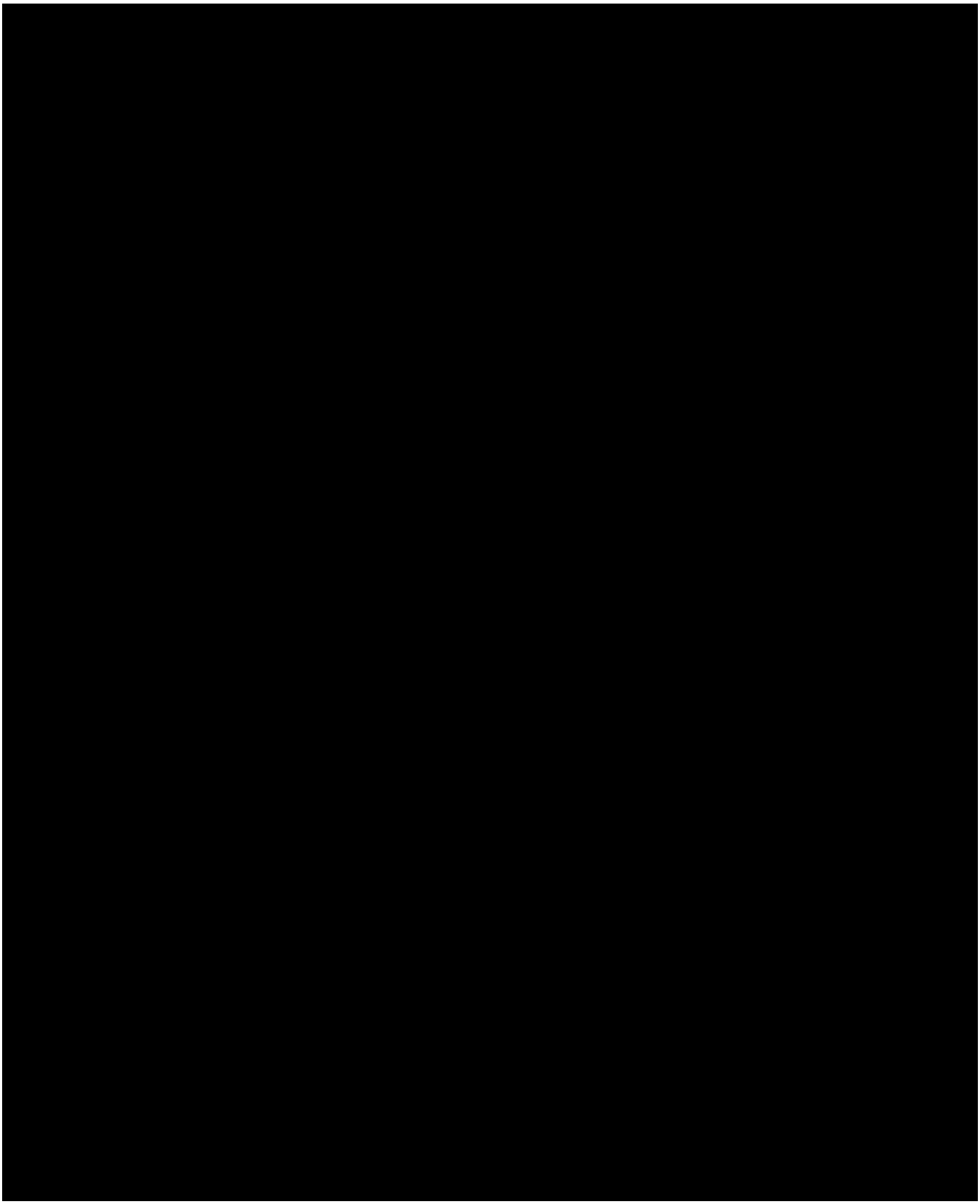
Not applicable.

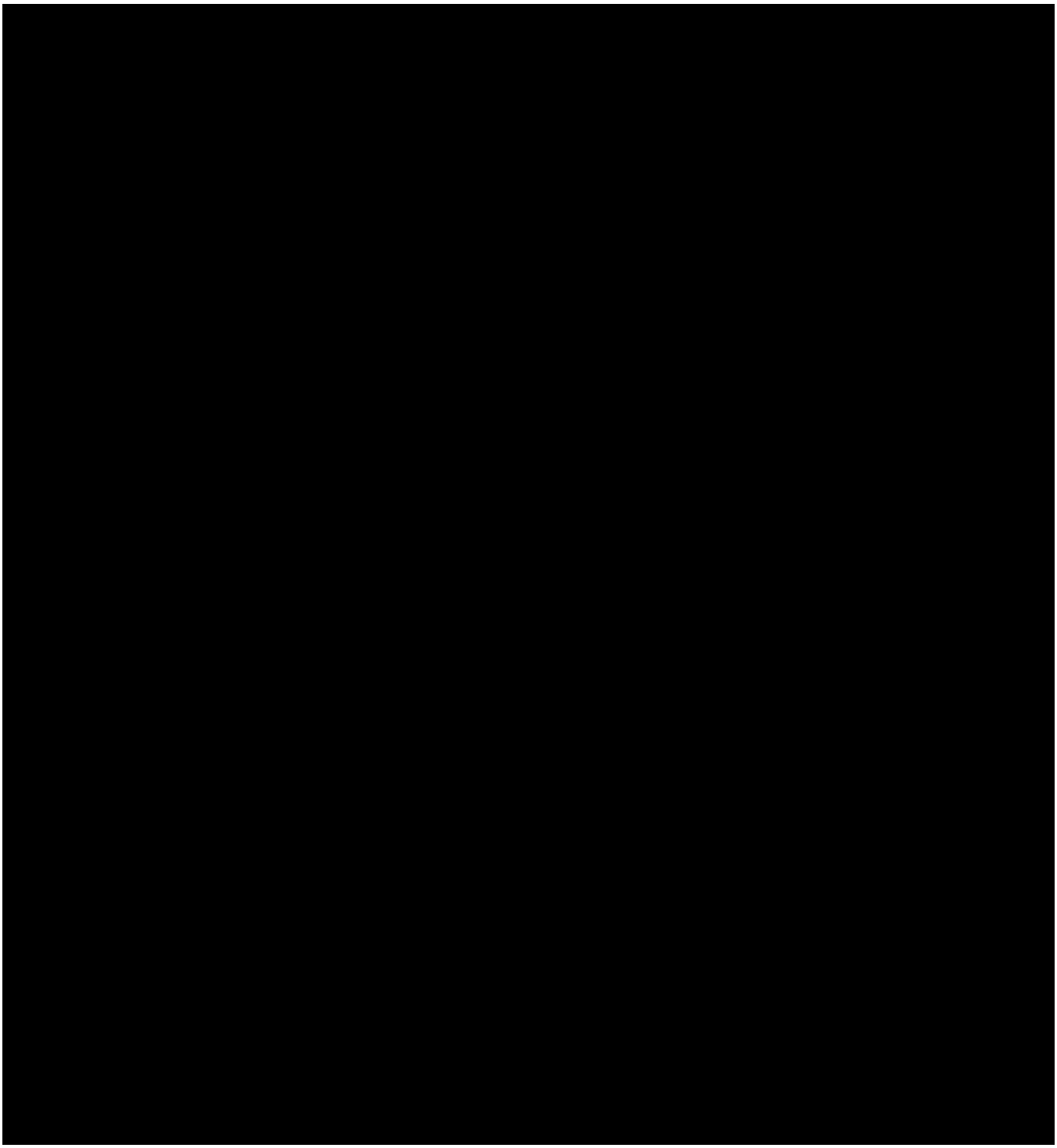
[redacted]

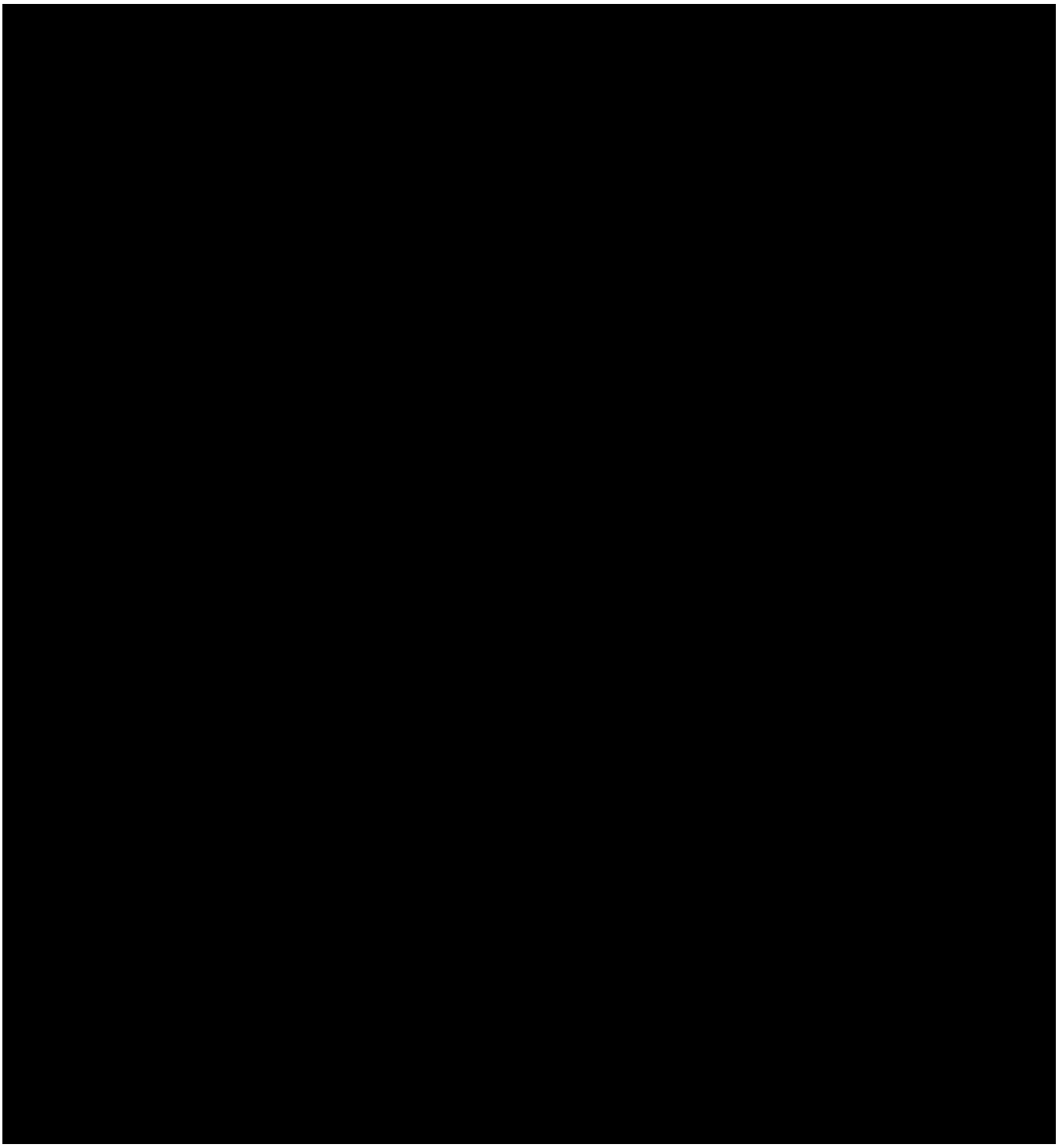
[redacted]

[redacted]









[redacted]

Sample Collection and Storage

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

- [redacted]

[redacted]

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

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

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

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

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

[redacted]

[redacted]

9.10 SARS-CoV-2 Testing

Diagnostic testing for SARS-CoV-2 infection refers to a molecular test (PCR) or 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 report having recent direct contact with someone known to have COVID-19, the subject should undergo diagnostic testing for SARS-CoV-2.

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

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

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

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

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

Approximately 240 subjects will be randomized into 1 of 3 treatment arms on Day 1 in a 3:3:2 ratio, resulting in approximately 90 subjects in each BMS-986165 dose arm and 60 subjects in the placebo arm. Sample size is based on the power to compare the response rates of the BMS-986165 3 mg BID treatment arm with placebo, or the BMS-986165 6 mg BID treatment arm with placebo for each of the co-primary endpoints at Week 12 (Day 85). A Bonferroni adjustment will be used to compare the BMS-986165 3 mg BID and BMS-986165 6 mg BID active treatment groups to placebo. Response rates for clinical remission and endoscopic response are based on published response rates using similar endpoints.[27] [redacted]. With a 2-sided chi-square test at a significance level 0.025 and a sample size of 90 subjects for each BMS-986165 treatment arm and 60 subjects in the placebo arm, [redacted] Additionally, with a 2-sided chi-square test at a significance level of 0.025 and a sample size of 90 subjects for each BMS-986165 treatment arm, and 60 in the placebo arm, [redacted]

[redacted]

10.2 Populations for Analyses

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

FAS = Full Analysis Set; IRT = interactive response technology; [redacted]

10.3 Endpoints

10.3.1 Primary Endpoints

The co-primary efficacy endpoints for BMS-986165 3 mg BID compared to placebo and BMS-986165 6 mg BID compared to placebo are:

- Clinical remission at Week 12 assessed as the proportion of subjects achieving clinical remission at Week 12
- Endoscopic Response at Week 12 assessed as the proportion of subjects achieving an endoscopic response at Week 12

10.3.2 Secondary Endpoints

Secondary efficacy endpoints for BMS-986165 doses compared to placebo are defined below:

- Clinical response at Week 12 assessed as the proportion of subjects achieving clinical response at Week 12
- PRO2 remission at Week 12 assessed as the proportion of subjects achieving PRO2 remission at Week 12
- Change from baseline in SES-CD at Week 12

[redacted]

10.4 Efficacy Analyses

The SAP will be developed and finalized before database lock for the interim analysis, if any, (see Section 10.6.3), and will provide detailed specifications of the analysis of all efficacy endpoints and safety and will also describe the selection of subjects to be included in the analyses and procedures for accounting for missing data. This section provides a summary of planned statistical analyses of the efficacy endpoints.

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. Subjects who continue the randomized double-blind treatment group will be summarized according to their original treatment assignment during the Maintenance Period. Subjects who switch to open-label treatment of the 6 mg BID dose at Week 12 or Week 26 will be summarized separately.

Subjects who were enrolled prior to Protocol v3.0 and were assigned to BMS-986165 12 mg QD will not be included in the primary efficacy analysis. Further details of summarizing data for these subjects will be included in the SAP.

10.4.1 Co-primary Endpoint Analyses

The co-primary endpoints, the proportion of subjects achieving clinical remission at Week 12 and the proportion of subjects achieving endoscopic response at Week 12, will be analyzed separately using stratified Cochran-Mantel-Haenszel (CMH) tests stratified by geographic region (US, Japan, [redacted] Differences in response rates and corresponding 2-sided 95% and 97.5% confidence intervals (CIs) will be provided along with the point estimates and corresponding 95% and 97.5% CIs for each treatment group using a binomial model. The odds ratio (odds in an active treatment group/odds in placebo), and the corresponding 2-sided 95% and 97.5% CIs will be provided as well.

10.4.2 Imputation Methods for Co-primary Endpoints

Non-responder imputation (NRI) will be used for co-primary efficacy endpoints for subjects who discontinue treatment prior to Week 12 and have no Week 12 assessments after treatment discontinuation, [redacted] initiate use or continue to use prohibited medications in the Induction Period, require surgical procedure(s) for treatment of CD or related complications in the Induction Period, or have otherwise missing endpoint data at the Week 12 (Day 85) timepoint, ie, the NRI will be the primary method of imputation for the co-primary efficacy endpoints.

10.4.3 Sensitivity Analyses for the Co-primary Endpoints

The following sensitivity analysis will be performed on the co-primary efficacy endpoints:

[redacted]

Additional sensitivity analyses of the co-primary endpoints may be defined in the SAP.

10.4.4 Secondary Endpoint Analyses

The analysis model for the binary secondary endpoints will use CMH tests [redacted] Differences in response rates and corresponding 2-sided 95% and 97.5% CIs will be provided along with the point estimates and corresponding 95% and 97.5% CIs for each treatment group using a binomial model. The odds ratio (odds in an active treatment group/odds in placebo), and the corresponding 2-sided 95% and 97.5% CIs will be provided as well.

The analysis model for continuous secondary endpoints will use analysis of covariance (ANCOVA) [redacted] baseline value will be added into the model as a covariate. Treatment differences based on least squares means and the corresponding 2-sided 95% and 97.5% CIs will be provided for the difference between each active treatment and placebo.

10.4.5 Imputation Methods for Secondary Endpoints

NRI will be used for subjects who discontinue treatment prior to Week 12 and have no Week 12 assessments after treatment discontinuation, [redacted] initiate use or continue to use prohibited medications in the Induction Period, require surgical procedure(s) for treatment of CD of related complications in the Induction Period, or have otherwise missing endpoint data at the specified timepoint for binary endpoints.

For continuous secondary efficacy endpoints, a multiple imputation (MI) analysis will be used for subjects who discontinue study treatment prior to Week 12 and have no Week 12 assessments after treatment discontinuation, and for subjects who require a protocol-prohibited medication/therapy/surgical procedure that could improve the disease prior to the Week 12 endpoint, or who have otherwise missing endpoint data at the specified time point for continuous endpoints.

10.4.6 Adjustment for Multiplicity of Co-primary and Secondary Endpoints

Alpha will be split in 2 separate testing branches at a 2-sided alpha=0.025 for BMS-986165 3 mg BID compared to placebo and BMS-986165 6 mg BID compared to placebo. The testing order of co-primary and secondary endpoints will be tested in the sequence shown in Table 18.

Table 18: Testing Order of Co-primary and Secondary Endpoints

BMS-986165 3 mg BID Comparisons to Placebo (alpha=0.025)	BMS-986165 6 mg BID Comparisons to Placebo (alpha=0.025)
Co-primary Endpoints	
Clinical remission at Week 12 Endoscopic response at Week 12	Clinical remission at Week 12 Endoscopic response at Week 12
Secondary Endpoints	
1. Clinical response at Week 12	1. Clinical response at Week 12
2. PRO2 remission at Week 12	2. PRO2 remission at Week 12
3. Change from baseline in SES-CD at Week 12	3. Change from baseline in SES-CD at Week 12

There will be no multiplicity adjustment for any other endpoints including exploratory efficacy endpoints; however, nominal p-values will be provided as descriptive statistics.

10.5 Safety Analyses

Safety analyses will be performed using the as-treated population. Subjects will be summarized according to the treatment they are taking at the start of the AE for those subjects who switch to active treatment or a different active dose level during the Maintenance Period. For analysis, all recorded AEs will be listed and tabulated by system organ class, preferred term, and treatment. Vital signs and clinical laboratory test results will be listed and summarized by treatment. ECG readings will be evaluated by the investigator and abnormalities, if present, will be summarized and listed.

10.6 Other Analyses

[redacted]

10.6.3 Week 12 Analysis

When all randomized subjects have completed the Week 12 efficacy assessments or have discontinued prior to Week 12, the database will be locked and the primary analysis will be conducted. Details of this analysis will be described in the SAP. An unblinded BMS team that is independent from the blinded study team will review the results of this primary analysis. 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.

10.6.4 Interim Analysis

In addition to the primary efficacy analysis conducted when 12-week data are available for all randomized subjects, interim analyses may be performed. The purpose of interim analyses 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 0.05 level, a modified Haybittle-Peto method[28] 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 endpoints.

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 results of the interim analyses 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.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
5-ASA	5-aminosalicylate
6-MP	6-mercaptopurine
ACR20	American College of Rheumatology 20
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AEI	adverse event of interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
Anti-HBc	hepatitis B core antibody
Anti-HCV	hepatitis C virus antibody
AP	abdominal pain
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(0-24h)	area under the concentration-time curve from 0 to 24 hours
AUC(0-INF)	area under the concentration-time curve extrapolated to infinity
AZA	azathioprine
BCRP	breast cancer resistance protein
BID	twice daily
BMS	Bristol-Myers Squibb
BSS	Bristol Stool Scale
Cavg	average concentration
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
C. difficile	*Clostridium difficile*
CFR	Code of Federal Regulations
[redacted]	[redacted]
CI	confidence interval
CK	creatine kinase
Cmax	maximum plasma concentration

Term	Definition
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease 2019
Ctrough	trough observed plasma concentration
CYP450	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
Emax	direct effect
ET	Early Termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle-stimulating hormone
GDH	glutamate dehydrogenase
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
Hct	hematocrit
HCV	hepatitis C virus
HCV RNA	hepatitis C virus ribonucleic acid
HIV	human immunodeficiency virus
[redacted]	[redacted]
IB	Investigator Brochure
IBD	inflammatory bowel disease
[redacted]	[redacted]
IC50	half-maximal inhibitory concentration
ICF	informed consent form

Term	Definition
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
IFNα	interferon alpha
IFN-γ	interferon gamma
Ig	immunoglobulin
IgA	immunoglobulin A
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
[redacted]	[redacted]
IGRA	interferon gamma release assay
IHC	immunohistochemistry
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
LOCF	last observation carried forward
LOR	loss of response
LTBI	latent tuberculosis infection
LTE	long-term extension
MTX	methotrexate
[redacted]	[redacted]
NOAEL	no-observed-adverse-effect-level
NRI	non-responder imputation

Term	Definition
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
OL	open-label
OLE	Open-Label Extension
OTC	over-the-counter
PASI	Psoriasis Area and Severity Index
PASI 75	≥ 75% reduction in the Psoriasis Area and Severity Index
PASI 90	≥ 90% reduction in the Psoriasis Area and Severity Index
PCR	polymerase chain reaction
PD	pharmacodynamic
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PK	pharmacokinetics
PO	by mouth
PRA	Pharmaceutical Research Associates
PRO	patient (or subject) reported outcome
PRO2 or CDAI/PRO2	patient (or subject) reported outcome based on the stool frequency and abdominal pain components of the CDAI
[redacted]	[redacted]
QD	once daily
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
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF	stool frequency
[redacted]	[redacted]

Term	Definition
SLE	systemic lupus erythematosus
sPGA	static Physician's Global Assessment
STAT	signal transducer and activator of transcription
TB	tuberculosis
TBNK	T cells, B cells, and natural killer cells
TDAR	T-cell-dependent antibody response
TDM	therapeutic drug monitoring
Tmax	time of maximum concentration
TNF	tumor necrosis factor
TNFi	tumor necrosis factor inhibitor
TYK2	tyrosine kinase 2
ULN	upper limit of normal
[redacted]	[redacted]
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with:

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

The study will be conducted in compliance with the protocol. The protocol, any revisions/amendments, and the subject informed consent form (ICF) 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 subjects; (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
- 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 Bristol-Myers Squibb (BMS).

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the ICF must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from 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 sample ICF, which will include all elements required by ICH GCP and applicable regulatory requirements. The sample ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

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 subject 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 subject is proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Explain the nature of the study to the subject and answer all questions regarding the study.
- Inform subject that his/her participation is voluntary. Subject will be required to sign a statement of informed consent that meets the requirements of 21CFR50, 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 subject to inquire about the details of the study.
- Obtain an ICF signed and personally dated by subject and by the person who conducted the informed consent discussion.
- Include a statement in subject's medical record that written informed consent was obtained before subject 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 subject 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 subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the case report form (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 (AE) tracking/reporting, protocol-required assessments, and/or drug accountability records).

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

STUDY TREATMENT RECORDS

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

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

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

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

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

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

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

RECORDS RETENTION

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

investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

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

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

RETURN OF STUDY TREATMENT

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

If …	Then
Study treatments supplied by BMS (including its vendors)	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the site's 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 (eg, incinerator, licensed sanitary landfill, or licensed waste disposal vendor) must be documented.

- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

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

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

STUDY AND SITE START AND CLOSURE

The Sponsor/designee reserves the right to close the study site or to terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local regulatory authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

DISSEMINATION OF CLINICAL STUDY DATA

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

In the European Union (EU), the summary of results and summary for laypersons will be submitted within 1 year of the end of trial in EU/European Economic Area and third countries.

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, subinvestigator, or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant

contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable subjects with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who make the most significant contributions, as defined above, will be considered by BMS for authorship of the primary publication. 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 subject administered study treatment 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 treatment, whether or not considered related to the study treatment.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis. • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify ”intentional overdose” as the verbatim term.
Events <u>NOT</u> 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 subject 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 subject 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. A potential drug-induced liver injury (DILI) is also considered an important medical event. (See Section 9.3.8 for the definition of potential DILI.)

Pregnancy and potential DILI must follow the same transmission timing and processes to BMS as used for SAEs. (See Section 9.3.6 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 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 subject, causing minimal discomfort, and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used 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 to PRA Drug Safety within 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]-434-951-3482)

Europe/East Asia Pacific: [redacted]

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

Americas: [redacted]

Europe/East Asia Pacific: [redacted]

[redacted]

[redacted]

APPENDIX 5 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

Appendix 5 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 subjects, refer to Section 6.1 of the protocol. Only the contraception methods as described in Section 6.1 are acceptable for this study.

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

Note: Documentation can come from the site personnel's review of the 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 in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. Suggested guidelines for the duration of the washout periods for HRT types are presented below. Investigators should use their judgement in checking serum FSH levels.

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

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

End of Relevant Systemic Exposure

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

CONTRACEPTION GUIDANCE FOR FEMALE SUBJECTS OF CHILDBEARING POTENTIAL

At least an acceptable, less than highly effective means of contraception should be continued until the end of 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 subjects 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 subjects 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 • Intrauterine device (IUD)[b] • 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 drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.

- Continuous abstinence must begin at least 30 days prior to initiation of study therapy.
- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP subjects who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2 of the protocol.
- 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] Intrauterine devices and intrauterine hormone-releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

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 subjects 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

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.3.6 and APPENDIX 3, Adverse Events and Serious Adverse Events Definitions and Procedures for Evaluating, Follow-up, and Reporting.

APPENDIX 7 EXAMPLES OF WASHOUT TIMES REQUIRED PRIOR TO RANDOMIZATION

Medications/treatments	Discontinuation Prior to Randomization
5-azathioprine	≥ 4 weeks
6-mercaptopurine	≥ 4 weeks
Abatacept (CTLA4Ig)	≥ 12 weeks
Adalimumaba	≥ 8 weeks Washout period waived if undetectable levels on TDM assay
Alemtuzumab	≥ 12 months
Apheresis: lymphocyte apheresis or selective monocyte or granulocyte apheresis (eg, Cellsorba™)	≥ 12 months
Atacicept (TACI-Ig)	≥ 48 weeks
Belimumab	≥ 14 weeks
Certolizumab pegola	≥ 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
Epratuzumabb	≥ 18 weeks
Infliximaba	≥ 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
Investigational therapies	≥ 4 weeks
Janus kinase inhibitors	≥ 8 weeks
Leflunomide	≥ 12 weeks (or more than 5 half-lives, whichever is longer)
Lenalidomide with cholestyramine	≥ 24 weeks
Methotrexate	≥ 4 weeks
Mycophenolate mofetil	≥ 4 weeks
Natalizumab	≥ 8 weeks
Ocrelizumaba	≥ 24 weeks
Pimecrolimus	≥ 4 weeks
Plasmapheresis	24 weeks

Medications/treatments	Discontinuation Prior to Randomization
Retinoids	≥ 4 weeks
Rituximab	≥ 12 months
Sirolimus	≥ 4 weeks
Tabalumab	≥ 14 weeks
Tacrolimus	≥ 4 weeks
Thalidomide	≥ 4 weeks
Other TNF inhibitors	≥ 8 weeks Washout period waived if undetectable levels on TDM assay
Tocilizumab	≥ 12 weeks
Ustekinumaba	≥ 8 weeks For subjects who have received > 12 weeks of ustekinumab treatment: washout period waived if undetectable levels on a TDM assay
Vedolizumaba	Subjects who have completed > 14 weeks vedolizumab treatment: ≥ 4 weeks, or washout period waived if undetectable levels on a TDM assay Subjects who have received ≤ 14 weeks of vedolizumab treatment: ≥ 8 weeks.

[a] The washout period for the following biologics 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: (i) infliximab, (ii) adalimumab, (iii) certolizumab pegol, or (iv) vedolizumab (if received at least 14 weeks of vedolizumab therapy), (v) ustekinumab (if received > 12 weeks of therapy). Subjects who have received < 14 weeks of vedolizumab therapy, or < 12 weeks of ustekinumab therapy must complete the washout period for those medication. If a TDM assay is used to waive the washout period for one of the 5 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 after the TDM assay is obtained.

[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.

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

APPENDIX 8 SUBJECT DIARY

For each study day, subjects will also record the date and time of study treatment administration, and the number of capsules taken. A paper copy of the Bristol Stool Scale [redacted] will be provided to subjects to help with the daily documentation of the number of very soft (loose) or liquid (watery) stools (BSS Type 6 or 7). Only Type 6 and Type 7 stools are to be recorded and considered for the calculation of the stool frequency for measures of disease activity and clinical status, eg, remission. The frequency of Type 1 through Type 5 stools are not to be recorded.

Day/Date	How many liquid or very soft stools?	How would you rate your abdominal pain?	How would you rate your general well-being?	Did you use diphenoxylate or loperamide for diarrhea? (Also mark "Yes" if any narcotics were used.)
Sunday __ / __ /__ mm dd yy		None……..0 Mild……...1 Moderate...2 Severe……3	Generally well…….0 Slightly under par…1 Poor…….2 Very Poor……3 Terrible……...4	Yes No
Monday __ / __ /__ mm dd yy		None……..0 Mild……...1 Moderate...2 Severe……3	Generally well…….0 Slightly under par…1 Poor…….2 Very Poor……3 Terrible……...4	Yes No
Tuesday __ / __ /__ mm dd yy		None……..0 Mild……...1 Moderate...2 Severe……3	Generally well…….0 Slightly under par…1 Poor…….2 Very Poor……3 Terrible……...4	Yes No
Wednesday __ / __ /__ mm dd yy		None……..0 Mild……...1 Moderate...2 Severe……3	Generally well…….0 Slightly under par…1 Poor…….2 Very Poor……3 Terrible……...4	Yes No
Thursday __ / __ /__ mm dd yy		None……..0 Mild……...1 Moderate...2 Severe……3	Generally well…….0 Slightly under par…1 Poor…….2 Very Poor……3 Terrible……...4	Yes No
Friday __ / __ /__ mm dd yy		None……..0 Mild……...1 Moderate...2 Severe……3	Generally well…….0 Slightly under par…1 Poor…….2 Very Poor……3	Yes No

Day/Date	How many liquid or very soft stools?	How would you rate your abdominal pain?	How would you rate your general well-being?	Did you use diphenoxylate or loperamide for diarrhea? (Also mark "Yes" if any narcotics were used.)
			Terrible……...4	
Saturday __ / __ /__ mm dd yy		None……..0 Mild……...1 Moderate...2 Severe……3	Generally well…….0 Slightly under par…1 Poor…….2 Very Poor……3 Terrible……...4	Yes No

APPENDIX 9 INTERPRETATION OF HBV AND HCV TEST RESULTS

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 6.2).

Hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), and hepatitis B surface antibody (HBsAb) are evaluated at screening, with reflex to HBV DNA testing in subjects with HBsAg negative, anti-HBc 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
- anti-HBc negative
- HBsAb negative

Immune due to natural infection - does not meet exclusion criteria on HBV
- HBsAg negative
- anti-HBc positive
- HBsAb positive

Immune due to hepatitis B vaccination - does not meet exclusion criteria on HBV
- HBsAg negative
- anti-HBc negative
- HBsAb positive

Acutely infected – meets exclusion criteria on HBV
- HBsAg positive
- anti-HBc positive
- IgM anti-HBc positive
- HBsAb negative

Chronically infected - meets exclusion criteria on HBV
- HBsAg positive
- anti-HBc positive
- IgM anti-HBc negative
- HBsAb negative

Interpretation unclear
- HBsAg negative
- anti-HBc positive
- HBsAb negative

HBV DNA testing will be performed in subjects with a negative HBsAg, but a positive anti-HBc antibody 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, anti-HBc 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 2).

- 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 LOR arm will have additional HBV DNA testing at the first 3 study visits after entry to the LOR 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, 22 and 26, 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 10 CROHN'S DISEASE ACTIVITY INDEX VARIABLES

The CDAI score consists of eight variables including 4 subject-reported outcomes. Variables 1, 2, 3, and 5 will be obtained from the subject diary, as outlined in Section 9.1. The Standard Height and Weight Table (below) must be used to calculate variable 8. The score from each variable is weighted by applying the multiplier shown. The total CDAI score is then determined by calculating the sum of the individual, weighted scores.

CDAI Score		
VARIABLE #	VARIABLE DESCRIPTION	MULTIPLIER
1	Number of liquid or soft stools (each day for 7 days)	x2
2	Abdominal pain (0=none, 1=mild, 2=moderate, 3=severe)	x5
3	General well-being (0=generally well,1=slightly under par, 2=poor, 3=very poor, 4=terrible)	x7
4	Number of listed complications (arthritis or arthralgia, iritis or uveitis, erythema nodosum or pyoderma gangrenosum or aphthous stomatitis, anal fissure or fistula or abscess, other fistula, fever over 37.8°C [100°F])	x20
5	Use of diphenoxylate or loperamide for diarrhea (0=no, 1=yes)	x30
6	Abdominal mass (0=no, 2=questionable, 5=definite)	x10
7	Hematocrit (males, 47-Hct [%], females, 42-Hct [%])	x6
8	Body weight (1 - weight/standard weight) x 100 (add or subtract according to sign)	x1
TOTAL CDAI SCORE		SUM OF ABOVE

CDAI = Crohn's Disease Activity Index; Hct = hematocrit

Sources: Best et al, Gastroenterology 1976;70:439-444; Best et al, Gastroenterology 1979;77: 843-846; Sandborn et al, Gastroenterology 2002;122:512-530.

STANDARD HEIGHT AND WEIGHT TABLES (Use to calculate CDAI Score)

Actual Height cm (Inches)	Standard Weight - Men kg (Pounds)	Standard Weight – Women kg (Pounds)
147.3 (58.0)		52.2 (115.0)
148.6 (58.5)		52.6 (116.0)
149.9 (59.0)		53.1 (117.0)
151.1 (59.5)		53.6 (118.3)
152.4 (60.0)		54.2 (119.5)
153.7 (60.5)		54.8 (120.8)
154.9 (61.0)		55.3 (122.0)
156.2 (61.5)		56.0 (123.5)
157.5 (62.0)	61.7 (136.0)	56.7 (125.0)
158.8 (62.5)	62.1 (137.0)	57.4 (126.5)
160.0 (63.0)	62.6 (138.0)	58.0 (128.0)
161.3 (63.5)	63.0 (139.0)	58.7 (129.5)
162.6 (64.0)	63.5 (140.0)	59.4 (131.0)
163.8 (64.5)	64.1 (141.3)	60.1 (132.5)
165.1 (65.0)	64.6 (142.5)	60.8 (134.0)
166.4 (65.5)	65.2 (143.8)	61.4 (135.5)
167.6 (66.0)	65.8 (145.0)	62.1 (137.0)
168.9 (66.5)	66.4 (146.5)	62.8 (138.5)
170.2 (67.0)	67.1 (148.0)	63.5 (140.0)
171.5 (67.5)	67.8 (149.5)	64.2 (141.5)
172.7 (68.0)	68.5 (151.0)	64.9 (143.0)
174.0 (68.5)	69.2 (152.5)	65.5 (144.5)
175.3 (69.0)	69.8 (154.0)	66.2 (146.0)
176.5 (69.5)	70.5 (155.5)	66.9 (147.5)
177.8 (70.0)	71.2 (157.0)	67.6 (149.0)
179.1 (70.5)	71.9 (158.5)	68.3 (150.5)
180.3 (71.0)	72.6 (160.0)	68.9 (152.0)
181.6 (71.5)	73.4 (161.8)	69.6 (153.5)
182.9 (72.0)	74.1 (163.5)	70.3 (155.0)
184.2 (72.5)	75.0 (165.3)	
185.4 (73.0)	75.7 (167.0)	
186.7 (73.5)	76.6 (169.0)	

Actual Height cm (Inches)	Standard Weight - Men kg (Pounds)	Standard Weight – Women kg (Pounds)
188.0 (74.0)	77.5 (171.0)	
189.2 (74.5)	78.4 (172.8)	
190.5 (75.0)	79.1 (174.5)	
191.8 (75.5)	80.2 (176.8)	
193.0 (76.0)	81.2 (179.0)	

*Height in shoes with one-inch heels

*Indoor clothing weighing 5 pounds for men and 3 pounds for women

*Centimeters x 0.3937 = inches/ *Pounds x 0.4535 = kilograms

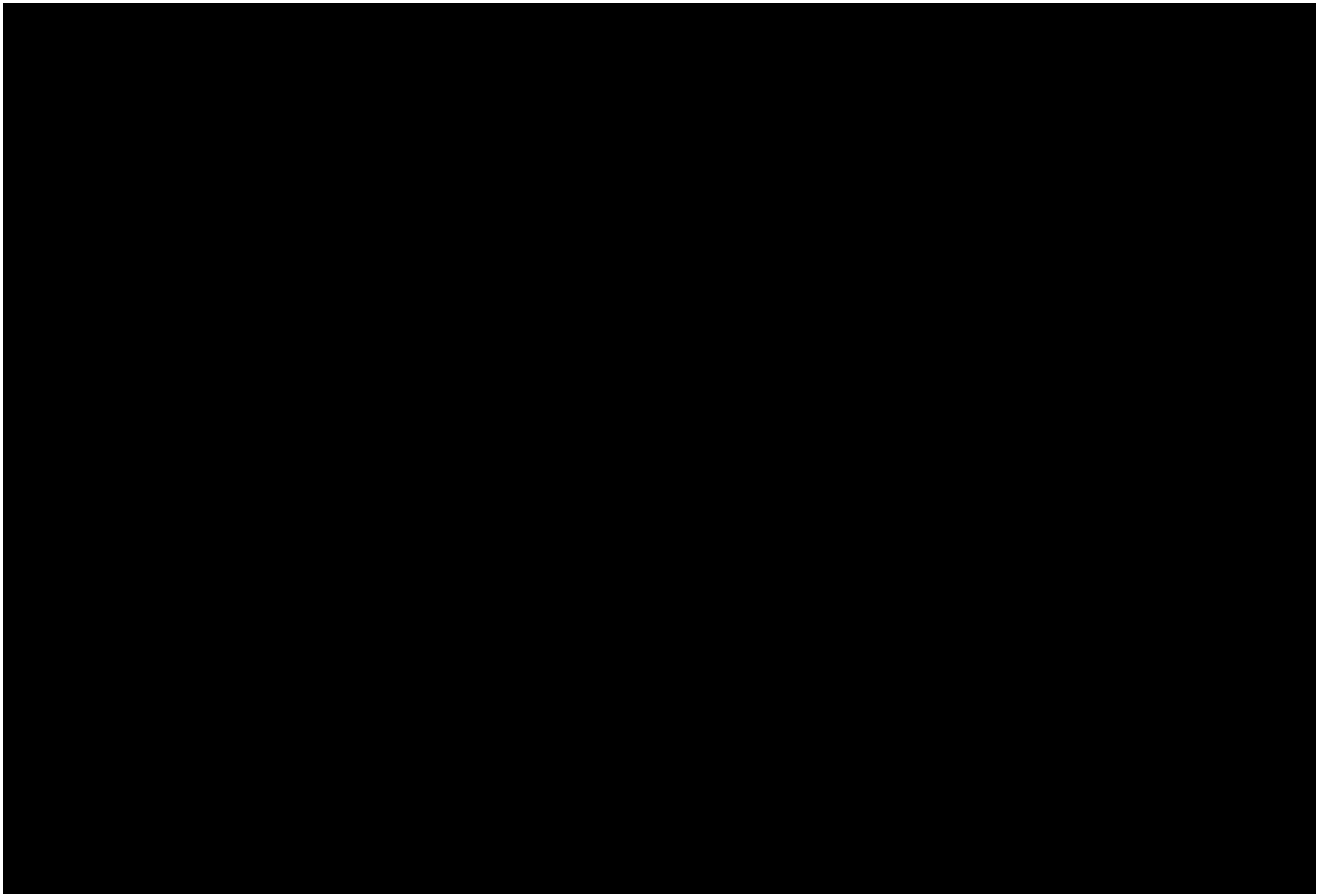
APPENDIX 12 DEFINITIONS OF SIMPLE ENDOSCOPIC SCORE FOR CROHN'S DISEASE

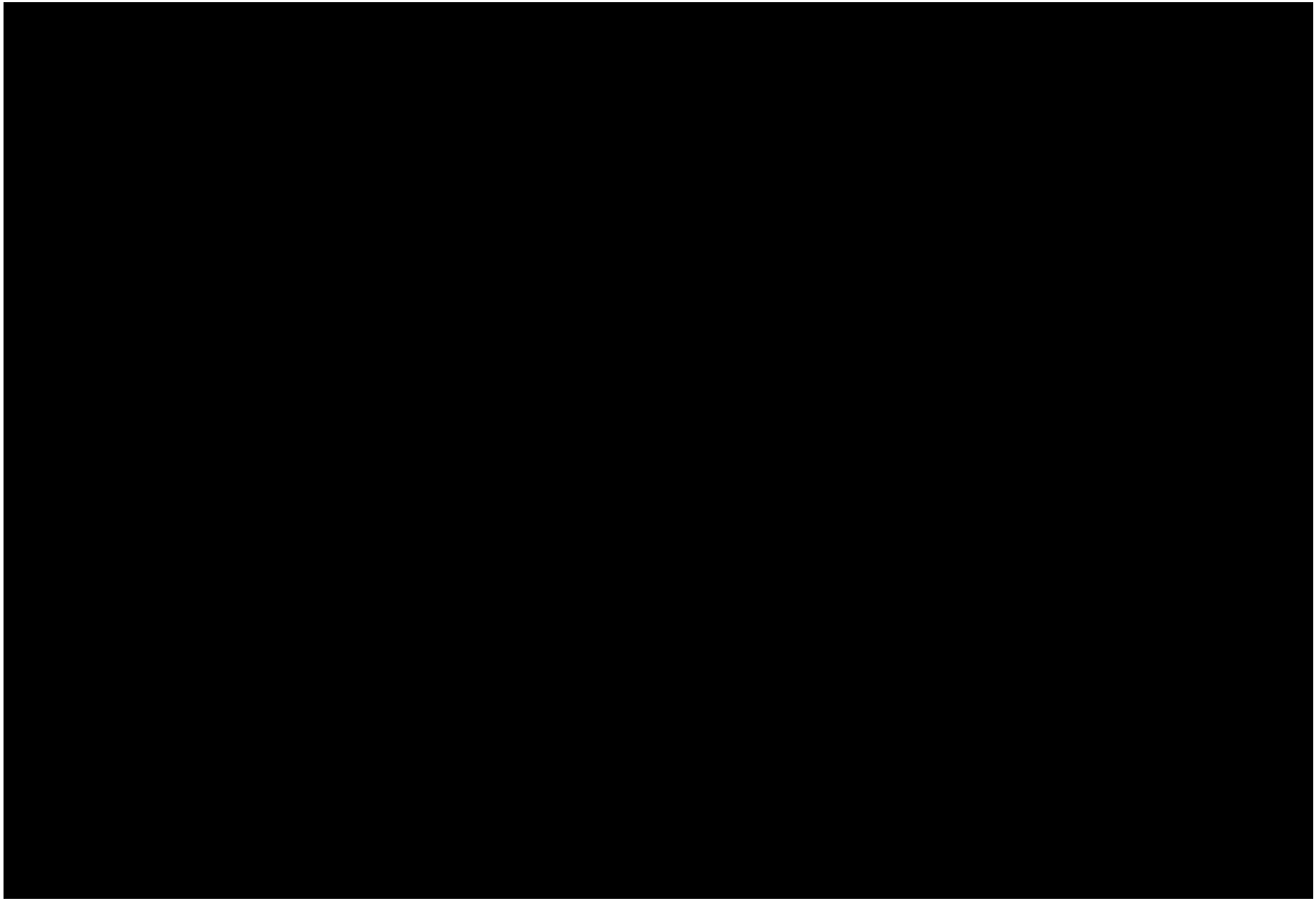
Definitions of Simple Endoscopic Score for Crohn's Disease				
	Simple Endoscopic Score for Crohn's Disease values			
Variable	0	1	2	3
Size of Ulcers	None	Aphthous ulcers	Large ulcers	Very large ulcers
		(Ø 0.1 to 0.5 cm)	(Ø 0.5 to 2 cm)	(Ø>2 cm)
Ulcerated Surface	None	<10%	10-30%	>30%
Affected surface	Unaffected segment	<50%	50-75%	>75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

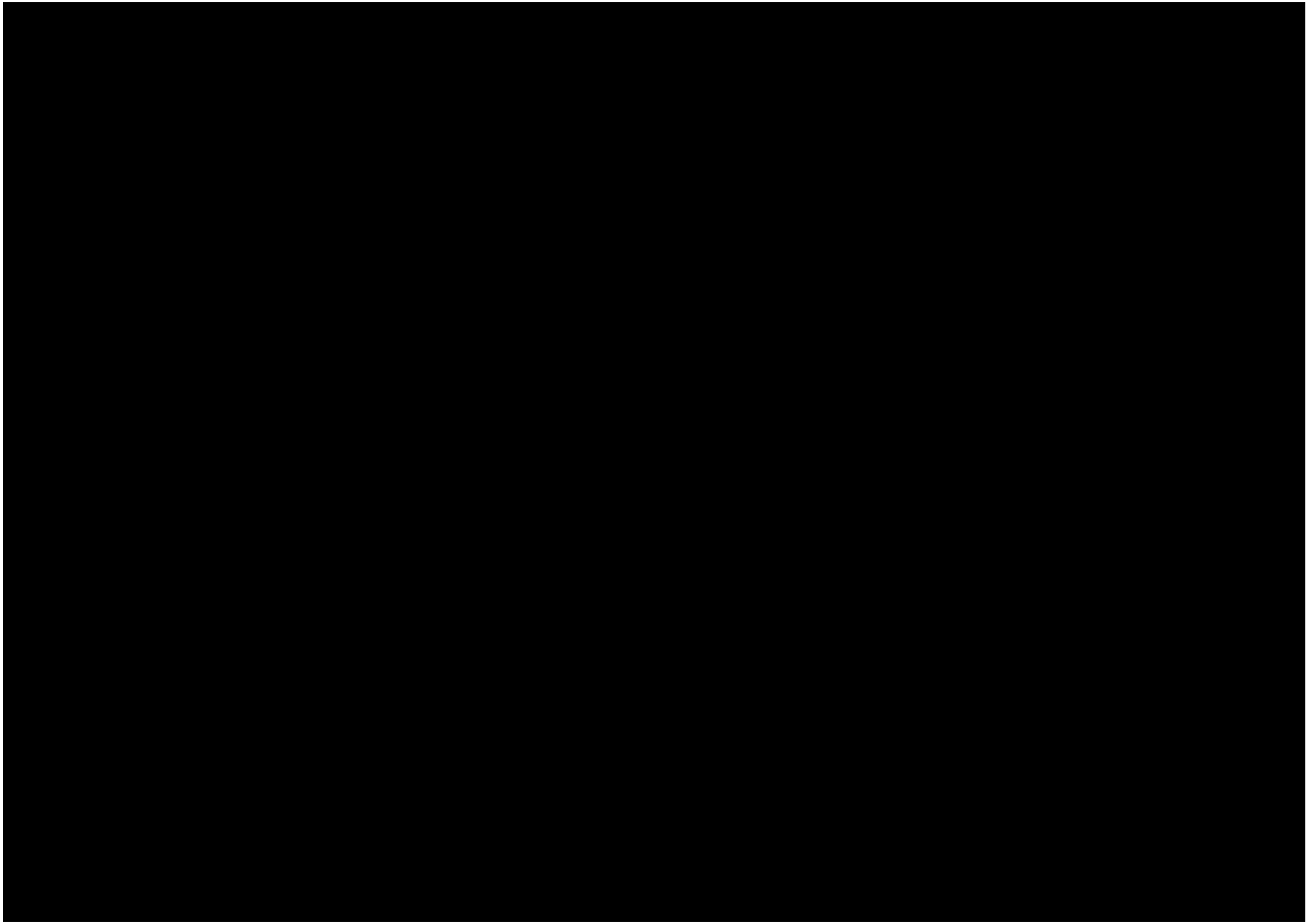
Ø = diameter

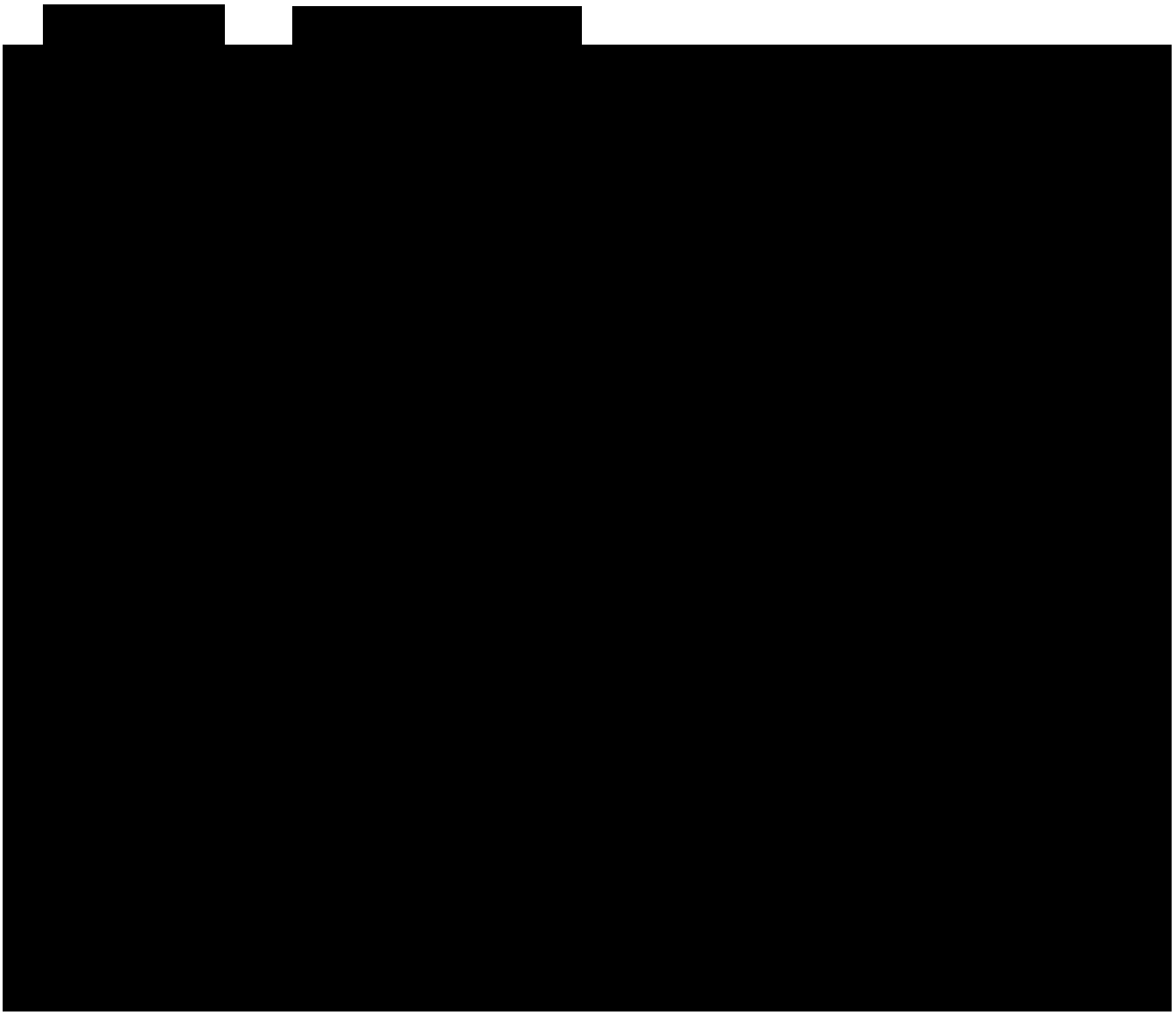
Reference: Daperno M, D'Haens G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc 2004;60:505-12.

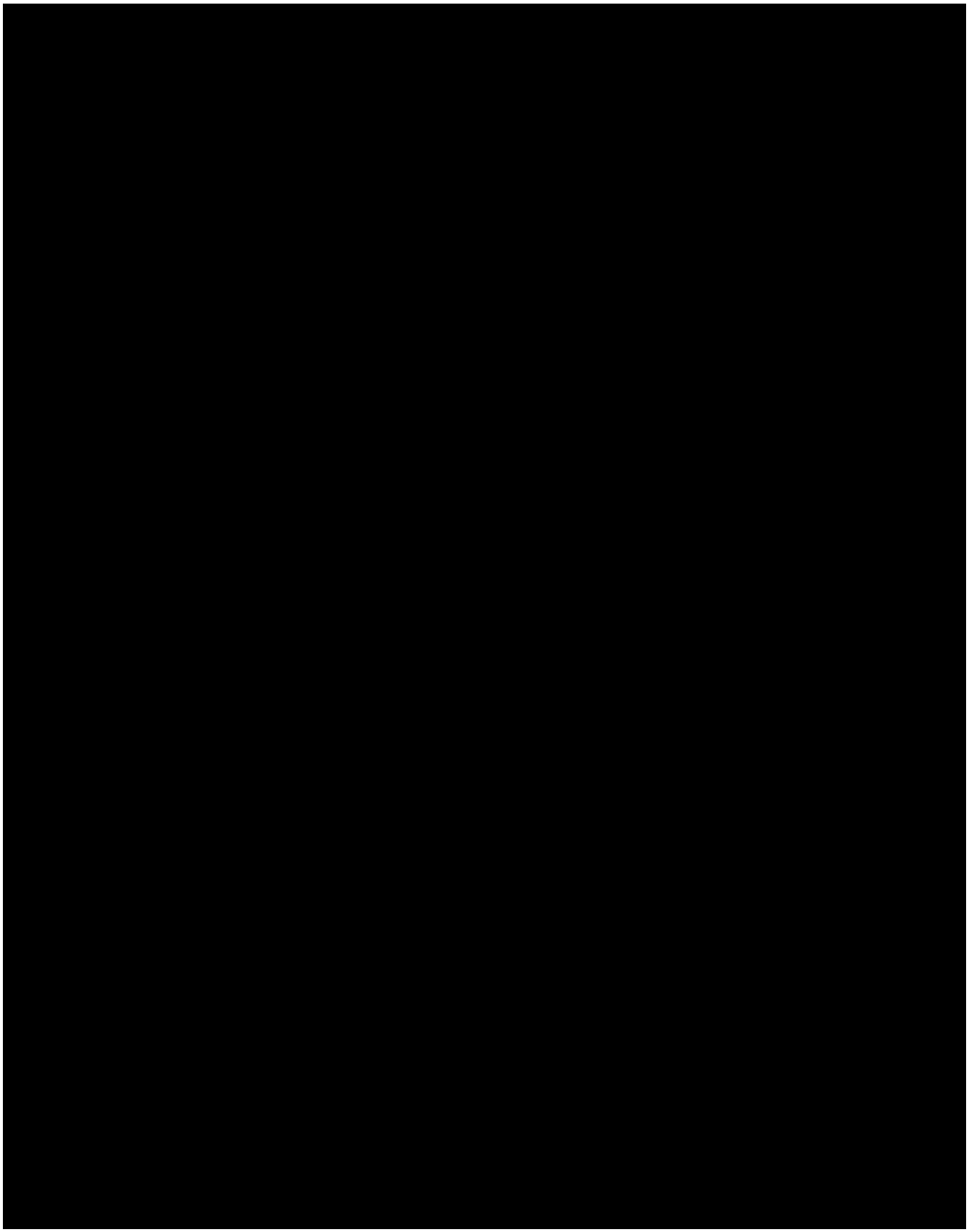
[redacted]

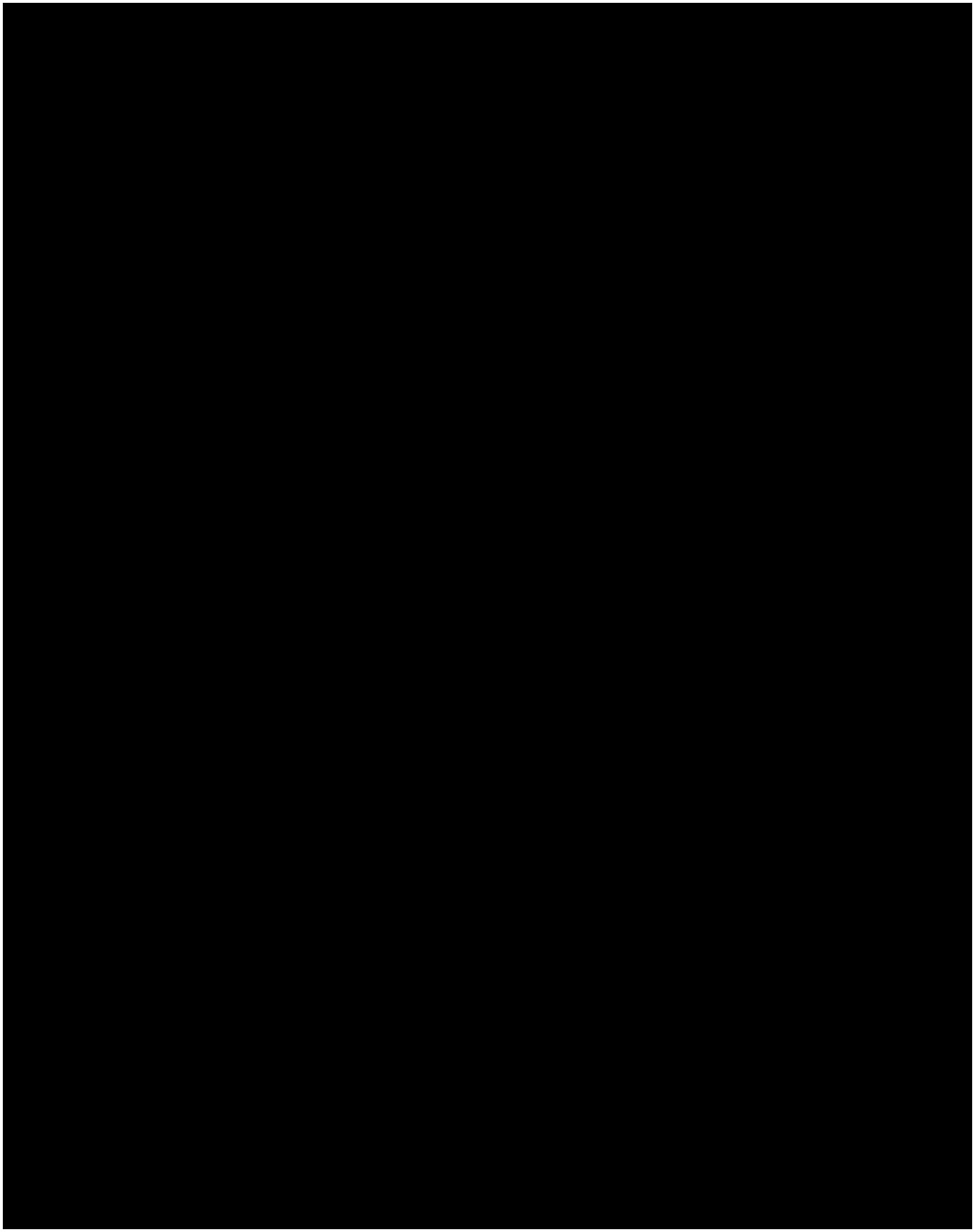












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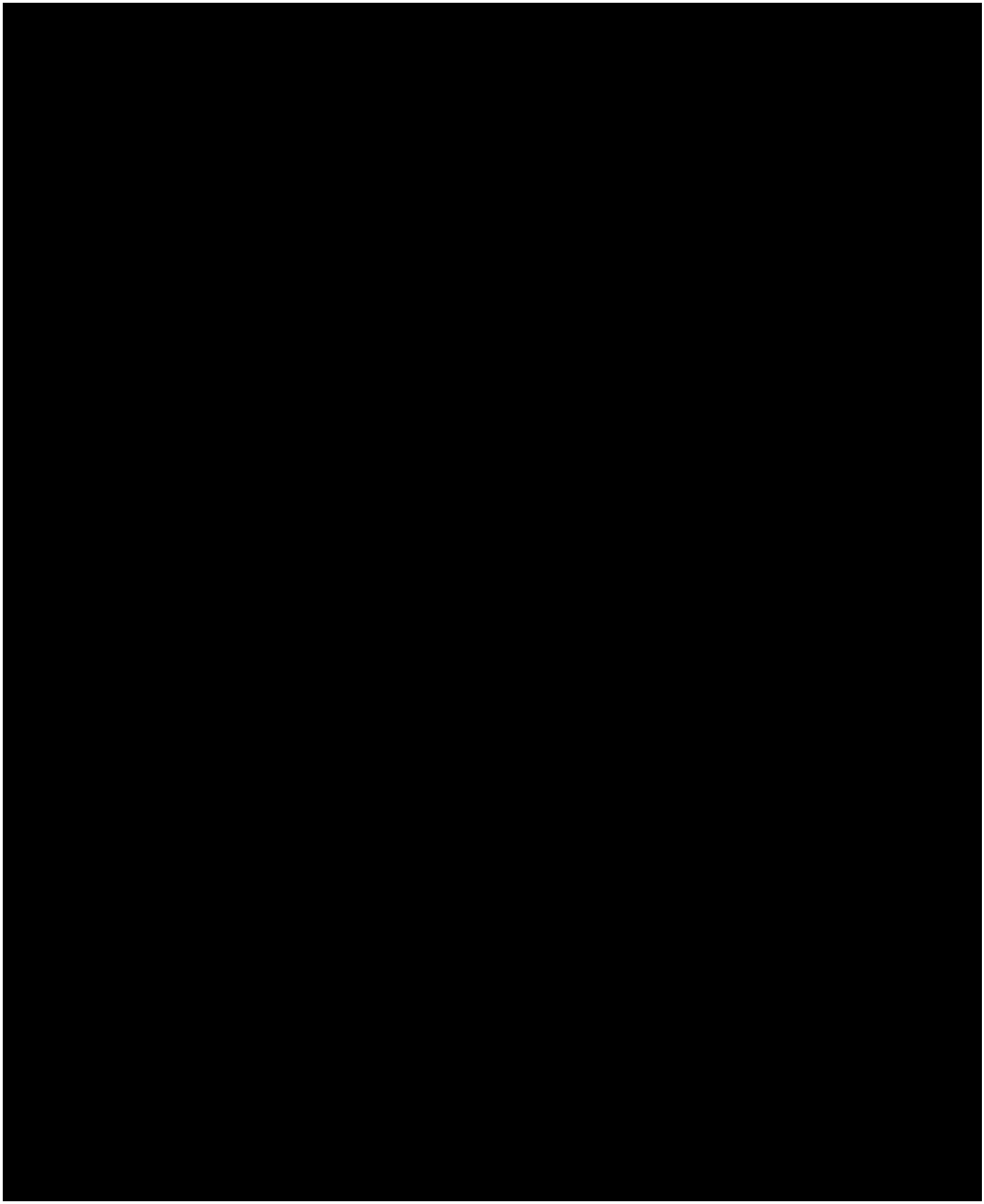

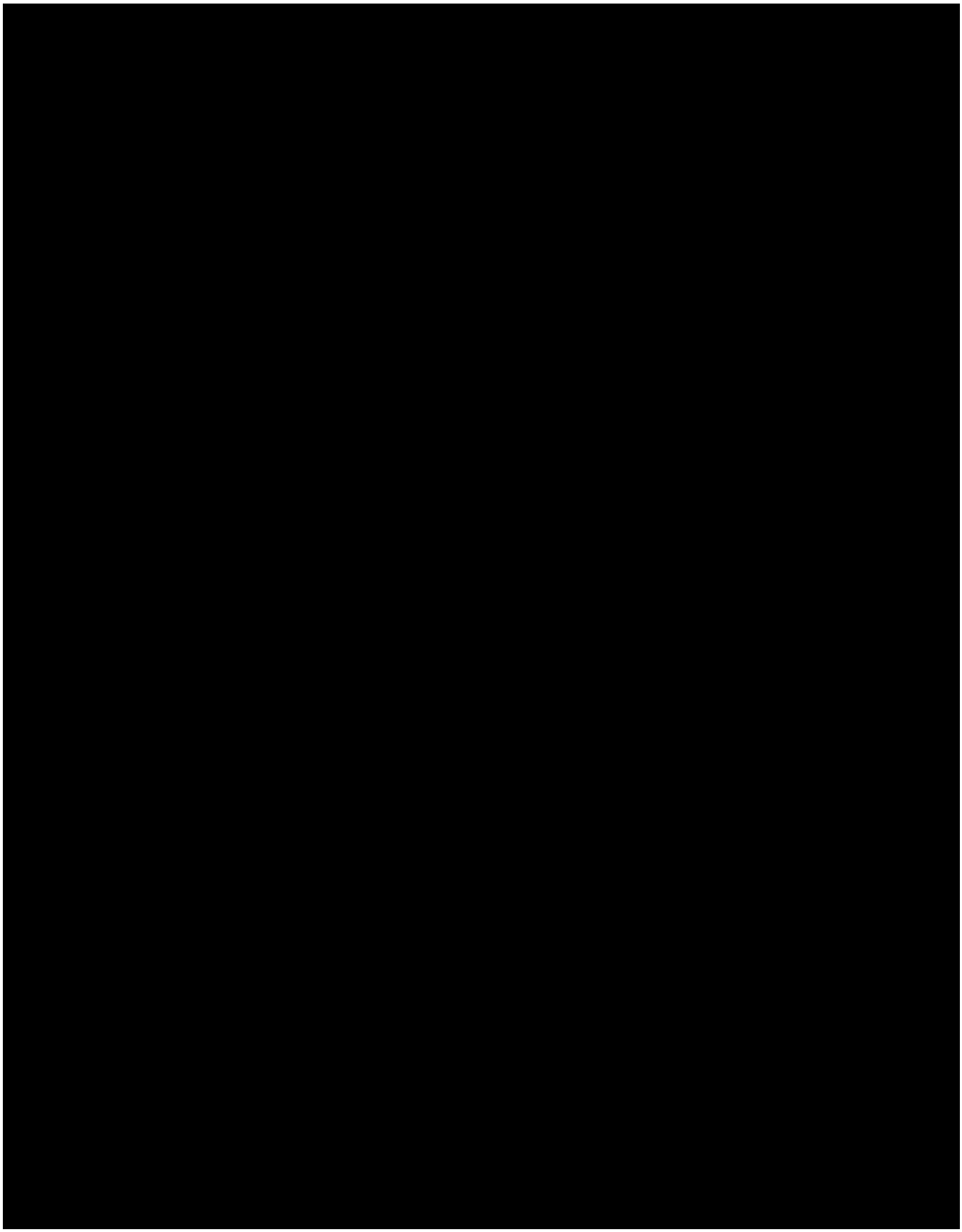

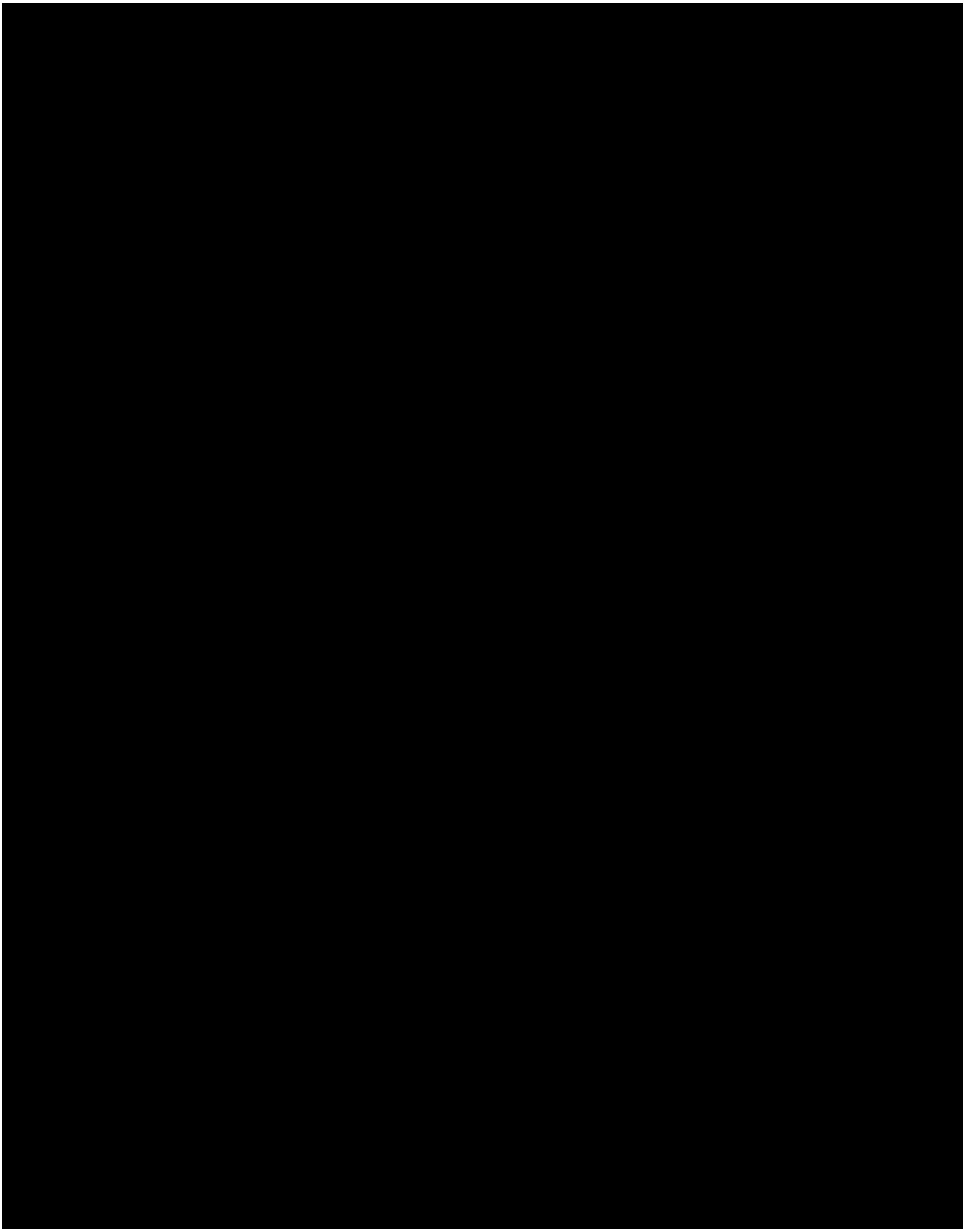

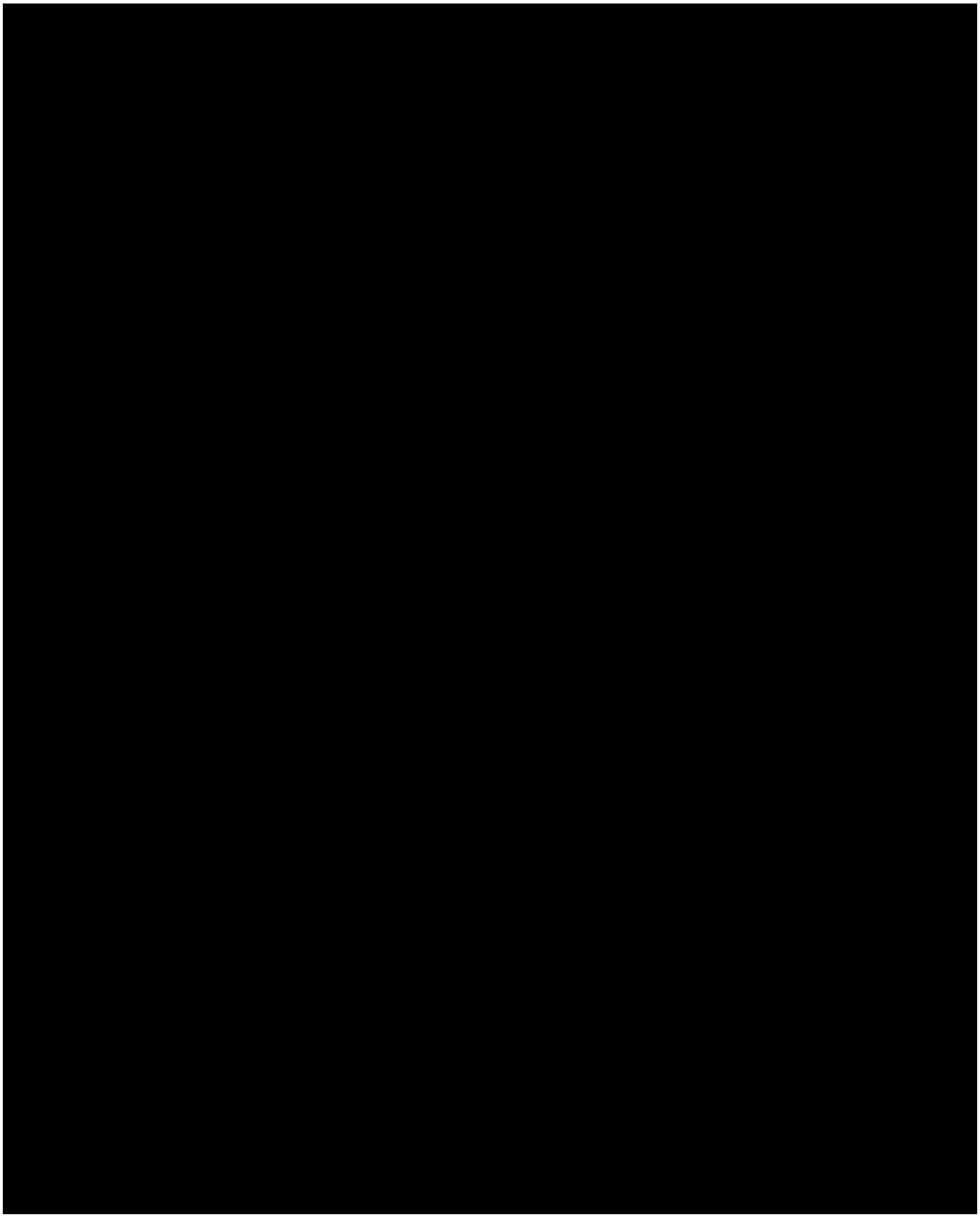

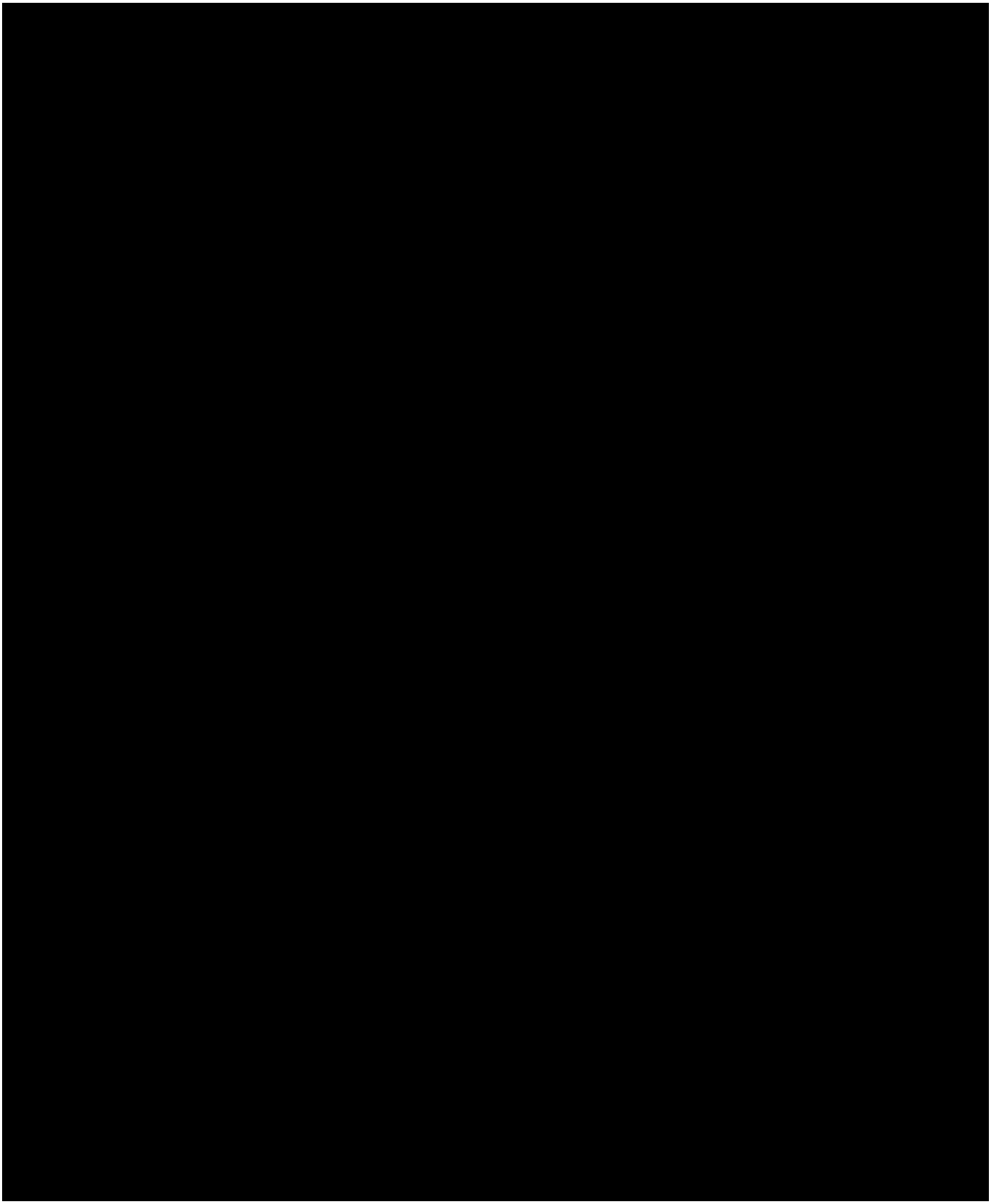

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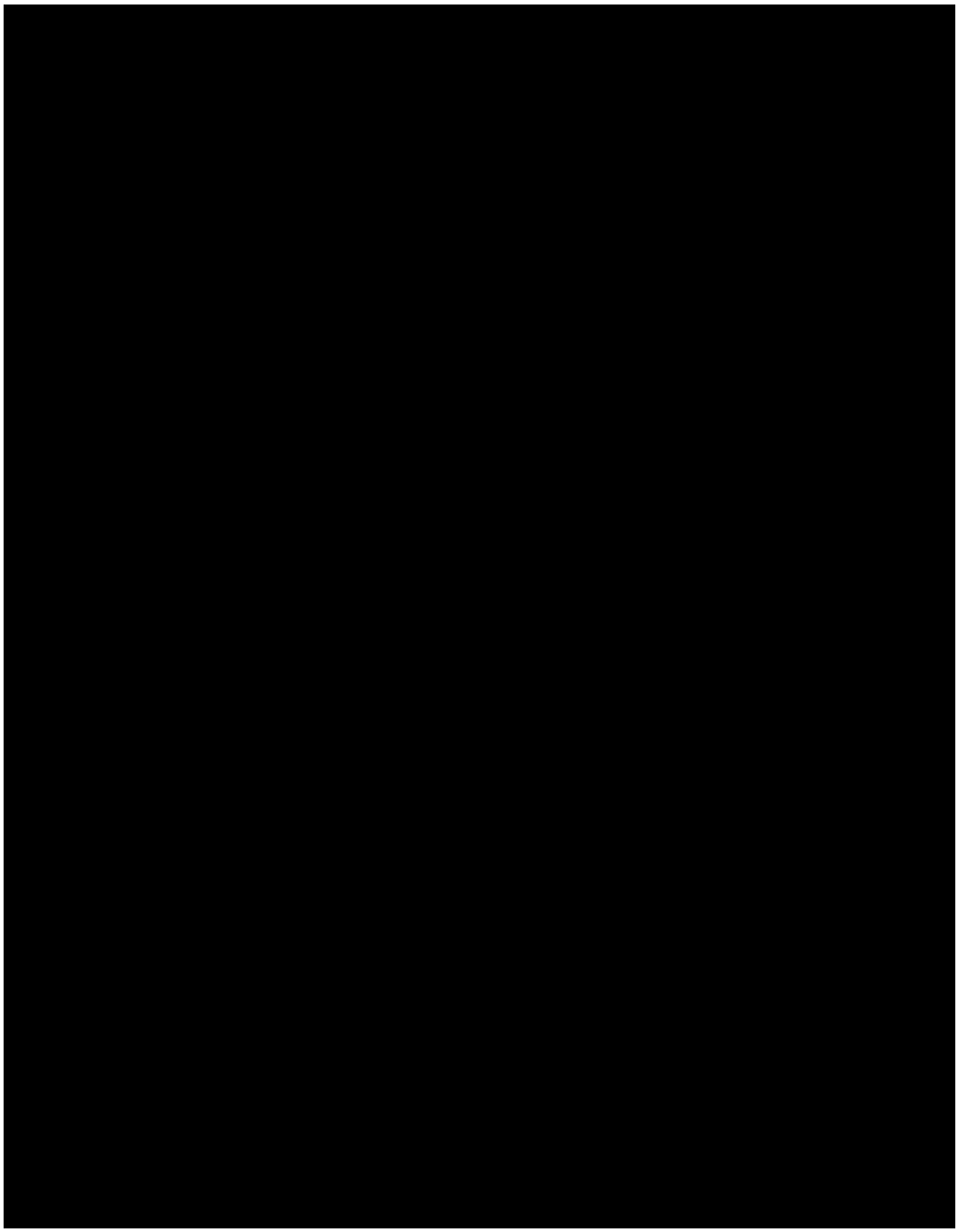

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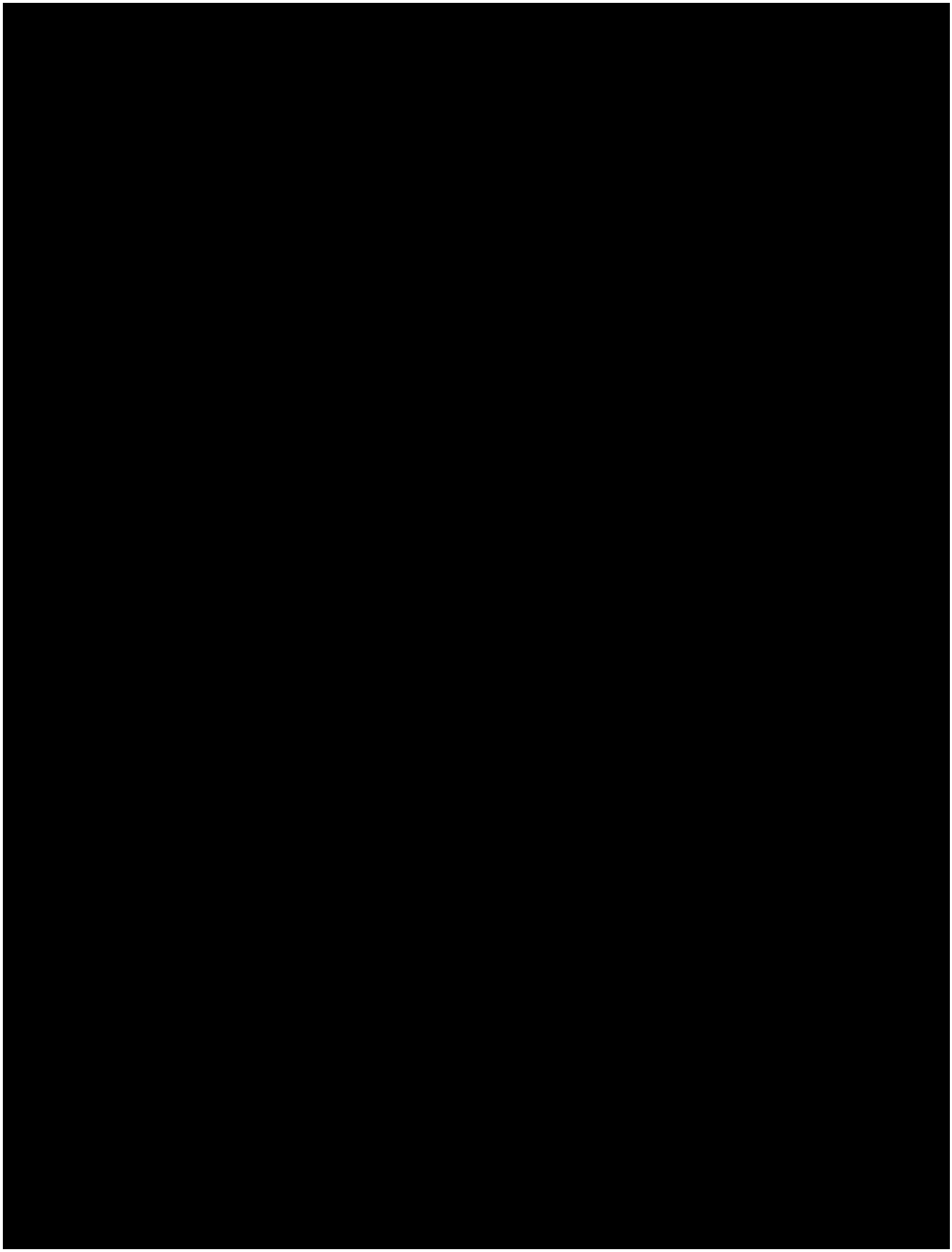

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APPENDIX 19 COVID-19 VACCINES

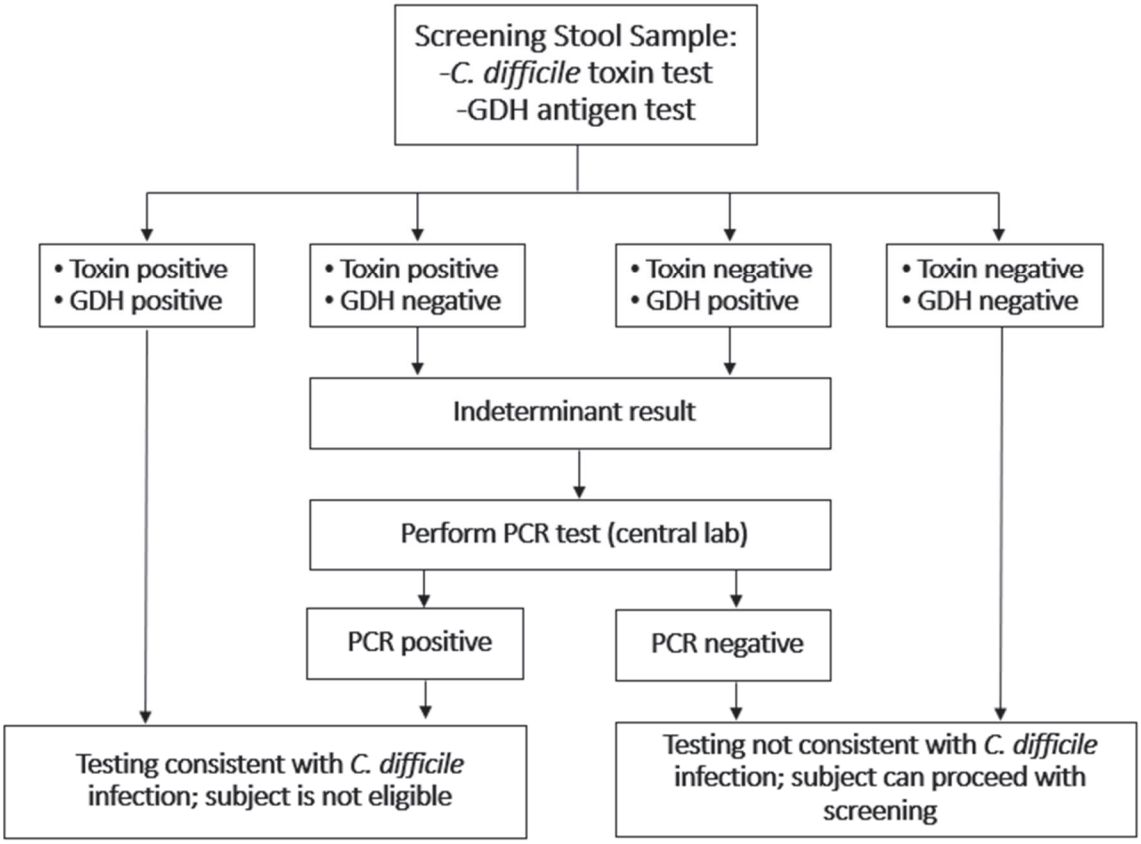
If a subject has received a specific coronavirus disease of 2019 (COVID-19) vaccination, the type of vaccine received should be recorded on the concomitant medication page, if given during the study, or the past history page, if given prior to enrollment.

- Administration of a live vaccine is prohibited 90 days prior to the randomization visit; during the induction period, maintenance period, or open-label extension (OLE) period; 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 subject at risk. Ideally, AEs attributable to a vaccine should have resolved prior to enrollment.
- Administration of vaccinations must be reported along with dosage information, dates of administration and vaccine name/trade name on the Prior and Concomitant Medications form. A separate logline should be entered for each vaccine administered with the dose number following the vaccine name/trade name.

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

APPENDIX 20 CLOSTRIDIUM DIFFICILE INFECTION SCREENING

Subjects must provide a stool sample for *Clostridium difficile* (*C. difficile*) testing at the screening visit. The central lab performs glutamate dehydrogenase (GDH) and *C. difficile* toxin analysis on the sample to confirm the subject is negative for the bacterium. The following chart presents the procedures to be followed to determine eligibility:



C. difficile = *Clostridium difficile*; GDH = glutamate dehydrogenase; PCR = polymerase chain reaction

Please contact the medical monitor with any questions related to *C. difficile* testing or infection.

APPENDIX 21 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for the Protocol Amendment 4, 06-Aug-2021

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

- Reconfiguration of secondary and exploratory study endpoints in response to expert consensus on treatment targets in inflammatory bowel disease (IBD)
- [redacted]
- Removal of exclusion criterion that prohibited the participation of subjects who had previously experienced inadequate response or loss of response to ustekinumab
- 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]

The amendment 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 amendment is provided in the summary of key changes table, as shown below:

SUMMARY OF CHANGES OF PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
2 Schedule of Activities, Tables 1-4 3.2.3 Benefit/Risk Assessment 4.3 Exploratory Endpoints 6.2 Exclusion Criteria 7.7.1 Prohibited and/or Restricted Treatments 8.2.1 Temporary IP Discontinuation (new section) 9.3.2 Time Period and Frequency for AE/SAE Collection [redacted] 9.10 SARS-CoV-2 Testing (new section)	Added information, instructions, and measures to be taken related to SARS-CoV-2 infection including the following: • Diagnostic testing at screening • [redacted] • Exclusion criteria for known, active infections of COVID-19	Provides guidance to investigators related to SARS-CoV-2

SUMMARY OF CHANGES OF PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 19 COVID-19 Vaccines (new appendix)	• Criteria for temporary discontinuation of IP • Documentation of AE/SAE related events • Administration of COVID-19 vaccine prior to or during study enrollment	
2 Schedule of Activities, Table 1	Removed fasting requirement for blood tests at screening	Reduces subject burden
2 Schedule of Activities, Table 1 6.5.1 Retesting During the Screening Period; Rescreening Appendix 20 Clostridium Difficile Infection Screening	Clarified screening algorithm for C. difficile testing	Clarifies screening process for subjects who have indeterminate C. difficile screening test results
[redacted]	[redacted]	[redacted]
2 Schedule of Activities, Tables 2-4 5.1.1 Screening Period	Clarified that endoscopies should be performed within a window of 7 days prior to the visit day	Limits confounding effects of bowel preparation, endoscopy procedure, and sedation on other clinical assessments
2 Schedule of Activities, Tables 2-3 9.2 Laboratory Assessments 9.5.3 Clinical Safety Laboratory Assessments	Clarified hematocrit may be performed by a local laboratory at Weeks 2, 4, 8, and 52, in addition to Weeks 12 through 44	Ensures prompt CDAI score calculation
3.2.3 Benefit/Risk Assessment	Added efficacy and safety findings from recent BMS-986165 studies	Adds further safety and efficacy context for how BMS-986165 is expected to affect CD subjects
4 Objectives and Endpoints 10.3.2 Secondary Endpoints 10.3.3 Exploratory Endpoints 10.4.6 Adjustment for Multiplicity of Co-primary and Secondary Endpoints, Table 18	Reconfigured secondary and exploratory endpoints	Endpoints updated in response to STRIDE II expert consensus on treatment targets in IBD[a]
5.1.1 Screening Period 6.1 Inclusion Criteria 6.2 Exclusion Criteria 7.7.1 Prohibited or Restricted Treatments [redacted]	Removed exclusion of subjects with inadequate response or loss of response to ustekinumab	Allows previously excluded subjects to participate based on results from other BMS-986165 studies

SUMMARY OF CHANGES OF PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
5.1.4 Open-label Extension Period	Clarified subjects who need rescue treatment must discontinue study treatment	Clarifies participation requirement that was previously implied
5.1.4 Open-label Extension Period 5.1.4.1 Post-treatment Follow-up 7.8 Treatment After the End of the Study	[redacted]	Clarifies subject options for continuing treatment
6.1 Inclusion Criteria	New Inclusion Criterion 3)l was added. Inclusion Criterion 3)j was changed to "Not applicable" and its content was amended to create new criterion 3)m.	Clarifies contraceptive requirements for male and female subjects to align with BMS-986165 program guidance
6.2 Exclusion Criteria	Exclusion Criteria 1)m, 1)o, 3)d, and 4)m were changed to "Not applicable." These previous exclusion criteria were amended to create new criteria 1)s, 1)t, 3)e, and 4)n, respectively.	Clarifies previously unspecified details and exceptions to specific exclusion criteria
6.2 Exclusion Criteria 7.7.1 Prohibited and/or Restricted Treatments	Added types of vaccines that are not prohibited before, during, or after the study	Clarifies previously unspecified exceptions to the prohibition of vaccine administration before, during, and after the study
6.2 Exclusion Criteria	Exclusion Criterion 4)e was clarified to not exclude subjects with Gilbert's syndrome	Clarifies previously unspecified exception to the exclusion of subjects with high bilirubin
7.3.3 Unblinding for Week 12 Analysis (new section)	Included details for unblinding BMS personnel for the Week 12 analysis	Clarifies unblinding procedures for the Week 12 analysis and clinical study report
8.1 Discontinuation from Study Treatment	Included criteria for liver-related laboratory abnormalities	Clarifies procedures and discontinuation criteria for subjects with elevated liver-related laboratory values
9 Study Assessments and Procedures	Clarified that study data may be used for additional analyses related to CD and other inflammatory diseases	Clarifies potential future analyses
9.1 Efficacy Assessments	Changed Robarts Clinical Trials to Alimentiv Clinical Trials	Updates vendor information

SUMMARY OF CHANGES OF PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
9.3.8 Potential Drug-induced Liver Injury	Added language to mandate follow-up testing in subjects with suspected DILI AEs.	Includes analysis of root cause in potential DILI occurrences to ensure subject safety
Study Acknowledgment/Disclosure 6.2 Exclusion Criteria 6.5 Screen Failures 7.3.1 Maintaining the Blind 7.8 Treatment After the End of the Study 9.3.2 Time Period and Frequency for Collecting AE and SAE Information 9.8.1 Additional Research Collection Appendix 2 Study Governance Considerations Appendix 3 Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting Appendix 5 Women of Childbearing Potential Definitions and Methods of Contraception	Updated text in multiple sections of the protocol due to changes in BMS protocol standards	Reflects current BMS procedures, policies, and guidelines

[a] Refer to: Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: An update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative of the International Organization for the Study of IBD (IOIBD): Determining therapeutic goals for treat-to-target strategies in IBD. Gastroenterology 2021;160(5):1570-83.