1.0 Title Page

Clinical Study Protocol M16-006

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study of the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Crohn's Disease

Incorporating Administrative Change 1 and Amendments 1, 2, 3, 4, 5, 6, and 6.01 (United States Only)

AbbVie Investigational Product:	Risankizumab
Date:	01 September 2020
Development Phase:	3
Study Design:	Randomized, Double-Blind, Placebo-Controlled Parallel Group Design
EudraCT Number:	2016-003123-32
Investigators:	Multicenter Study (Investigator information is on file at AbbVie)

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* The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	17 February 2017
Amendment 1	05 July 2017
Amendment 2	29 September 2017
Amendment 3	09 July 2018
Amendment 4	22 February 2019
Amendment 5	19 December 2019
Amendment 6	28 July 2020

The purpose of this amendment is to:

- Modification of language in Section 3.2 on the re-evaluation of the benefit and risk in light of the COVID-19 pandemic, to subjects participating in the study in Section 3.2

  Rationale: *To clarify the effect of immunomodulatory therapies on the course of COVID-19 is currently unknown*
- Addition of Endpoint definitions in Section 5.3.3

  Rationale: *To include endpoints definitions for newly added secondary endpoints in Section 5.3.3.2 and Section 5.3.3.3*
- Revision of Co-Primary Endpoints in Section 5.3.3.1

  Rationale: *Co-Primary endpoints were revised based on regulatory input*
- Section 5.3.3.2 updated to reflect new secondary endpoint ranking addition of new secondary endpoints, and update terms

  Rationale: *Reassessment based on evidence from the risankizumab CD Phase 2 study (Study M15-993), regulatory feedback, clinical relevance of endpoints to patients and physicians, alignment with study changes and updated terms*
- Revision to Determination of Sample Size in Section 8.2

  Rationale: *To update power calculation for revised co-primary endpoint*

An itemized list of all changes made to this protocol under this amendment can be found in Appendix K.

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M16-006
Name of Study Drug: Risankizumab (ABBV-066)	**Phase of Development:** 3
Name of Active Ingredient: Risankizumab	**Date of Protocol Synopsis:** 01 September 2020
Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study of the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Crohn's Disease	
Objective: The objective of Study M16-006 is to evaluate the efficacy and safety of risankizumab versus placebo during induction therapy in subjects with moderately to severely active Crohn's disease (CD).	
Investigators: Multicenter	
Study Sites: Approximately 400 sites	
Study Population: Males and females aged ≥ 18 to ≤ 80 years of age, or minimum age of adult consent according to local regulations at the Baseline visit, or aged 16 to < 18 years of age where locally permitted and who meet the definition of Tanner stage 5 development (refer to Appendix J) at the Baseline visit, with a diagnosis of moderately to severely active CD, defined as: 1. average daily stool frequency (SF) ≥ 4 (when calculating SF, only the number of liquid or very soft stools should be recorded) and/or average daily abdominal pain (AP) score ≥ 2; plus 2. endoscopic evidence of mucosal inflammation as measured by the Simple Endoscopic Score for CD (SES-CD). All eligible scores exclude the presence of narrowing component and are confirmed by a central reader. Endoscopic activity is defined as a SES-CD of ≥ 3. The number of subjects enrolled with a SES-CD of ≥ 3 to < 6 for ileocolonic or colonic disease or SES-CD of 3 for isolated ileal disease will be no more than 85 subjects. Once cap of no more than 85 subjects is reached, enrollment criterion will be an eligibility SES-CD of ≥ 6 for ileocolonic or colonic disease, or eligibility SES-CD of ≥ 4 for isolated ileal disease. The study will enroll both subjects who have had an inadequate response (IR) to prior biologic therapy (bio-IR) and subjects who have not (non-bio-IR). The bio-IR enrollment will be approximately 540 subjects and the non-bio-IR enrollment will be approximately 315 subjects. The **bio-IR** population is defined as subjects with documented intolerance or inadequate response to one or more of the approved anti-TNF or anti-integrin biologics for CD (infliximab, adalimumab, certolizumab, vedolizumab, ustekinumab and/or natalizumab). The **non-bio-IR** population will include subjects who had an inadequate response or intolerance to conventional therapy. Conventional therapy is defined as one or more of the following: aminosalicylates, oral locally acting steroids (e.g., budesonide, beclomethosone), systemic corticosteroids (prednisone or equivalent), or immunomodulators. This population will also include subjects who have received biologic therapy in the past but stopped therapy based on reasons other than inadequate response or intolerance (e.g., change in reimbursement coverage, well-controlled disease). The percent of subjects with exposure, including intolerance or inadequate response, to ustekinumab will be no more than 20%.	
Number of Subjects to be Enrolled: Approximately 855 for the primary ITT population used for efficacy analysis; additionally, up to 85 subjects with lower SES-CD will be enrolled	

Methodology:

Study M16-006 is a randomized, double blind, placebo-controlled 12-week induction study.

Subjects (n = 855) will be randomized 2:2:1 to 1200 mg risankizumab or 600 mg risankizumab or placebo intravenous (IV) given at Baseline, Weeks 4 and 8. The randomization will be stratified by number of prior biologics failed (0, 1, > 1), Baseline steroid use (yes, no), and Baseline SES-CD (original, alternative), where the stratum of "original" includes the patients with baseline SES-CD of ≥ 6 (or ≥ 4 for subjects with isolated ileal disease), and the stratum of "alternative" includes the patients with baseline SES-CD of ≥ 3 to < 6 for ileocolonic or colonic disease or SES-CD of 3 for isolated ileal disease.

Visits during the study will occur at Baseline and Weeks 4, 8, and 12/Premature Discontinuation (PD) to collect clinical and laboratory assessments of disease activity. Subjects who do not achieve clinical response at Week 12 will be offered blinded risankizumab therapy in Induction Period 2 with evaluation for clinical response at Week 24.

All subjects will be provided with a subject diary where they will record CD related symptoms throughout the study. Subjects will also be dispensed a patient information card at Screening. Additionally, subjects will complete symptom, quality of life (QoL) and work productivity questionnaires throughout the study. Clinical labs including, but not limited to, urinalysis, chemistry and hematology, high-sensitivity C-reactive protein (hs-CRP), serum risankizumab concentrations, and serum anti-drug antibody (ADA) levels will be collected throughout the study. In addition, stool samples for calprotectin analysis will be collected and should be taken before starting bowel preparations for endoscopy. All endoscopies will be evaluated using SES-CD and will be confirmed by a central reader. Biopsy to confirm diagnosis (during Screening) or to rule out dysplasia/malignancy may be performed during the same time points as the endoscopy. Optional exploratory research samples may be taken during the study.

At the Week 12/PD visit, all subjects will undergo an endoscopy for evaluation of mucosal inflammation. It is expected that all subjects who remain in the study through at least Week 8 will have a Week 12/PD endoscopy. All subjects achieving clinical response, defined as ≥ 30% decrease in average daily SF and/or ≥ 30% decrease in average daily AP score (both not worse than Baseline) at Week 12 may be eligible to enter Study M16-000. Subjects are not eligible to enter Study M16-000 until endoscopy has been completed (local reader results will be used for stratification for Study M16-000).

All subjects who do not achieve clinical response at Week 12 may be eligible to receive blinded risankizumab treatment in Induction Period 2 as specified below. Subjects are not eligible to enter Induction Period 2 until the Week 12 endoscopy has been completed.

<u>Induction Period 2:</u>

At Week 12, subjects who do not achieve clinical response will be randomized by Interactive Response Technologies (IRT) to Induction Period 2, a double-blind, double-dummy 12-week treatment period.

Subjects who received IV risankizumab induction treatment with inadequate clinical response at Week 12 will be randomized 1:1:1 to:

- Group 1: 1200 mg IV risankizumab
- Group 2: 360 mg SC risankizumab
- Group 3: 180 mg SC risankizumab

Methodology (Continued):

Subjects who received IV placebo induction treatment will receive:

- Group 4: 1200 mg IV risankizumab

The IV risankizumab dose or matching IV placebo will be given at Weeks 12, 16, and 20. The SC risankizumab dose or matching SC placebo will be given at Weeks 12, and 20. At Week 24, subjects who received treatment in Induction Period 2 will be reassessed and undergo a third endoscopy for evaluation of mucosal inflammation. Subjects who achieve clinical response at Week 24 may be eligible to enter Study M16-000. Subjects without clinical response at Week 24, as well as all subjects who terminate the study early (including subjects who are eligible for, but do not enter Induction Period 2), will be discontinued and have a follow-up call 140 days from the last dose of study drug to obtain information on any new or ongoing AEs.

Concomitant aminosalicylates, immunomodulators (azathioprine [AZA], 6-mercaptopurine [6-MP], methotrexate [MTX]), and/or CD-related antibiotics.

Subjects taking aminosalicylates, immunomodulators, and/or CD-related antibiotics at Baseline must continue these treatments for the duration of the study. Initiating and/or increasing doses of aminosalicylates, immunomodulators, and/or CD-related antibiotics during the study is prohibited. Decreasing doses of aminosalicylates, immunomodulators, and/or CD-related antibiotics is prohibited during the study, except in the event of moderate-to-severe treatment related toxicities and after discussion with the AbbVie Therapeutic Area Medical Director (TA MD). CD-related antibiotics may be discontinued in Induction Period 2 at the discretion of the Investigator.

Note: the duration of the study includes Induction Period 2.

Concomitant Corticosteroids

Subjects taking corticosteroids at Baseline must continue their concomitant treatment at the Baseline dose for the duration of the 12-week induction period. Initiation and/or increasing doses of systemic and/or CD related corticosteroids during the entire study is prohibited. Decreasing doses of corticosteroids is prohibited during the 12-week induction period, except in the event of moderate-to-severe treatment related toxicities and after discussion with the AbbVie TA MD.

Subjects who receive Induction Period 2 treatment during Weeks 12 to 24 will be allowed to taper their corticosteroids at the discretion of the Investigator. Increasing doses above the Baseline dose is prohibited.

Dose Selection

This study will evaluate two IV doses of risankizumab (600 mg and 1200 mg) during induction. The selection of the doses in this study is informed by the analysis of the safety and efficacy data, as well as the exposure-response relationship of efficacy, of a Phase 2 study in subjects with CD that explored 200 mg and 600 mg doses. The results from the Phase 2 study suggest a potential for increased benefit with 1200 mg administration.

Methodology (Continued):

Induction Period 2 will evaluate IV (1200 mg Q4w) or SC (180 mg or 360 mg Q8w; maintenance dosing regimen) risankizumab. The purpose of Induction Period 2 is to evaluate the efficacy and safety of re-induction of risankizumab (1200 mg IV at Weeks 12, 16, and 20) versus initiating maintenance dosing on clinical response status. Data from the Phase 2 study in subjects with CD suggested that re-induction with 600 mg IV increased both clinical response and clinical remission in subjects with inadequate response at Week 12. The selection of the SC doses is informed by the analysis of the safety and efficacy data, as well as the exposure-response relationship of efficacy, of the maintenance period during the Phase 2 study in subjects with CD that evaluated 180 mg SC risankizumab for maintenance. The results from the Phase 2 study suggest a potential for increased benefit with 360 mg SC administration for maintenance regimen.

Data Monitoring Committee (DMC)

An external independent DMC will review unblinded safety data on a cohort level, at a minimum of 6-month intervals throughout the course of the study. At the timing of this amendment, the DMC has provided recommendation that the study may continue without modification and allowed enrollment to begin for 16 - 17 year-olds. A patient information card with information of the symptoms and signs of hypersensitivity reactions, infusion related reactions as well as late stage reactions will be provided to the patients at Screening so that any such events once occurred will be reported immediately by the patients to the investigator.

A separate DMC charter will be prepared outside of the protocol and will describe the roles and responsibilities of the DMC member, frequency and triggers of data reviews, and relevant safety data to be assessed. The cardiac adjudication committee (CAC) and anaphylaxis adjudication committee (AAC) adjudicates blinded data and the DMC reviews the data in an unblinded manner. Unblinded adjudicated cardio-cerebrovascular events and anaphylactic reactions will be presented to the DMC for review on a periodic basis. Communications from the DMC to the Study Teams will not contain information that could potentially unblind the team to subject treatment assignments.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Males or females ≥ 18 and ≤ 80 years of age or minimum age of adult consent according to local regulations at the Baseline Visit. Where locally permissible, subjects 16 to < 18 years of age who meet the definition of Tanner stage 5 for development (refer to Appendix J), at the Baseline Visit (sites will be notified when adolescents may enroll).
2. Confirmed diagnosis of CD for at least 3 months prior to Baseline. Appropriate documentation of biopsy results consistent with the diagnosis of CD, in the assessment of the Investigator, must be available.
3. Crohn's disease activity index (CDAI) score 220 – 450 at Baseline.
4. Endoscopic evidence of mucosal inflammation as documented by an SES-CD of ≥ 3. All eligible scores exclude the presence of narrowing component and are confirmed by a central reader. (Once cap of no more than 85 subjects is reached, enrollment criterion will be an SES-CD of ≥ 6 for ileocolonic or colonic disease or SES-CD of ≥ 4 for isolated ileal disease.)
5. Average daily SF ≥ 4 and/or average daily AP score ≥ 2 at Baseline.
6. Demonstrated intolerance or inadequate response to one or more of the following categories of drugs: aminosalicylates, oral locally acting steroids, systemic steroids (prednisone or equivalent), immunomodulators, and/or biologic therapies
    - Demonstration of intolerance requires no minimum dose or duration of use (intolerance includes patients with a known TPMT genetic mutation or low activity).
    - Inadequate response is defined as outlined below:
        - Oral aminosalicylates (e.g., mesalamine, sulfasalazine, olsalazine, balsalazide):
            - Signs and symptoms of persistently active disease, in the opinion of the Investigator, during a current or prior course of at least 4 weeks of treatment with 2.4 g/day mesalamine, 4 g/day sulfasalazine, 1 g/day olsalazine, or 6.75 g/day balsalazide,
        - Oral locally acting steroids (e.g., budesonide, beclomethasone):
            - Signs and symptoms of persistently active disease, in the opinion of the Investigator, during or after a course of at least 4 weeks of treatment with 9 mg/day budesonide or 5 mg/day beclomethasone,

              or
            - Inability to taper oral budesonide to at or below 6 mg/day without recurrent active disease,
        - IV or Oral systemic steroids (prednisone or equivalent):
            - Signs and symptoms of persistently active disease, in the opinion of the Investigator, during or after tapering of at least one regimen consisting of a dose equivalent to prednisone ≥ 40 mg/day orally for 3 weeks or intravenously for 1 week,

              or
            - Inability to taper oral systemic steroids to at or below a dose equivalent to prednisone 10 mg/day without recurrent active disease,

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

- Immunomodulators:
  - Signs and symptoms of persistently active disease, in the opinion of the Investigator, during a current or prior course of at least 90 days of treatment with one or more of the following:
    - AZA: ≥ 2.0 mg/kg/day rounded to the nearest available tablet or half tablet formulation (≥ 1 mg/kg/day for subjects in Japan, Korea, Hong Kong, Taiwan, Singapore, or China) (or a documented 6-TGN level of ≥ 230 pmol/8 × 10^8 RBC)
    - 6-MP: ≥ 1 mg/kg/day rounded to the nearest available tablet or half tablet formulation (≥ 0.6 mg/kg/day for subjects in Japan, Korea, Hong Kong, Taiwan, Singapore, or China) (or a 6-TGN level of ≥ 230 pmol/8 × 10^8 RBC)
    - MTX: ≥ 15 mg/week subcutaneous (SC) or intramuscular (IM)
      - *Note:* Oral MTX use is allowed during the study, however prior or current use of oral MTX is not sufficient for inclusion into the study
- Biologic Therapies for CD:
  - Signs and symptoms of persistently (in the opinion of the Investigator) active disease despite a history of one or more of the following:
    - At least one 6-week induction regimen of infliximab (≥ 5 mg/kg IV at Weeks 0, 2, and 6),
    - At least one 4-week induction regimen of adalimumab (one 160 mg SC dose at Week 0, followed by one 80 mg SC dose at Week 2 [or one 80 mg SC dose at Week 0, followed by one 40 mg SC dose at Week 2, in countries where this dosing regimen is approved]),
    - At least one 4-week induction regimen of certolizumab pegol (400 mg SC at Weeks 0, 2, and 4),
    - At least one 6-week induction regimen of vedolizumab (300 mg IV at Weeks 0, 2, and 6)
    - At least one 12-week induction regimen of natalizumab (300 mg IV every 4 weeks)
    - At least one 8-week induction regimen of ustekinumab [260 mg (≤ 55 kg) or 390 mg (> 55 to ≤ 85 kg) or 520 mg (> 85 kg) IV, followed by 90 mg SC at Week 8] (Once cap of no more than 20% ustekinumab exposed subjects is reached, subjects with prior ustekinumab exposure will not be allowed to enroll.)

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

- Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit of the above biologics
- Note: Subjects who discontinued biologics for reasons other than inadequate response as defined above or intolerance (e.g., change of insurance) must meet the criteria for intolerance or inadequate response to aminosalicylates, oral locally acting steroids, systemic steroids (prednisone or equivalent), and/or immunomodulators as defined above

7. If female, subject must meet the criteria as stated in Section 5.2.4 of this protocol *Contraception Recommendations*. Females of childbearing potential must have a negative serum pregnancy test result during Screening, and a negative urine pregnancy at Baseline. Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) during Screening do not require pregnancy testing at Baseline.

   Note: Subjects with borderline serum pregnancy test at Screening must have a serum pregnancy test ≥ 3 days later to document continued lack of a positive result.
8. Subjects must be able and willing to give written informed consent and to comply with the requirements of this study protocol. In Japan, if the subject is < 20 years old, a subject's parent or legal guardian must be willing to give written informed consent.

Main Exclusion:

1. Subject with a current diagnosis of ulcerative colitis or indeterminate colitis.

<u>Concomitant Medications and Treatments</u>

2. Subject on CD-related antibiotics who has not been on stable doses for greater than, or discontinued within, 14 days prior to Baseline.
3. Subject on oral aminosalicylates who has not been on stable doses for greater than, or discontinued within, at least 14 days prior to Baseline.
4. Subject taking oral corticosteroids:
   - Budesonide > 9 mg/day
   - Beclomethasone > 5 mg/day
   - Prednisone or equivalent > 20 mg/day
   - Or has not been on the current course for ≥ 14 days prior to Baseline and on a stable dose for ≥ 7 days prior to Baseline
5. Subject on immunomodulators (AZA, 6-MP, MTX) who:
   - Has not been on the current course for ≥ 42 days prior to Baseline, and
   - Has not been on a stable dose for ≥ 35 days prior to Baseline

<u>Medications and Treatments During the Screening Period</u>

6. Subject who received IV anti-infectives within 35 days prior to Baseline visit or oral/intramuscular anti-infectives (non-CD-related) within 14 days prior to the Baseline visit. This does not apply to TB prophylaxis.
7. Subject who received exclusive enteral nutrition or any parenteral nutrition within 35 days prior to Baseline.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

Medications and Treatments During the Screening Period (Continued)

8. Subject who received any live bacterial or viral vaccination within 30 days (8 weeks for Japan) prior to Screening or during the Screening Period.
9. Subject who received cyclosporine, tacrolimus, or mycophenolate mofetil within 35 days prior to Baseline.
10. Subject who received fecal microbial transplantation within 35 days prior to Baseline.

Prior Medications and Treatments

11. Subject who received any:
    - Approved biologics: infliximab, adalimumab, certolizumab, vedolizumab, natalizumab) within 8 weeks prior to Baseline, or ustekinumab within 12 weeks prior to Baseline

      Note: If there is proper documentation of an undetectable drug level measured by a commercially available assay for any of the approved biologics above, there is no minimum washout prior to Baseline.
    - Any investigational biologic or other agent or procedure within 35 days or 5 half-lives prior to Baseline, whichever is longer.
12. Subject with prior exposure to p19 inhibitors (e.g., risankizumab).
13. Subject has been taking combination of two or more of the following: oral budesonide, or oral beclomethasone and/or oral prednisone (or equivalent) simultaneously, with the exception of inhalers, within 14 days prior to Screening or during the Screening period.
14. Subject who received IV/intramuscular corticosteroids within 14 days prior to Screening or during the Screening period.
15. Subject who received therapeutic enema or suppository, other than required for endoscopy, within 14 days prior to endoscopy used for Screening or during the Screening period.
16. Subject who received apheresis (e.g., Adacolumn apheresis) ≤ 60 days prior to Screening or during the Screening period.
17. Subject who has concomitant cannabis use either recreational or for medical reasons within 14 days prior to Baseline or any history of clinically significant drug, or alcohol abuse in the last 12 months.

CD Related

18. Subject with currently known complications of CD such as:
    - abscess (abdominal or perianal),
    - symptomatic bowel strictures,
    - > 2 missing segments of the following 5 segments: terminal ileum, right colon, transverse colon, sigmoid and left colon, and rectum
    - fulminant colitis,
    - toxic megacolon,
    - or any other manifestation that might require surgery while enrolled in the study.
19. Subject with ostomy or ileoanal pouch.
20. Subject diagnosed with short gut or short bowel syndrome.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

21. Subject with surgical bowel resection within the past 3 months prior to Baseline, or a history of ≥ 3 bowel resections.

Safety

22. Subject who has a known hypersensitivity to risankizumab or the excipients of any of the study drugs or the ingredients of Chinese hamster ovary (CHO).
23. Subjects with the following chronic or active infections:
    - Active, chronic, or recurrent infection that based on the Investigator's clinical assessment makes the subject unsuitable candidate for the study,
    - Infection with C. *difficile* toxin or other intestinal pathogen during Screening,
    - Are infected with human immunodeficiency virus (HIV),
    - QuantiFERON®-TB test or Purified Protein Derivative (PPD) skin test, or both, according to local guidelines, will be performed during Screening. QuantiFERON®-TB test is preferred for subjects who received BCG vaccination or were exposed to other Mycobacteria species. Subjects with a positive test result (or indeterminate results that have been repeated) may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active tuberculosis. Subjects with a history of active TB who have documented completion of a full course of anti-TB therapy may be allowed to enter the study after consultation with the AbbVie TA MD. If latent TB is established, TB prophylaxis/treatment should be initiated and maintained according to local country guidelines.
    - Have active hepatitis B or hepatitis C defined as:
        - HBV: hepatitis B surface antigen (HBs Ag) positive (+), or detected sensitivity on the HBV deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) qualitative test for hepatitis B core antibody (HBc Ab) positive subjects;
        - HCV: HCV ribonucleic acid (RNA) detectable in any subject positive with anti-HCV antibody (HCV Ab)
24. Subject with a previous history of dysplasia of the gastrointestinal tract or found to have dysplasia, other than completely removed low-grade dysplastic lesions, in any biopsy performed during the Screening endoscopy.
25. Subject with a known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly.
26. Subject with current or previous history of malignancy other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix.
27. Subject who has severe, progressive, or uncontrolled renal, hepatic, hematological, endocrine, disorder or symptoms thereof.
28. Female subjects who is pregnant, breastfeeding, or is considering becoming pregnant during the study or for approximately 140 days after the last dose of study drug.
29. Subject who has any condition, including any physical, psychological, or psychiatric condition, which in the opinion of the Investigator, would compromise the safety of the subject or the quality of the data and renders the subject an unsuitable candidate for the study.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

Safety (Continued):

30. Screening laboratory and other analyses show any of the following abnormal results:
    - Aspartate transaminase (AST), alanine transaminase (ALT) > 2 × upper limit of the reference range;
    - White blood cell (WBC) count < 3.0×10^9/L;
    - Total bilirubin ≥ 2 mg/dL; except for subjects with isolated elevation of indirect bilirubin relating to Gilbert syndrome;
    - Estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula < 30 ml/min/1.73 m^2.
    - Hemoglobin < 8 g/dL
    - Platelets < 100,000/µL
    - Positive serum pregnancy test at the Screening visit or positive urine pregnancy test at the Baseline visit.

    Laboratory values can be re-tested once during the screening period after discussion and clearance with the TAMD. If the re-tested lab value(s) remain(s) exclusionary, the subject will be considered a screen failure. Redrawing samples if previous samples were unable to be analyzed would not count as a retest since previous result was never obtained.
31. No known active COVID-19 infection. Subject must not have signs/symptoms associated with COVID-19 infection.

    Subjects who do not meet COVID-19 eligibility criteria must be screen failed and may only rescreen after they meet the following COVID-19 viral clearance criteria:
    - Symptomatic subjects: At least 2 negative viral tests in a row completed locally, ≥ 24 hours apart after at least 10 days have passed since recovery, defined as resolution of fever without use of antipyretics and improvement in respiratory symptoms (e.g., cough, shortness of breath)
    - Asymptomatic subjects: At least 2 negative viral tests in a row completed locally, ≥ 24 hours apart after at least 10 days have passed since prior positive result (Note: subjects who develop symptoms will follow guidance above for symptomatic subjects)

    Frequency or timing of COVID-19 testing and interval between testing for the above viral clearance criteria may be adjusted to account for epidemiological trends, updated information regarding infectivity and local/institutional guidelines.

Investigational Product:	Risankizumab
Doses:	Risankizumab 1200 mg IV Q4W* Risankizumab 600 mg IV Q4W Risankizumab 180 mg SC Q8W Risankizumab 360 mg SC Q8W * If the 1200 mg dose is discontinued due to any reason, subjects will continue to enroll into the study and be randomized to either 600 mg risankizumab or placebo at 2:1 ratio. The randomization ratio and sample size may be further updated in an amendment to the protocol. Subjects already randomized to treatment arms, including Induction Period 2, will receive blinded 600 mg risankizumab IV.
Mode of Administration:	Risankizumab solution for infusion (IV) Risankizumab solution for injection (SC)
Reference Therapy:	Placebo for risankizumab
Dose:	N/A
Mode of Administration:	Placebo solution for infusion (IV) Placebo solution for injection (SC)

Duration of Treatment: 12 or 24 weeks

The study will include a Screening period of up to 35 days and a double-blind induction period of 12 weeks. All subjects who do not achieve clinical response at Week 12 will be eligible to receive treatment in Induction Period 2 with risankizumab over a subsequent 12 week period. There will be a follow up call 140 days from the last dose of study drug to obtain information on any new or ongoing AEs for those subjects who do not roll over into Study M16-000 or discontinue from the study prematurely.

Criteria for Evaluation:

Endpoint Definitions:

- **Clinical remission:** average daily SF $\leq$ 2.8 and not worse than Baseline AND average daily AP score $\leq$ 1 and not worse than Baseline
- **Enhanced clinical response:** $\geq$ 60% decrease in average daily SF and/or $\geq$ 35% decrease in average daily AP score and both not worse than Baseline, and/or clinical remission
- **Clinical response:** $\geq$ 30% decrease in average daily SF and/or $\geq$ 30% decrease in average daily AP score and both not worse than Baseline
- **Endoscopic response:** decrease in SES-CD > 50% from Baseline (or for subjects with isolated ileal disease and a Baseline SES-CD of 4, at least a 2 point reduction from Baseline), as scored by central reviewer
- **Ulcer-free endoscopy:** SES-CD ulcerated surface subscore of 0 in subjects with SES-CD ulcerated surface subscore $\geq$ 1 at Baseline, as scored by a central reviewer
- **Endoscopic remission:** SES-CD $\leq$ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable, as scored by a central reviewer

Criteria for Evaluation (Continued):

Endpoint Definitions (Continued):

- **CDAI clinical response:** reduction of CDAI ≥ 100 points from baseline
- **CDAI clinical remission:** CDAI < 150
- **SF remission:** average daily SF ≤ 2.8 and not worse than baseline
- **AP remission:** average daily AP score ≤ 1 and not worse than baseline

Efficacy:

Co-Primary Endpoints:

- Proportion of subjects with CDAI clinical remission at Week 12
- Proportion of subjects with endoscopic response at Week 12

Ranked Secondary Endpoints:

1. Proportion of subjects with clinical remission at Week 12
2. Proportion of subjects with CDAI clinical response at Week 4
3. Proportion of subjects with CDAI clinical response at Week 12
4. Change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-fatigue) at Week 12
5. Proportion of subjects with CDAI clinical remission at Week 4
6. Proportion of subjects with CDAI clinical response and endoscopic response at Week 12
7. Proportion of subjects with SF remission at Week 12
8. Proportion of subjects with AP remission at Week 12
9. Proportion of subjects with endoscopic remission at Week 12
10. Proportion of subjects with enhanced clinical response at Week 4
11. Proportion of subjects with ulcer-free endoscopy at Week 12
12. Proportion of subjects with enhanced clinical response at Week 12
13. Proportion of subjects with resolution of extra-intestinal manifestations (EIMs) at Week 12, in subjects with any EIMs at Baseline
14. Proportion of subjects with CD-related hospitalization through Week 12
15. Proportion of subjects without draining fistulas at Week 12 in subjects with draining fistulas at Baseline

For further information, including non-ranked endpoints, refer to protocol

Pharmacokinetics:

Serum risankizumab concentrations will be determined from samples collected just prior to dosing at Weeks 4, 8, and 12/PD, and at Week 24 for subjects who receive treatment in Induction Period 2.

Additionally, intensive pharmacokinetic assessment will be performed in 20 subjects after the 3rd induction dose (Week 8 to 12). For Subjects who consent to the intensive pharmacokinetic assessment, in addition to the time points above, blood samples will be collected at Week 8 immediately after completion of infusion and 2 hours post completion of infusion, and at Weeks 9, 10, and 11. Refer to Appendix H for more details.

Criteria for Evaluation (Continued):

Immunogenicity:

Serum ADAs will be determined from samples collected just prior to dosing at Baseline and Weeks 4, 8, and 12/PD, and at Week 24 for subjects who receive treatment in Induction Period 2.

Safety:

Safety analyses will be performed on safety set which includes all subjects who receive at least one dose of study drug. Incidence of adverse events (AEs), changes in vital signs, physical examination results, and clinical laboratory data will be assessed throughout the study.

Exploratory Research Variables and Validation Studies (Optional):

Prognostic, surrogate, predictive and pharmacodynamics biomarkers signatures may be investigated. Samples for different applications, including but not limited to, pharmacogenetic, epigenetic, transcriptomic, proteomic, metabolomics, metagenomic and targeted investigations will be collected at various time points. Assessments will include but may not be limited to nucleic acids, proteins, metabolites or lipids.

Statistical Methods:

Efficacy:

The co-primary endpoints are the proportion of subjects with CDAI clinical remission at Week 12 and proportion of subjects with endoscopic response at Week 12. A total of approximately 855 subjects will be randomized into two risankizumab treatment groups and the placebo group in a 2:2:1 ratio (342 subjects for risankizumab 600 mg dose group, 342 subjects for risankizumab 1200 mg dose group, and 171 subjects for placebo group). When all patients complete their Week 12/PD visit, the database will be locked for the final analysis of 12-week induction period. When all the patients who enter the induction Period 2 finish Week 24/PD visit, the database will be locked for the whole study and all the planned analysis for the induction Period 2 will be performed.

Assuming the Week 12 CDAI clinical remission rate will be 37% for one of the risankizumab dose groups and 17% for the placebo group, a sample size of 342 subjects for each of the risankizumab dose groups and 171 for the placebo group will have 99% power to detect the treatment difference between the risankizumab dose groups and placebo in CDAI clinical remission rates at Week 12 using Fisher's exact test at alpha of 0.025 (two-sided).

The bio-IR population is approximately 540 subjects. The study will have 92% power to detect the treatment difference between one of the risankizumab dose groups and placebo in CDAI clinical remission at Week 12 using a Fisher's exact test a 0.025 significant level (two-sided) for the bio-IR population, assuming the Week 12 CDAI clinical remission rate will be 34% for the risankizumab dose groups and 15% for the placebo group for bio-IR subjects. The non-bio-IR population is approximately 315 subjects. The study will have 70% power to detect the treatment difference between one of the risankizumab dose groups and placebo in CDAI clinical remission, at Week 12 using a Fisher's exact test a 0.025 significant level (two-sided) for the non-bio-IR sub-population, assuming the Week 12 CDAI clinical remission rate will be 42% for the risankizumab dose groups and 21% for the placebo group for non-bio-IR subjects.

Statistical Methods (Continued):

Efficacy (Continued):

The comparisons between each risankizumab dose versus placebo for the primary efficacy variable will be performed using the Cochran-Mantel-Haenszel (CMH) test adjusted by prior biologic use (0, 1, > 1) and Baseline steroid use (yes, no). Both of the co-primary efficacy endpoints will be tested at statistically significant of 0.025 for each of the risankizumab dose groups versus placebo to adjust for multiplicity. A CMH based two-sided 95% confidence interval for the difference between treatment groups will be calculated.

The intent-to-treat (ITT) set includes all randomized subjects who have taken at least one dose of study drug. The primary population for efficacy analysis are the subjects in the intent-to-treat analysis set who had baseline eligibility SES-CD of ≥ 6 (≥ 4 for isolated ileal disease). Subjects who discontinue prior to Week 12 for any reason will be considered as "not-achieved" for CDAI clinical remission and endoscopic response endpoints.

In general, continuous secondary efficacy variables will be analyzed using a Mixed-Effect Model Repeated Measure (MMRM) model including factors for treatment group, visit, visit by treatment interaction, and stratification variables, for the longitudinal continuous endpoints. The MMRM analysis is considered primary for inferential purposes.

Pharmacokinetics and Immunogenicity:

Serum risankizumab concentrations will be summarized at each time point for each dosing regimen using descriptive statistics. Population pharmacokinetic analyses combining the data from this study and other studies may be performed. Relationships between risankizumab exposures and efficacy and safety variables of interest may be explored.

ADA incidence will be summarized by cohorts and study visits. ADA titers will be tabulated for each subject at the respective study visits. The effect of ADAs on risankizumab pharmacokinetics, efficacy and/or safety variable(s) and/or any additional analyses will be explored.

Safety:

Adverse events, laboratory data and vital signs are the primary safety parameters in this study. All safety comparisons will be performed between treatment groups using the safety set. Treatment emergent AEs are defined as events that begin or worsen either on or after the first dose of the study drug and within 140 days after the last dose of the study drug for subjects who do not participate in Study M16-000 or until first dose of study drug in Study M16-000 if the subject is enrolled in Study M16-000.

An overview of treatment-emergent AEs, AEs leading to death and AEs leading to premature discontinuation (see details in the statistical analysis plan [SAP]), AEs by Medical Dictionary for Drug Regulatory Activities (MedDRA version) preferred term and system organ class, AEs by maximum relationship to study drug, and AEs by maximum severity will be summarized by number and percentage.

Changes in laboratory data will be described using statistical characteristics and compared between treatment groups will be performed using a one-way Analysis of Variance (ANOVA). In addition, shift tables and listings will be provided for abnormal values, whereby the normal range of the analyzing laboratory will be used. Vital signs will be analyzed similarly.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

6-MP	6-Mercaptopurine
AAC	Anaphylaxis adjudication committee
ADA	Anti-Drug Antibody
AE	Adverse event
ALT	Alanine transaminase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AAC	Anaphylaxis adjudication committee
AP	Abdominal Pain
AST	Aspartate transaminase
ATEMS	AbbVie Temperature Excursion Management System
AZA	Azathioprine
BCG	Bacillus Calmette-Guérin
Bio-IR	Inadequate Response to biologic therapy
BUN	Blood urea nitrogen
CAC	Cardiac Adjudication Committee
CD	Crohn's disease
CDAI	Crohn's disease activity index
CHO	Chinese Hamster Ovary
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease - 2019
CRA	Clinical Research Associate
CSS	Crohn's Symptom Severity
CTCAE	Common Terminology Criteria for Adverse Events
CXR	Chest x-ray
DILI	Drug-induced Liver Injury
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture

EIM	Extra-Intestinal Manifestations
ePRO	Electronic Patient Reported Outcome
EQ-5D-5L	European Quality of Life 5 Dimensions
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FCP	Fecal Calprotectin
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HBc Ab	Hepatitis B core antibody
Hbs Ab	Hepatitis B surface antibody
Hbs Ag	Hepatitis B surface antigen
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
HCT	Hematocrit
HIV	Human immunodeficiency virus
hs-CRP	High-sensitivity C-Reactive Protein
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGRA	Interferon-Gamma Release Assay
IL	Interleukin
IR	Inadequate response
IM	Intramuscular
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technologies
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
MACE	Major Adverse Cardiovascular Events
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Drug Regulatory Activities

MI	Multiple Imputation
MMR	Measles Mumps-Rubella
MMRM	Mixed-Effect Model Repeated Measure
MMRV	Measles Mumps-Rubella Varicella
MTX	Methotrexate
nAb	Neutralizing antibodies
NRI	Non-responder imputation
N/A	Not Applicable
OC	Observed Case
OL	Open-Label
OPV	Oral Polio Vaccine
PCR	Polymerase Chain Reaction
PD	Premature Discontinuation
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetics
PMM	Pattern Mixture Model
POR	Proof of Receipt
PPD	Purified protein derivative
QoL	Quality of Life
Q4w	Every 4 Weeks
Q8w	Every 8 Weeks
RBC	Red blood cell
RNA	Ribonucleic Acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF	Stool Frequency
SF-36	36-Item Short Form Health Status Survey
SUSAR	Suspected Unexpected Serious Adverse Reactions
TA MD	Therapeutic Area Medical Director
TB	Tuberculosis
TNF	Tumor Necrosis Factor

ULN	Upper Limit of Normal
WBC	White blood cell
WOCBP	Women of Childbearing Potential
WPAI-CD	Work Productivity and Impairment Questionnaire – Crohn's disease

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3.0 Introduction

Crohn's disease (CD) encompasses a spectrum of clinical and pathological processes manifested by focal asymmetric, transmural, and occasionally granulomatous inflammation that can affect any segment of the gastrointestinal tract and presents with symptoms of fatigue, prolonged diarrhea with or without gross bleeding, abdominal pain, weight loss, and fever.[1] The disease can affect persons of any age, and its onset is most common in the second and third decades. Females are affected slightly more than males, and the risk for disease is higher in some ethnic groups.[2,3] The incidence of CD has steadily increased in developed countries over the past 3 decades[4] with recent estimates varying from 12.7 and 20.2 cases/100,000, and a prevalence of 319 and 322 cases/100,000 in North America and Europe, respectively.[5] In Asia, the incidence of CD is estimated to be 0.5 to 1.0 cases per 100,000 persons, with a prevalence rate ranging from 3.6 to 7.7.[6,7]

The exact cause of CD is still unknown, but is hypothesized to be the result of a dysregulated immune system in the context of a genetically susceptible individual. It is thought that a combination of a patient's genetics, microbiome, immune response, and the environment result in an excessive and abnormal immune response in the gut that results in pathology seen in CD.[2]

The aim of medical treatment in CD has been focused on controlling inflammation and reducing symptoms.[8] In addition to improving symptoms, an emerging goal of therapy is to heal the gut mucosa. Resolution of intestinal ulcers, also known as mucosal healing has been associated with positive clinical benefits, including higher rates of clinical remission, fewer hospitalizations, and fewer abdominal surgeries.[9,10] However, improvement of the appearance of the intestinal mucosa may be more difficult to achieve than symptomatic improvement alone.

Conventional pharmaceutical therapies (e.g., corticosteroids, aminosalicylates, thiopurines, methotrexate) are limited, do not always completely abate the inflammatory process, and have significant adverse effects.[1,11] The advent of anti-TNFα agents

(e.g., adalimumab) and integrin inhibitors (e.g., vedolizumab) have been shown to achieve clinical remission in patients refractory to conventional therapies.[9-13]

Despite the benefits of available biologic therapies, many patients do not respond to initial treatment (primary loss of response) or lose treatment over time (secondary loss of response). Regarding anti-TNF agents, approximately 40% of patients will experience primary non-response and secondary non-response occurs in 38% of patients at 6 months and 50% of patients at 1 year.[12,14-17] Additionally, some patients are not candidates for available biologic therapies. Therefore new therapeutic options are required in order to continue to improve the outcome of patients with CD.

Risankizumab is a fully humanized mAb of the IgG1 subclass directed towards IL-23p19. The antibody has been engineered to reduce Fcγ receptor and complement binding and potential charge heterogeneity. Risankizumab binds with high affinity to human IL-23 and inhibits IL-23 stimulated IL-17 production at inhibitory concentration (IC) 50 concentrations below 10 pM, as compared with 167 pM for ustekinumab in the same system. Risankizumab does not affect IL-12 at a maximum tested concentration (33 nM) and it does not inhibit IL-12 stimulated IFN-γ production.

3.1 Differences Statement

This study is designed to evaluate the efficacy and safety of two risankizumab induction doses versus placebo in subjects with moderately to severely active CD. The primary differences between Study M16-006 and the prior Phase 2 study of risankizumab in CD is that this study will test a higher dosing of 1200 mg. Additionally, the endpoints in this study are different to reflect the changing regulatory requirements for pivotal registrational studies for new agents for the treatment of CD.

3.2 Benefits and Risks

Data suggest that altered immune regulation at the epithelial barrier leads to an overproduction of inflammatory cytokines, tissue destruction, and aberrant tissue repair in CD. Among the cytokines implicated in CD pathogenesis, data at the genetic, human

biology and clinical level strongly implicate IL-23 in this disease.[18,19] The preclinical and clinical profiles of risankizumab suggest that it may have the potential to address unmet medical need in CD. The data observed in the Phase 2 study, suggest that risankizumab will alleviate signs and symptoms of active CD and reduce mucosal inflammation. Participation in this study may help to generate future benefit for subjects with CD.

Though there are no serious adverse drug reactions known to be associated with risankizumab therapy, risks of participating in this study include risk of infection and risks related to the study specific procedures of blood sampling, infusion and injection of study drug, and colonoscopy with biopsy.

Blood sampling, intravenous (IV) infusions and subcutaneous (SC) injections can cause local bruising, inflammation, and pain. Colonoscopy and biopsy, although generally well tolerated, can be associated with diarrhea, abdominal pain, and in more severe cases, perforation, bleeding, effects from anaesthetic medications, and infection.

Local reactions to IV or SC administered biologic therapies are uncommon, and are usually limited to redness, swelling or induration at the injection site. Manifestations of systemic hypersensitivity reactions include anaphylaxis, pruritus, hypotension, and respiratory distress. Both local and systemic hypersensitivity reactions are readily detectable, transient in nature, and manageable with standard medical treatment. Subjects will be closely monitored during drug administration.

As with any immune modulating agent, risankizumab has the potential to impair immune function resulting in a risk of infection. This will be addressed by clinical monitoring for adverse events (AEs) during the treatment and follow up periods. Subjects with positive screening for M. Tuberculosis (TB) (skin/interferon-gamma release assay [IGRA] test positive) will be further worked up for signs and symptoms of active TB (e.g., chest x-ray [CXR]). Subjects with active TB will be excluded from enrolling in the study. Subjects with latent TB will be allowed to enroll in line with local guidelines. If latent TB is established, TB prophylaxis/treatment should be initiated and maintained according to

local country guidelines. Subjects with current signs or symptoms of infection or history of serious infection will not be included in the study.

The role of IL-23 in tumor immunity is not well established at this time, but an increased risk of cancer from an IL-23 antagonist, though considered small, cannot be excluded.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, though there is no known DILI risk with risankizumab, this study requires timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to ensure subjects' safety.

An independent Data Monitoring Committee (DMC) will be assessing all potential safety signals and will be unblinded to treatment allocation. The DMC will review unblinded safety data on a cohort level, at a minimum of 6-month intervals throughout the course of the study. At the timing of this amendment, the DMC has provided recommendation that the study may continue without modification and allowed enrollment to begin for 16 - 17 year-olds. A patient information card with information of the symptoms and signs of hypersensitivity reactions, infusion related reactions as well as late stage reactions will be provided to the patients at Screening so that any such events once occurred will be reported immediately by the patients to the investigator.

Increases in major adverse cardiovascular events (MACE) including myocardial infarction, cerebrovascular accident, and cardiovascular death have been reported in drugs with similar mechanism of action to risankizumab (e.g., p40 inhibitors). However, the incidence of MACE has not been observed in longer term studies. While the likelihood of increased MACE is small, all suspected cardiovascular events (serious or nonserious) observed in this study will be adjudicated by an independent adjudication committee. An independent cardiac adjudication committee (CAC) will be adjudicating observed cardio- and cerebro-vascular events and will remain blinded to treatment allocation. In addition, an independent anaphylaxis adjudication committee (AAC) will be adjudicating observed potential anaphylactic events and will remain blinded to treatment allocation.

The benefit-risk profile is considered appropriate for an experimental therapy at this stage of clinical development.

In view of the COVID-19 pandemic, the benefit-risk profile of various immunomodulatory therapies on COVID-19 is being evaluated based on real world and clinical trial data. At this time, the effects of risankizumab on the course of COVID-19 are not well defined.

4.0 Study Objective

The objective of Study M16-006 is to evaluate the efficacy and safety of risankizumab versus placebo during induction therapy in subjects with moderately to severely active CD.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

The study was designed to enroll approximately 855 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled. In addition to the 855 subjects, up to 85 subjects with a lower SES-CD, defined as an eligibility SES-CD of ≥ 3 to < 6 for ileocolonic or colonic disease or SES-CD of 3 for isolated ileal disease will be enrolled in order to inform treatment effect in this patient population, but these subjects will not be included in the primary ITT population for efficacy analysis.

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of risankizumab as an induction therapy in subjects with moderately to severely active CD, defined as:

1. average daily stool frequency (SF) ≥ 4 (when calculating SF, only the number of liquid or very soft stools should be recorded) and/or average daily abdominal pain (AP) score ≥ 2; plus

2. endoscopic evidence of mucosal inflammation as measured by the Simple Endoscopic Score for CD (SES CD). All eligible scores exclude the presence of narrowing component and are confirmed by a central reader. Endoscopic activity is defined as SES-CD of ≥ 3.

The number of subjects enrolled with a SES-CD of ≥ 3 to < 6 for ileocolonic or colonic disease or SES-CD of 3 for isolated ileal disease will be no more than 85 subjects. Once cap of no more than 85 subjects is reached, enrollment criterion will be an eligibility SES-CD of ≥ 6 for ileocolonic or colonic disease, or eligibility SES-CD of ≥ 4 for isolated ileal disease.

All endoscopies will be centrally read to document eligibility and for assessment at the time points indicated in Appendix C.

The study will enroll both subjects who have had an inadequate response (IR) to prior biologic therapy (bio-IR) and subjects who have not (non-bio-IR).

The **bio-IR** population is defined as subjects with documented intolerance or inadequate response to one or more of the approved anti-TNF or anti-integrin biologics for CD (infliximab, adalimumab, certolizumab, vedolizumab, ustekinumab and/or natalizumab). The bio-IR population will be approximately 540 subjects.

The **non-bio-IR** population will include subjects who had an inadequate response or intolerance to conventional therapy. Conventional therapy is defined as one or more of the following: aminosalicylates, oral locally acting steroids (e.g., budesonide, beclomethosone), systemic corticosteroids (prednisone or equivalent), or immunomodulators. This population will also include subjects who have received biologic therapy in the past but stopped therapy based on reasons other than inadequate response or intolerance (e.g., change in reimbursement coverage, well-controlled disease). The non-bio IR population will be approximately 315 subjects.

The percent of subjects with exposure, including intolerance or inadequate response, to ustekinumab will be no more than 20%.

The study duration may be up to 49 weeks, including a Screening period of up to 35 days, a 12-week induction period, a 12-week Induction Period 2 for those subjects who do not achieve clinical response at Week 12, and a 140 day follow up period from the last dose of study drug.

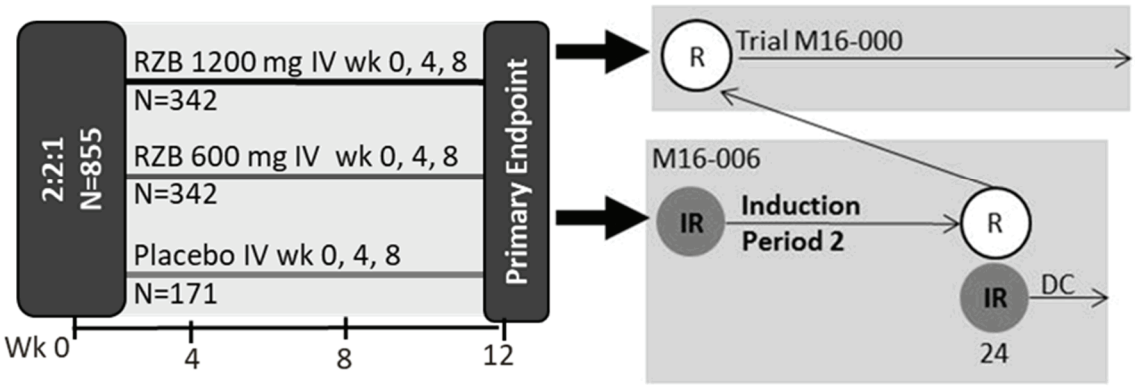
Visits for clinical evaluation will occur at Baseline, Weeks 4, 8, and 12/PD. Subjects, who do not achieve clinical response at Week 12 will be offered blinded induction therapy with risankizumab in Induction Period 2 with additional visits at Weeks 12, 16 and 20 and evaluation for clinical response at Week 24.

At the study visit indicated in Appendix C, all subjects will be provided with a subject diary where they will record CD related symptoms throughout the study. Subjects will also be dispensed the patient information card at Screening. Additionally, subjects will complete symptom, quality of life (QoL) and work productivity questionnaires throughout the study as indicated in Appendix C. Clinical labs including, but not limited to, urinalysis, chemistry and hematology, high sensitivity C-reactive protein (hs-CRP), serum risankizumab concentrations, and serum anti-drug antibody (ADA) levels may be collected. In addition, stool samples for calprotectin analysis will be collected and should be taken before starting bowel preparations for endoscopy. All endoscopies will be evaluated using SES-CD and will be confirmed by a central reader. Biopsy to confirm diagnosis (during Screening) or to rule out dysplasia/malignancy may be performed during the same time points as the endoscopy. Optional exploratory research samples may be taken during the study.

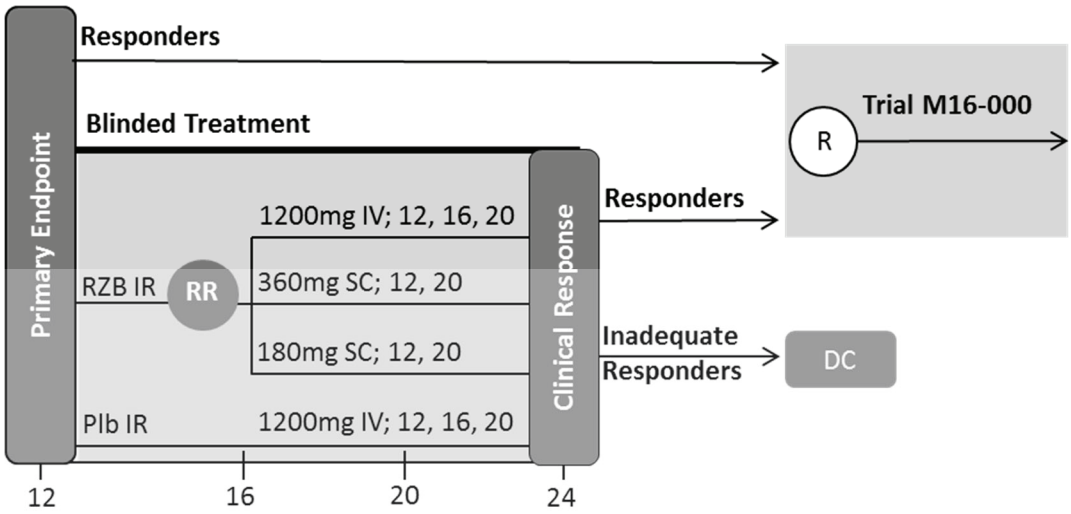
Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the study and randomized in a 2:2:1 ratio as shown in Figure 1. At the timing of this amendment, the DMC has provided recommendation that the study may continue without modification and allowed enrollment to begin for 16 - 17 year-olds.

Figure 1. Study M16-006 Study Schematic

a. 12-Week Induction Period



b. Induction Period 2



DC = discontinued; IR = subjects with inadequate clinical response to induction; IV = intravenous; R = subjects with clinical response; RR = re-randomize

Screening Period

Within 35 days prior to the Baseline visit, subjects will receive a full explanation of the study design and study procedures, provide a written informed consent, and undergo the screening procedures as outlined in Appendix C. Once written informed consent is obtained, subjects will undergo screening procedures.

The length of time between Screening and the Baseline visit must allow time for endoscopy central reading and lab results. The Screening period (35 days ± 7 days is granted around all study visits) may be extended as necessary after consultation with the AbbVie Therapeutic Area Medical Director (TA MD) for subjects who require initiation of prophylactic anti-TB therapy, or in case of external circumstances (e.g., due to the delay of availability of screening test results).

Laboratory values that are exclusionary can be re-tested once during the screening period upon discussion and clearance with TA MD. If the re-tested lab value(s) remain(s) exclusionary, the subject will be considered a screen failure. Redrawing samples if previous samples were unable to be analyzed would not count as a retest since the previous result was never obtained.

Clinical laboratory assessments as specified in Appendix C will only need to be repeated at Baseline if the time between Screening and Baseline is > 14 days, or if the subject's health status has changed to warrant a repeat test.

All subjects need to have their average daily SF, average daily AP, and CDAI calculated and meeting eligibility criteria before randomization at Baseline.

12-Week Induction Period

At the Baseline visit, subjects who meet all the inclusion criteria and none of the exclusion criteria described in Section 5.2.1 and Section 5.2.2 will be enrolled into the study and randomized to the double-blind induction period where they will receive either risankizumab 1200 mg IV, risankizumab 600 mg IV, or placebo, given at Baseline and

Weeks 4 and 8. The randomization at Baseline will be stratified by number of prior biologics failed (0, 1, > 1), steroid use at Baseline (yes, no), and Baseline SES-CD (original, alternative).

During this period of the study, subjects will visit the study site at Weeks 4, 8 and 12/PD. Subjects who do not achieve clinical response at Week 12 and choose to continue in the study will have additional visits at Weeks 16, 20 and 24 for blinded Induction Period 2 with risankizumab. A ± 7-day window is permitted around scheduled study visits. An effort will be made to bring subjects back to their original scheduled visit (calculated from Baseline) if they are out of the visit window.

At the Week 12/PD visit, all subjects will undergo an endoscopy for evaluation of mucosal inflammation. It is expected that all subjects who remain in the study through at least Week 8 will have a Week 12/PD endoscopy. All subjects achieving clinical response, defined as ≥ 30% decrease in average daily SF and/or ≥ 30% decrease in average daily AP score (both not worse than Baseline) at Week 12 may be eligible to enter Study M16-000. Subjects are not eligible to enter Study M16-000 until endoscopy has been completed (local reader results will be used for stratification for Study M16-000).

All subjects who do not achieve clinical response at Week 12 will be able to receive blinded risankizumab in Induction Period 2, as specified below. Subjects are not eligible to receive blinded Induction Period 2 therapy until endoscopy has been completed.

Induction Period 2

At Week 12, subjects who do not achieve clinical response will be randomized by Interactive Response Technologies (IRT) to Induction Period 2, a double-blind, double-dummy 12-week treatment period.

Subjects who received risankizumab induction treatment will be randomized 1:1:1 to:

- Group 1: 1200 mg IV risankizumab

- Group 2: 360 mg SC risankizumab
- Group 3: 180 mg SC risankizumab

Subjects who received placebo induction treatment will receive:

- Group 4: 1200 mg IV risankizumab

The IV risankizumab dose or matching IV placebo will be given at Weeks 12, 16, and 20. The SC risankizumab dose or matching SC placebo will be given at Weeks 12, and 20.

At Week 24, subjects who participated in the blinded Induction Period 2 will be reassessed and undergo a third endoscopy for evaluation of mucosal inflammation. Subjects who achieve clinical response at Week 24 may be eligible to enter Study M16-000. Subjects without clinical response at Week 24, as well as all subjects who terminate the study early (including subjects who are eligible for but do not participate in the blinded Induction Period 2), will be discontinued and have a follow-up call 140 days from the last dose of study drug to obtain information on any new and/or ongoing AEs.

Concomitant aminosalicylates, corticosteroids, immunomodulators (azathioprine [AZA], 6-mercaptopurine [6-MP], methotrexate [MTX]), and/or CD-related antibiotics

Subjects taking aminosalicylates, immunomodulators, and/or CD-related antibiotics at Baseline must continue their concomitant treatment for the duration of the study. Initiating and/or increasing doses of aminosalicylates, immunomodulators, and/or CD-related antibiotics during the study is prohibited. Decreasing doses of aminosalicylates, immunomodulators, and/or CD-related antibiotics is prohibited during the study, except in the event of moderate-to-severe treatment related toxicities and after discussion with the AbbVie Therapeutic Area Medical Director (TA MD). CD-related antibiotics may be discontinued in Induction Period 2 at the discretion of the Investigator.

Note: the duration of the study includes Induction Period 2.

Concomitant Corticosteroids

Subjects taking corticosteroids at Baseline must continue their concomitant treatment at the Baseline dose for the duration of the 12-week induction period. Initiation and/or increasing doses of systemic and/or CD related corticosteroids during the entire study is prohibited. Decreasing doses of corticosteroids is prohibited during the 12-week induction period, except in the event of moderate-to-severe treatment related toxicities and after discussion with the AbbVie Therapeutic Area Medical Director (TA MD).

Subjects who receive blinded therapy in Induction Period 2 during Weeks 12 to 24 will be allowed to taper their corticosteroids at the discretion of the Investigator. While stopping the taper is permitted, increasing doses above the Baseline dose is prohibited.

Follow-Up Period/Premature Discontinuation (PD)

Subjects may discontinue treatment at any time during the study participation (Section 5.4). Subjects who end study participation early will have a PD visit and complete the procedures outlined for the PD visit in Appendix C as soon as possible after the last dose of study drug and preferably prior to the administration of any new therapies.

Subjects who discontinue the study or subjects who complete the Week 12/Week 24 visit and do not roll-over into Study M16-000 will have a follow-up call 140 days from the last dose of study drug to obtain information on any new or ongoing AEs.

Re-Screen

Subjects who initially screen fail for the study may be permitted to re-screen following re-consent. The subject must meet all the inclusion and none of the exclusion criteria at the time of re-screening in order to qualify for the study. There is no minimum period of time a subject must wait to re-screen for the study.

If the subject had a complete initial screening evaluation including the TB test, Hepatitis B virus (HBV), Hepatitis C virus (HCV), human immunodeficiency virus (HIV) and electrocardiogram (ECG), these tests will not be required to be repeated for

re-screening provided the conditions noted in Section 5.3.1.1 are met and no more than 90 days have passed since the collection date of the testing.

If a subject is being rescreened within 14 days (≤ 14 days have passed) from the collection date of the previous screening testing, it is not required to repeat Screening testing for chemistry/hematology, urinalysis, serum pregnancy, and C. *difficile* provided that the subject's health status has not changed to warrant a repeat test. In this case, all Baseline testing should be performed at the Baseline visit.

If rescreening occurs more than 14 days (> 14 days have passed) from the collection date of the previous screening testing then new samples (chemistry/hematology, urinalysis, serum pregnancy, and C. *difficile*) should be collected during Rescreening. In this case, chemistry/hematology, urinalysis do not need to be repeated at the Baseline visit if Baseline occurs within 14 days (≤ 14 days) from the date of rescreening testing provided that the subject's health status has not changed to warrant a repeat test.

All subjects need to have their average daily SF, average daily AP, and CDAI calculated in order to verify eligibility criteria before randomization at Baseline.

An endoscopy with biopsy will not be required to be repeated for re-screening provided the conditions noted in Section 5.3.1.1 are met and the endoscopy is within 45 days of the Baseline visit. Sites may contact the AbbVie TA MD if there are questions on if subjects should or should not be re-screened.

5.2 Selection of Study Population

It is anticipated that approximately 855 subjects with active moderate to severe CD will be enrolled at approximately 400 sites worldwide. Both non-bio-IR and bio-IR subjects will be included. The bio-IR population will be a minimum of approximately 540 subjects and the non-bio-IR population will be a minimum of approximately 315 subjects.

A subject may be enrolled in this study provided that he/she has met all of the inclusion criteria and none of the exclusion criteria specified in this protocol.

5.2.1 Inclusion Criteria

1. Male or female aged ≥ 18 to ≤ 80 years, or minimum age of adult consent according to local regulations, at the Baseline Visit. Where locally permissible, subjects 16 to < 18 years of age who meet the definition of Tanner stage 5 for development (refer to Appendix J) at the Baseline Visit (sites will be notified when adolescents may enroll).
2. Confirmed diagnosis of CD for at least 3 months prior to Baseline. Appropriate documentation of biopsy results consistent with the diagnosis of CD, in the assessment of the Investigator, must be available.
3. Crohn's disease activity index (CDAI) score 220 – 450 at Baseline.
4. Endoscopic evidence of mucosal inflammation as documented by the SES-CD of ≥ 3. All eligible scores exclude the presence of narrowing component and are confirmed by a central reader. (Once cap of no more than 85 subjects is reached, enrollment criterion will be an SES-CD of ≥ 6 for ileocolonic or colonic disease or SES-CD of ≥ 4 for isolated ileal disease.)
5. Average daily SF ≥ 4 and/or average daily AP score ≥ 2 at Baseline.
6. Demonstrated intolerance or inadequate response to one or more of the following categories of drugs: aminosalicylates, oral locally acting steroids, systemic steroids (prednisone or equivalent), immunomodulators, and/or biologic therapies
    - Demonstration of intolerance requires no minimum dose or duration of use (intolerance includes patients with a known TPMT genetic mutation or low activity).
    - Inadequate response is defined as outlined below:
        - Oral aminosalicylates (e.g., mesalamine, sulfasalazine, olsalazine, balsalazide):

- Signs and symptoms of persistently active disease, in the opinion of the Investigator, during a current or prior course of at least 4 weeks of treatment with 2.4 g/day mesalamine, 4 g/day sulfasalazine, 1 g/day olsalazine, or 6.75 g/day balsalazide,

○ Oral locally acting steroids (e.g., budesonide, beclomethasone):

- Signs and symptoms of persistently active disease in the opinion of the Investigator, during or after a course of at least 4 weeks of treatment with 9 mg/day budesonide or 5 mg/day beclomethasone,

  or

- Inability to taper oral budesonide to at or below 6 mg/day without recurrent active disease,

○ IV or Oral systemic steroids (prednisone or equivalent):

- Signs and symptoms of persistently active disease in the opinion of the Investigator, during or after tapering of at least one regimen consisting of a dose equivalent to prednisone ≥ 40 mg/day orally for 3 weeks or intravenously for 1 week,
- or
- Inability to taper oral systemic steroids at or below a dose equivalent to prednisone 10 mg/day without recurrent active disease,

○ Immunomodulators:

- Signs and symptoms of persistently active disease in the opinion of the Investigator, during a current or prior course of at least 90 days of treatment with one or more of the following:
  - AZA: ≥ 2.0 mg/kg/day rounded to the nearest available tablet or half tablet formulation (≥ 1 mg/kg/day for subjects in Japan, Korea, Hong Kong, Taiwan, Singapore, or China) (or a documented 6-TGN level of ≥ 230 pmol/8 × 10^8 RBC)
  - 6-MP: ≥ 1 mg/kg/day rounded to the nearest available tablet or half tablet formulation (≥ 0.6 mg/kg/day for subjects in Japan, Korea, Hong Kong, Taiwan, Singapore, or China) (or a 6 TGN level of ≥ 230 pmol/8 × 10^8 RBC)
  - MTX: ≥ 15 mg/week subcutaneous (SC) or intramuscular (IM)

- *Note:* Oral MTX use is allowed during the study, however prior or current use of oral MTX is not sufficient for inclusion into the study

- Biologic therapies for CD:
  - Signs and symptoms of persistently (in the opinion of the Investigator) active disease despite a history of one or more of the following:
    - At least one 6-week induction regimen of infliximab (≥ 5 mg/kg IV at Weeks 0, 2, and 6),
    - At least one 4-week induction regimen of adalimumab (one 160 mg SC dose at Week 0, followed by one 80 mg SC dose at Week 2 [or one 80 mg SC dose at Week 0, followed by one 40 mg SC dose at Week 2, in countries where this dosing regimen is approved]),
    - At least one 4-week induction regimen of certolizumab pegol (400 mg SC at Weeks 0, 2, and 4),
    - At least one 6-week induction regimen of vedolizumab (300 mg IV at Weeks 0, 2, and 6),
    - At least one 12-week induction regimen of natalizumab (300 mg IV every 4 weeks)
    - At least one 8-week induction regimen of ustekinumab [260 mg (≤ 55 kg) or 390 mg (> 55 to ≤ 85 kg) or 520 mg (> 85 kg) IV, followed by 90 mg SC at Week 8] (Once cap of no more than 20% ustekinumab exposed subjects is reached, subjects with prior ustekinumab exposure will not be allowed to enroll.)
  - Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit of the above biologics
  - Note: Subjects who discontinued biologics for reasons other than inadequate response as defined above or intolerance (e.g., change of insurance) must meet the criteria for intolerance or inadequate response to aminosalicylates, oral locally acting steroids, systemic steroids (prednisone or equivalent), and/or immunomodulators as defined above

7. If female, subject must meet the criteria as stated in Section 5.2.4 of this protocol *Contraception Recommendations.* Females of childbearing potential must have a

negative serum pregnancy test result during Screening, and a negative urine pregnancy at Baseline. Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) during Screening do not require pregnancy testing at Baseline.

Note: Subjects with borderline serum pregnancy test at Screening must have a serum pregnancy test ≥ 3 days later to document continued lack of a positive result.

8. Subject must be able and willing to give written informed consent and to comply with the requirements of this study protocol. In Japan, if the subject is < 20 years old, a subject's parent or legal guardian must be willing to give written informed consent.

Rationale for Inclusion Criteria

1 – 6	To select the adequate subject population with a disease status representative of the target population for evaluation
7	The impact of risankizumab on pregnancy and reproduction is unknown
8	In accordance with harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

1. Subject with a current diagnosis of ulcerative colitis or indeterminate colitis.

Concomitant Medications and Treatments

2. Subject on CD-related antibiotics who has not been on stable doses for greater than, or discontinued within, 14 days prior to Baseline.
3. Subject on oral aminosalicylates who has not been on stable doses for greater than, or discontinued within, at least 14 days prior to Baseline.
4. Subject taking oral corticosteroids:
   - Budesonide > 9 mg/day
   - Beclomethasone > 5 mg/day

- Prednisone or equivalent > 20 mg/day
- Or has not been on the current course for ≥ 14 days prior to Baseline and on a stable dose for ≥ 7 days prior to Baseline

5. Subject on immunomodulators (AZA, 6-MP, MTX) who:
   - Has not been on the current course for ≥ 42 days prior to Baseline, and
   - Has not been on a stable dose for ≥ 35 days prior to Baseline

Medications and Treatments **During** the Screening Period

6. Subject who received IV anti-infectives within 35 days prior to Baseline visit or oral/intramuscular anti-infectives (non-CD-related) within 14 days prior to the Baseline visit. This does not apply to TB prophylaxis.
7. Subject who received exclusive enteral nutrition or any parenteral nutrition within 35 days prior to Baseline.
8. Subject who received any live bacterial or viral vaccination within 30 days (8 weeks for Japan) prior to Screening or during the Screening Period.
9. Subject who received cyclosporine, tacrolimus, or mycophenolate mofetil within 35 days prior to Baseline.
10. Subject who received fecal microbial transplantation within 35 days prior to Baseline.

Prior Medications and Treatments

11. Subject who received any:
    - approved biologic agent: infliximab, adalimumab, certolizumab, vedolizumab, natalizumab within 8 weeks prior to Baseline or ustekinumab within 12 weeks prior to Baseline, or

      Note: If there is proper documentation of an undetectable drug level measured by a commercially available assay for any of the approved biologics above, there is no minimum washout prior to Baseline.
    - any investigational biologic or other agent or procedure within 35 days or 5 half-lives prior to Baseline, whichever is longer.

12. Subject with prior exposure to p19 inhibitors (e.g., risankizumab)
13. Subject has been taking combination of two or more of the following: oral budesonide, or oral beclomethasone and/or oral prednisone (or equivalent) simultaneously, with the exception of inhalers, within 14 days prior to Screening or during the Screening period.
14. Subject who received IV/intramuscular corticosteroids within 14 days prior to Screening or during the Screening period.
15. Subject who received therapeutic enema or suppository, other than required for endoscopy, within 14 days prior to endoscopy used for Screening or during the Screening period.
16. Subject who received apheresis (e.g., Adacolumn apheresis) ≤ 60 days prior to Screening or during the Screening period.
17. Subject who has concomitant cannabis use either recreational or for medical reasons within 14 days of Baseline or any history of clinically significant drug, or alcohol abuse in the last 12 months.

<u>CD Related</u>

18. Subject with currently known complications of CD such as:
    - abscess (abdominal or perianal),
    - symptomatic bowel strictures,
    - > 2 missing segments of the following 5 segments: terminal ileum, right colon, transverse colon, sigmoid and left colon, and rectum
    - fulminant colitis,
    - toxic megacolon,
    - or any other manifestation that might require surgery while enrolled in the study.
19. Subject with ostomy or ileoanal pouch.
20. Subject diagnosed with short gut or short bowel syndrome.

21. Subject with surgical bowel resection within the past 3 months prior to Baseline, or a history of ≥ 3 bowel resections.

Safety

22. Subject who has a known hypersensitivity to risankizumab or the excipients of any of the study drugs or the ingredients of Chinese hamster ovary (CHO).

23. Subjects with the following chronic or active infections:

- Active, chronic, or recurrent infection that based on the Investigator's clinical assessment makes the subject unsuitable candidate for the study,
- Infection with C. difficile toxin or other intestinal pathogen during Screening,
- Are infected with human immunodeficiency virus (HIV),
- QuantiFERON®-TB test or Purified Protein Derivative (PPD) skin test, or both, according to local guidelines, will be performed during Screening. QuantiFERON®-TB test is preferred for subjects who received Bacillus Calmette-Guérin (BCG) vaccination or were exposed to other Mycobacteria species. Subjects with a positive test result (or indeterminate results that have been repeated) may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active tuberculosis. Subjects with a history of active TB who have documented completion of a full course of anti-TB therapy may be allowed to enter the study after consultation with the AbbVie TA MD. If latent TB is established, TB prophylaxis/treatment should be initiated and maintained according to local country guidelines.
- Have active hepatitis B or hepatitis C defined as:
  - HBV: hepatitis B surface antigen (HBs Ag) positive (+), or detected sensitivity on the HBV deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) qualitative test for hepatitis B core antibody (HBc Ab) positive subjects;
  - HCV: HCV ribonucleic acid (RNA) detectable in any subject with positive anti-HCV antibody (HCV Ab)

24. Subject with a previous history of dysplasia of the gastrointestinal tract or found to have dysplasia, other than completely removed low-grade dysplastic lesions, in any biopsy performed during the Screening endoscopy.

25. Subject with a known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly.

26. Subject with current or previous history of malignancy other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix.

27. Subject who has severe, progressive, or uncontrolled renal, hepatic, hematological, endocrine, disorder or symptoms thereof.

28. Female subjects who is pregnant, breastfeeding, or is considering becoming pregnant during the study or for approximately 140 days after the last dose of study drug.

29. Subject who has any condition, including any physical, psychological, or psychiatric condition, which in the opinion of the Investigator, would compromise the safety of the subject or the quality of the data and renders the subject an unsuitable candidate for the study.

30. Screening laboratory and other analyses show any of the following abnormal results:

    - Aspartate transaminase (AST), alanine transaminase (ALT) > 2 × upper limit of the reference range;
    - White blood cell (WBC) count < 3.0×10^9/L;
    - Total bilirubin ≥ 2 mg/dL; except for subjects with isolated elevation of indirect bilirubin relating to Gilbert syndrome;
    - Estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula < 30 ml/min/1.73 m^2.
    - Hemoglobin < 8 g/dL

- Platelets < 100,000/μL
- Positive serum pregnancy test at the Screening visit or positive urine pregnancy test at the Baseline visit.

Laboratory values can be re-tested once during the screening period after discussion and clearance with the TA MD. If the re-tested lab value(s) remain(s) exclusionary, the subject will be considered a screen failure. Redrawing samples if previous samples were unable to be analyzed would not count as a retest since the previous result was never obtained

31. No known active COVID-19 infection. Subject must not have signs/symptoms associated with COVID-19 infection.

Subjects who do not meet COVID-19 eligibility criteria must be screen failed and may only rescreen after they meet the following COVID-19 viral clearance criteria:

- Symptomatic subjects: At least 2 negative viral tests in a row completed locally, ≥ 24 hours apart after at least 10 days have passed since recovery, defined as resolution of fever without use of antipyretics and improvement in respiratory symptoms (e.g., cough, shortness of breath)
- Asymptomatic subjects: At least 2 negative viral tests in a row completed locally, ≥ 24 hours apart after at least 10 days have passed since prior positive result (Note: subjects who develop symptoms will follow guidance above for symptomatic subjects)

Frequency or timing of COVID-19 testing and interval between testing for the above viral clearance criteria may be adjusted to account for epidemiological trends, updated information regarding infectivity and local/institutional guidelines.

Rationale for Exclusion Criteria

1	To avoid medical conditions that may compromise the ability to identify subjects with the correct diagnosis or to interpret medical importance of clinical results
2 – 17	To avoid bias for the evaluation of efficacy and safety by concomitant use of other medications or treatments and to ensure the safety of the subject

18 – 21	To avoid complications of CD that may compromise the evaluations of efficacy and safety
22 – 31	To ensure the safety of the subject and or others

5.2.3 Prior and Concomitant Therapy

5.2.3.1 Prior Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject has received within 35 days prior to Baseline, is receiving at the time of enrollment, or continues during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency in source documents and the (electronic case report forms) eCRFs.

CD specific medications (including but not limited to corticosteroids, aminosalicylates, immunomodulators [AZA, 6-MP, or MTX], and CD-related antibiotics) that the subject has received within 90 days of Baseline should be recorded on the appropriate page of the eCRF and should include the dates of administration and dosages. In addition, if a subject has ever received AZA, 6-MP, or MTX (oral or IM/SC), the duration of therapy, maximum dose, reason for use and reason(s) for termination of treatment will also be recorded in the appropriate eCRF.

For all subjects with a history of biologic use for inflammatory bowel disease, the history of previous use (including the names of biologic therapy used, duration of therapy, the highest known dose taken, reason for use and reason[s] for termination of treatment of the biologic agent will be recorded in the appropriate eCRF.

The AbbVie TA MD identified in Section 6.1.5 should be contacted if there are any questions regarding concomitant or prior therapy(ies).

5.2.3.2 Concomitant Therapy

Subjects taking aminosalicylates, immunomodulators, and/or CD-related antibiotics at Baseline must continue their concomitant treatment for the duration of the study. Initiating and/or increasing doses of aminosalicylates, immunomodulators, and/or CD-related antibiotics during the study is prohibited. Decreasing doses aminosalicylates, immunomodulators, and/or CD-related antibiotics is prohibited during the study, except in the event of moderate-to-severe treatment related toxicities and after discussion with the AbbVie TA MD. CD-related antibiotics may be discontinued in the blinded Induction Period 2 at the discretion of the Investigator.

Note: the duration of the study includes the Induction Period 2.

Concomitant Corticosteroids

Subjects taking corticosteroids at Baseline must continue their concomitant treatment at the Baseline dose for the duration of the 12-week induction period. Initiation and/or increasing doses of systemic and/or CD related corticosteroids during the entire study is prohibited. Decreasing doses of corticosteroids is prohibited during the 12-week induction period, except in the event of moderate-to-severe treatment related toxicities and after discussion with the AbbVie TA MD.

Subjects who receive blinded therapy in Induction Period 2 during Weeks 12 to 24 will be allowed to taper their corticosteroids at the discretion of the Investigator. While stopping the taper is permitted, increasing doses above the Baseline dose is prohibited.

Subjects may not be on both budesonide and prednisone (or equivalent) simultaneously, with exception of inhalers within 14 days prior to Screening.

Setons are authorized as concomitant therapy in subjects with perianal fistulas and should be documented in the eCRF under concomitant medications.

Changes in all concomitant medications will be assessed at each study visit from Baseline through Week 12/PD and during Weeks 12 to 24 visits for subjects who participate in the

blinded Induction Period 2. Any changes will be documented in the source documents and captured on the appropriate eCRF page.

Subjects should not be routinely pre-medicated prior to infusion of study drug. If in the Investigator's judgment the subject requires pre-medication based on prior medical history or symptoms with prior infusions of study drug in the current study, the AbbVie TA MD should be contacted regarding possible permitted pre-medication with diphenhydramine hydrochloride and acetaminophen (or equivalents). Individual dosage, timing, and route of administration would be determined by the Investigator. Any pre-medications administered must be recorded on the appropriate eCRF.

The AbbVie TA MD identified in Section 6.1.5 should be contacted if there are any questions regarding concomitant or prior therapy(ies).

5.2.3.3 Prohibited Therapy

- The following are prohibited medications during the study:
  - All biologic therapy with a potential therapeutic impact on the disease being studied including but not limited to the following:
  - Etanercept (Enbrel®);
  - Abatacept (Orencia®);
  - Anakinra (Kineret®);
  - Rituximab (Rituxan®);
  - Natalizumab (Tysabri®);
  - Tocilizumab (Actemra®);
  - Ustekinumab (Stelara®);
  - Belimumab (Benlysta®);
  - Infliximab (Remicade®);
  - Certolizumab pegol (Cimzia®);
  - Golimumab (Simponi®);
  - Adalimumab (Humira®)
  - Vedolizumab (Entyvio®);

- Investigational agents (e.g., tofacitinib, baracitinib, filgotinib)
- Live or attenuated vaccines are NOT allowed during the study and for 140 days after the last dose of study drug. Examples of such vaccines include but are not limited to the following:
  - live attenuated influenza
  - herpes zoster (e.g., Zostavax®)
  - rotavirus
  - varicella (chicken pox)
  - measles-mumps-rubella (MMR) or measles mumps rubella varicella (MMRV)
  - oral polio vaccine (OPV)
  - smallpox
  - yellow fever
  - Bacille Calmette-Guérin (BCG)
  - oral typhoid
- Cyclosporine, tacrolimus, or mycophenolate mofetil.
- Concomitant cannabis use either recreational or for medical reasons.
- Rectal therapy with any therapeutic enemas or suppositories, with the exception of those required for endoscopy, is prohibited during the study.
- Apheresis (e.g., Adacolumn apheresis).
- Exclusive enteral nutrition or any parenteral nutrition.

The AbbVie TA MD identified in Section 6.1.5 should be contacted if there are any questions regarding prohibited therapy.

5.2.4 Contraception Recommendations

If female, subject must be either postmenopausal defined as:

- Age ≥ 55 years with no menses for 12 or more months without an alternative medical cause.

- Age < 55 years with no menses for 12 or more months without an alternative medical cause AND an Follicle-Stimulating Hormone (FSH) level > 40 IU/L.

OR,

- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

OR, for women of childbearing potential (WOCBP):

- Practicing at least one of the following methods of birth control, prior to Baseline through at least 140 days after the last dose of study drug.
  - Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal, injectable) associated with the inhibition of ovulation, (must start at least 1 month prior to study.
  - Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, (must start at least 1 month prior to study).
  - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
  - Vasectomized sexual partner(s) (the vasectomized partner should have received medical assessment of the surgical success and is the sole sexual partner of trial participant).
  - Intrauterine device (IUD).
  - Intrauterine hormone-releasing system (IUS).
  - True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

5.3 Efficacy, Pharmacokinetic, Pharmacodynamic, Optional Exploratory Research/Validation Studies and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures described are listed in the following section of this protocol and are summarized in tabular format in Appendix C.

5.3.1.1 Study Procedures

The study procedures outlined in Appendix C are discussed in detail in this section, with the exception of the optional exploratory research/validation studies (discussed in Section 5.3.1.2 and Appendix D), pharmacokinetics and pharmacodynamics (discussed in Section 5.3.2), and the collection of AE information (discussed in Section 6.1.4). All study data will be recorded in source documents and on the appropriate eCRFs.

Study visits may be impacted by changes in local regulations due to the COVID-19 pandemic. This may include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study.

Informed Consent

At the Screening visit, the subject will sign and date a study specific, Independent Ethics Committee (IEC)/Independent Review Board (IRB) approved, informed consent form before any study procedures are performed or any medications are withheld from the subject in order to participate in this study. A separate informed consent will be required for each subject in order to participate in the optional exploratory research/validation studies. Details regarding how informed consent will be obtained and documented are provided in Section 9.3.

Due to the COVID-19 pandemic, modifications to the protocol may be necessary. Subjects should be informed of the changes to the conduct of the study relevant to their participation (e.g., cancellation of visits, change in laboratory testing site, etc.). Documentation of this notification or verbal consent should be maintained at the site as required per local regulatory requirements. A signed and dated informed consent form should be obtained from the subject afterwards as soon as possible.

Inclusion/Exclusion Criteria

Subjects will be evaluated to ensure they meet all inclusion criteria and have none of the exclusion criteria at both Screening and Baseline visits.

Medical and Surgical History

A complete medical and surgical history, including CD-onset date, history of CD medication use, and history of alcohol and tobacco use will be obtained from each subject at the Screening visit. An updated medical history will be obtained prior to study drug administration at Baseline, to ensure the subject is still eligible for enrollment, and updated as necessary.

Information on prior biologic, corticosteroid, immunomodulators (i.e., AZA, 6-MP, MTX), CD-related antibiotics, aminosalicylate or any other physician prescribed therapy for CD use will be obtained as outlined in Section 5.2.3.1.

A detailed medical history with respect to TB exposure will be documented. This information will include BCG vaccination, cohabitation with individuals who have had TB, and residence or work in TB endemic locations. Subjects with active TB (during Screening) or documented history of active TB who have documented completion of a full course of anti-TB therapy may be allowed to enter the study after consultation with the AbbVie TA MD. TB history and anti-TB therapy needs to be documented in the source documents and eCRFs.

Physical Examination

A physical examination including evaluation of extra intestinal manifestations (EIMs) will be performed at the designated study visits as specified in Appendix C.

A full physical examination will be performed as outlined in Appendix C. Physical examinations at all other visits (including unscheduled visits) are symptom based and should include the assessment of EIMs as part of calculating the Crohn's disease activity index (CDAI). The number of cutaneous fistulas should be recorded, including the number of fistulas draining upon gentle compression. Fistulas will be classified as abdominal or perianal/anal. Physical exam abnormalities noted by the Investigator at Baseline (including fistulas and fissures) will be recorded in the subject's medical history.

Abnormalities noted after the Baseline visit will be evaluated and documented by the Investigator as to whether they are AEs.

Additionally, physical examination findings that are related to or part of each subject's medical history will be captured on the appropriate medical history eCRFs.

Vital Signs

Vital sign determinations of systolic and diastolic blood pressure in sitting position, pulse rate, respiratory rate, and body temperature will be obtained at each visit. Blood pressure, pulse rate, and respiratory rate should be measured before blood draws are performed.

Height will be measured at the Screening visit only (with shoes off) for subjects ≥ 18 years of age. Height will be re-measured at Week 12 and Week 24 (if applicable) for subjects < 18 years of age at Baseline. Body weight will be measured at all scheduled visits, as specified in Appendix C. All measurements will be recorded in metric units where applicable.

TB Testing

All subjects will be tested for TB by either the QuantiFERON-TB Gold Test (or equivalent) or a TB Skin Test (PPD), or both, according to local guidelines, as specified in Appendix C.

For subjects treated with corticosteroids (equivalent to Prednisone 5 mg or above – with ongoing treatment or treatment within 1 month prior to TB screening), an Interferon-Gamma Release Assay (IGRA; QuantiFERON-TB Gold In-Tube test) must be performed during the Screening Period for all subjects including those with a prior history of Bacille Calmette-Guérin (BCG) administration or who were exposed to other Mycobacteria species.

For subjects NOT treated with corticosteroids (equivalent to Prednisone 5 mg or above – with ongoing treatment or treatment within 1 month prior to TB screening), a PPD skin test (alternatively, also known as tuberculin skin test) must be placed, or alternatively an Interferon-Gamma Release Assay (IGRA; QuantiFERON-TB Gold In-Tube test or T-SPOT TB test) must be performed during the Screening Period for all subjects. IGRA is preferred for subjects with a prior history of Bacille Calmette-Guérin (BCG) administration or who were exposed to other Mycobacteria species.

If PPD and/or the QuantiFERON®-TB Gold test (or IGRA equivalent) is positive, or if there is a repeat indeterminate (note: the first indeterminate results must be repeated) QuantiFERON®-TB Gold test (or IGRA equivalent) upon retesting, subjects may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. Subjects with a history of active TB who have documented completion of a full course of anti-TB therapy may be allowed to enter the study after consultation with the AbbVie TA MD. If active TB is diagnosed, the subject may not enroll in the study. If presence of latent tuberculosis is established, then tuberculosis prophylaxis should be initiated and maintained according to local country guidelines. It is also necessary to report the latent TB or positive TB testing in the source documents and eCRFs.

- QuantiFERON®-TB Gold Test is the preferred method which will be analyzed by the central laboratory (QuantiFERON test is preferred over TB Skin Test). However, if other IGRA equivalent tests are used, these may be performed by a certified local laboratory at the Investigator's discretion.
- If the QuantiFERON®-TB Gold Test is NOT possible (or if both the QuantiFERON®-TB Gold Test and the PPD Skin Test are required per local guidelines) the PPD Skin Test will be performed according to standard clinical practice.
    - The PPD Skin Test should be read by a licensed healthcare professional between 48 and 72 hours after administration. A subject who does not return within 72 hours will need to be rescheduled for another skin test.
    - The reaction will be measured in millimeters (mm) of induration and induration ≥ 5 mm is considered a positive reaction. The absence of induration will be recorded as "0 mm" not "negative."
- If PPD and/or the QuantiFERON®-TB Gold test (or IGRA equivalent) is positive, or if there is a repeat indeterminate QuantiFERON®-TB Gold test (or IGRA equivalent) upon retesting, subjects may continue in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active tuberculosis.
- If presence of latent tuberculosis is established, TB prophylaxis/treatment should be initiated and maintained according to local country guidelines.
- Subjects who have had an ulcerating reaction to the TB Skin Test in the past should not be re-exposed and should not be tested by a PPD skin test.
- In the case of a tuberculosis-related AE, a supplemental eCRF that provides additional information should be completed by the Investigator or designee.

If a CXR or other diagnostic tests are required to be performed to assess TB per local guidelines, this information will also be captured on the appropriate eCRF.

12-Lead Electrocardiogram (ECG)

A resting 12-lead ECG will be performed during Screening as specified in Appendix C. A qualified physician will interpret the clinical significance of any abnormal finding, sign,

and date each ECG. ECG findings, including any clinically significant findings will be documented in the source documents and later transcribed on to the appropriate eCRF. Each signed original ECG will be monitored by the responsible clinical research associate (CRA) and kept with subject's source documents onsite.

For subjects with a normal ECG taken within 90 days of Screening, a repeat ECG at Screening will not be required, provided source documentation is available. If there are other findings that are clinically significant, the Investigator must bring this to the attention of the AbbVie TA MD before the subject can be enrolled.

Subjects can have a repeat ECG at any time during the study as warranted, based on the opinion of the Investigator.

Clinical Laboratory Tests

Blood samples will be obtained for the laboratory tests listed in Table 1. Blood draws should be performed, as much as possible, after vital signs, efficacy assessments and questionnaires (CDAI, IBDQ, etc.) are obtained and before study drug administration during a visit.

A certified central laboratory will be utilized to process and provide results for the clinical laboratory tests. All abnormal laboratory tests that are considered clinically significant by the Investigator will be followed to a satisfactory resolution.

The central laboratory chosen for this study will provide instructions regarding the collection, processing and shipping of these samples.

For serum chemistry tests and some exploratory biomarker tests, it is preferred that the subject has fasted (8 hours, except for water) prior to sample collection, however it is not required. It must be recorded whether the subject has fasted or not at the time of collection in the laboratory request, source document, and eCRF.

If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from having blood drawn for laboratory testing at the study site, if possible, arrange for subjects to have laboratory work done at a local lab, hospital, or other facility. Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. Local lab results should be reviewed by the investigator as soon as possible.

If laboratory samples cannot be obtained, study drug administration may be continued provided the investigator has reviewed all prior laboratory results and confirms and discusses with the subject that there is no safety concern for the subject to continue use of the study drug in the absence of current labs.

Table 1. Clinical Laboratory Tests

Hematology	**Clinical Chemistry**[a]	**Screening Blood Tests**
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count WBC Differential Platelets Coagulation: INR[c]	General: Sodium Potassium Chloride Bicarbonate (CO_2) Urea (BUN) Creatinine Glucose Additional Chemistry Tests: Calcium Phosphate Total Protein Albumin Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline Phosphatase Gamma-Glutamyl Transferase (GGT/γ-GT) Bilirubin Total and Direct Lipid Panel: Cholesterol (total, LDL, and HDL) Triglycerides Additional Calculations: eGFR by simplified 4-MDRD (estimated by CKD-EPI formula; for Japan)[d]	HBs Ag HBs Ab HBc Ab HBV DNA PCR reflex only HCV Ab HCV RNA reflex only QuantiFERON-TB Gold or PPD Test HIV-1 and HIV-2
Urinalysis[b]		**Other Laboratory Tests:**
Leukocyte esterase Nitrite pH Protein Blood Specific Gravity Ketones Glucose Bilirubin		Serum pregnancy (bHCG) test Urine pregnancy test (Local) Optional: FSH, if needed to confirm postmenopausal status Tryptase[e] Histamine[e]
Stool Samples:		**Biomarkers:**
C. difficile toxin Fecal calprotectin (FCP)		High-Sensitivity C-Reactive Protein (hs-CRP)
PK/Immunogenicity:		**Optional Biomarkers:**
Serum risankizumab[e] Serum anti-drug antibodies (ADA)[e] Serum neutralizing antibodies (nAb)[e]		Blood, tissue and stool will be collected for optional exploratory research/validation studies[a]

a. It is preferred that the subject has fasted (8 hours, except for water) prior to sample collection, however it is not required.

b. A microscopic analysis will be performed by the central laboratory in the event the dipstick results show leukocytes, nitrite, protein, ketones, or blood greater than negative or glucose greater than normal.

c. INR test only drawn if ALT or AST > 3 × ULN (upper limit of normal) and Total Bilirubin ≤ 2 × ULN (Refer to Section 5.4.1, for additional information).

d. Only done at screening and calculated by the central laboratory.

e. To be done with the occurrence of a suspected anaphylactic reaction (an additional sample of tryptase to be collected if possible at least 2 weeks post-reaction or at the next study visit); for ADA these samples are collected in addition to those specified in Appendix C.

Hepatitis B Testing

All subjects will be tested for the presence of the HBV at Screening. A positive result for the Hepatitis B surface antigen (HBs Ag) will be exclusionary. Samples that are negative for HBs Ag will be tested for surface antibodies (HBs Ab) and core antibodies (HBc Ab Total). Subjects with HBs Ag (–), HBs Ab (–), and HBc Ab Total (+) require PCR qualitative testing for HBV DNA. Any HBV DNA PCR result that meets or exceeds detection sensitivity will be exclusionary.

Subjects with a negative HBs Ag test and tests showing the results below do not require HBV DNA PCR qualitative testing:

- HBc Ab Total (–) and HBs Ab (–)
- HBc Ab Total (–) and HBs Ab (+)
- HBc Ab Total (+) and HBs Ab (+)

For Japan only: for subjects with HBs Ab (+) and/or HBc Ab (+) at Screening, the HBV-DNA PCR test should be performed as outlined in Appendix C. In cases where the recurrence of HBV-DNA is observed, the subject should be discontinued from the study drug. Retesting according to Appendix C is not necessary with subjects who have a history of HBV vaccine and are HBs Ab (+).

Hepatitis C Testing

All subjects will be tested for the presence of the hepatitis C Virus (HCV) antibody at Screening. Subjects with positive HCV antibody will have a HCV RNA test. If the HCV RNA is positive then the subject will be excluded.

HIV

Subjects with a known history of HIV infection are excluded from study participation. HIV testing will be conducted as part of the infection screening at the Screening visit. The Investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report these results to their health agency per local

regulations, if necessary. If a subject has a confirmed positive result, the Investigator must discuss with the subject the potential implications to the subject's health and subject should be referred for clinical care promptly. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing. This testing is to be done at the central lab.

Anaphylaxis Testing

In the event of a suspected systemic post-dose hypersensitivity reaction, a serum risankizumab, ADA, and neutralizing antibody (nAb) sample should be collected once within 24 hours of the reaction. In addition to serum risankizumab, ADA, and nAb assays, blood tests to be conducted in the event of a systemic hypersensitivity reaction are:

- Tryptase: Optimally, measurement needs to be obtained from 15 minutes to 3 hours of symptom onset, and no later than 6 hours (as tryptase may remain elevated for 6 or more hours after the onset and therefore may still be informative if obtained after 3 hours); it is also requested to collect a follow-up tryptase level a minimum of 2 weeks after the recorded event or at the next study visit.
- Plasma histamine: optimally, within 5 to 15 minutes of the onset of symptoms, and no later than 1 hour.

Stool Samples Collected:

Fecal Calprotectin (FCP)

Fecal calprotectin will be performed for all subjects as indicated in Appendix C. If subjects are unable to provide a sample at the site visit, subjects will be sent home with a stool sample supply kit and the site will give instructions to assist with collection procedures. All stool samples should be collected before any bowel preparation for endoscopy is started and returned to the site per the instructions provided outside of this protocol.

The FCP results will remain blinded to Investigator, study site personnel and the subject throughout the study.

The central laboratory will be utilized to process and provide results for these laboratory tests. In order to maintain the study blind, local laboratory testing for FCP for routine subject monitoring should not be performed.

***C. Difficile* Stool Testing**

During the Screening period a stool sample will be collected and sent to the central laboratory for testing. The sample will be assessed for the presence of *C. difficile* toxin.

The sample must be shipped to the central laboratory using dry ice. Additional information is available in the laboratory manual provided by the central laboratory.

Subjects who are positive for *C. difficile* toxin may be treated appropriately and re-screened.

Urinalysis

Dipstick urinalysis will be completed by the sites at all required visits as listed in Appendix C. A microscopic urinalysis will only be performed by the central laboratory if the dipstick urinalysis results are abnormal, where abnormal is defined as leukocytes, nitrite, ketone, protein, blood or glucose value of greater than a trace.

Pregnancy Testing

A serum pregnancy test will be performed for all female subjects of childbearing potential during Screening.

The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is positive the subject is considered a screen failure. If the serum pregnancy test is borderline, it should be repeated to determine eligibility ≥ 3 days later. If the repeat serum pregnancy test is:

- Positive, the subject is considered a screen failure;
- Negative, the subject can be enrolled into the study;
- Still borderline ≥ 3 days later, this will be considered documentation of continued lack of a positive result and the subject can be enrolled into the study (unless prohibited locally) in the absence of clinical suspicion of pregnancy and other pathological causes of borderline results.

A urine pregnancy test will be performed for all WOCBP as indicated in Appendix C, prior to study drug administration. More frequent pregnancy tests will be performed throughout the study if required per local/country requirements.

- If the baseline urine pregnancy test performed at the site is negative, then dosing with study drug may begin. If the baseline urine pregnancy test performed at the site is positive, dosing with study drug must be withheld and a serum pregnancy test is required. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is negative, study drug may be started. If the serum pregnancy test is positive, study drug must be withheld and the subject must be discontinued from the study. In the event a pregnancy test result is borderline, a repeat test is required.
- If a urine pregnancy test post-baseline is positive, study drug will be temporarily discontinued and a serum pregnancy test is required. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is negative, study drug may be restarted. If the serum pregnancy test is positive, study drug will be permanently discontinued.

A pregnant or breastfeeding female will not be eligible for participation or continuation in this study or be allowed to continue study drug.

High-Sensitivity C-Reactive Protein (hs-CRP)

Blood samples for hs-CRP will be obtained per Appendix C. The hs-CRP results will remain blinded to Investigator, study site personnel and the subject.

Blood draws should be performed, as much as possible, after all efficacy assessments, questionnaires (CDAI, IBDQ, etc.), and vital sign determinations are obtained and before study drug administration during a visit. In order to maintain the study blind, local laboratory testing for hs-CRP for routine subject monitoring should not be performed.

Crohn's Disease Activity Index (CDAI)

Average daily SF, average daily AP score, and well-being will be calculated from the subject diary. During screening subjects will be instructed on how to calculate the number of very soft and liquid stools, including a visual depiction. Physical exam and appropriate laboratory values will be calculated at all study visits beginning at Baseline. The Screening period will be a minimum of 7 days to calculate the Baseline scores.

The CDAI scores must be calculated using a central laboratory hematocrit (Hct) value from the same visit for all visits, except Baseline, where the most recent Screening Hct value will be used. The final CDAI for all other visits will be calculated once the hematocrit value is received from the central lab. If the Hct is missing due to technical issues (e.g., lost sample, clotted sample, etc.), the Hct value from the preceding visit may be used.

Instructions to calculate CDAI

- To answer **questions one (1) through three (3)**, entries from the 7 days prior to the visit should be used as recorded by the subject from the diary.
- Diary entries should not be included in the 7 days evaluated prior to the visit if: (1) the day the subject received medication for bowel preparation prior to endoscopy, (2) the day the subject underwent an endoscopy, and (3) 2 days following the endoscopy. Diary entries, up to 14 days prior to the visit, will be used accordingly in order to provide the most recent data for 7 days prior to the respective study visit. The 7 days do not need to be consecutive.
- In **question four (4)**, for the section regarding presence of anal fistulas and other fistulas, all fistulas detectable on physical examination (draining and

non-draining) should be captured on the CDAI and calculated into the CDAI score.

- And the evaluation for fever should include all the days that are taken into account for the calculation of the CDAI.
- When completing **question five (5)** ("Taking Lomotil/Imodium/Loperamide/opiates for diarrhea, 0 = no, 1 = yes") on the CDAI, "no" should be answered if a subject is taking an opiate(s) solely for pain. The use of these medications takes into account only the day of the scheduled visit and is only assessing their use as anti-diarrheals.
- For **question seven (7)**, hematocrit results from central laboratory will be used for the CDAI calculation. If the hematocrit value contains more than one decimal point, the rounding will be allowed to the tenths decimal (e.g., Hct value 33.44 will be captured as 33.4, Hct value of 33.45 will be captured as 33.5). The Hct values either prior to completing the calculation or at the subtotal box 7 of the CDAI should not be rounded to a whole number.
- For **question eight (8)**, the height obtained at Screening should be used when selecting the standard weight in Appendix G, and this standard weight should be used for calculating every CDAI throughout subject participation in the study.
- Standard height is calculated by using the height obtained at Screening (without shoes) adding one inch or 2.5 cm. For subjects < 18 years of age at Baseline, height will be re-measured at Week 12 and Week 24 (if applicable) and standard height should be recalculated.
- If the body weight obtained at the time of assessment is not captured in kilograms (kg), then when converting into kg, rounding should occur using the second digit after the decimal (also known as the hundredth place) where if the number is 0 – 4, then keep the first digit after the decimal (also known as the tenth place) unchanged. If the second digit after the decimal is 5 – 9, then round up the first digit after the decimal (e.g., 90.246 would be captured as 90.2 and 97.687 would be captured as 97.7).
- The subtotal of box 8 should not be rounded to a whole number.

The calculation of the CDAI score is in Appendix F.

Endoscopy

An endoscopy will be performed on the following visits:

- During Screening*
- Week 12/PD
- Week 24

The same endoscopist, where possible, should perform all endoscopies. In addition, where possible, the Investigator or sub-Investigator should be the endoscopist for the study. It is expected that all subjects who remain in the study through at least Weeks 8 will have a Week 12/PD endoscopy.

* An endoscopy performed before the Screening visit, independently of the study, may be used as the Screening endoscopy, with the approval of the AbbVie TA MD, if the following conditions are met:

1. Biopsy confirmation of the diagnosis is available according to section "Biopsy During Endoscopy" below, as applicable.
2. The endoscopy took place within 45 days prior to Baseline visit.
3. The endoscopy was recorded in a video format as the endoscopic eligibility will be determined by the central reviewers.

All ileocolonoscopies will be performed and recorded at the site in a video format. Sites should also perform the SES-CD assessment and record the findings on the SES-CD score sheet (Appendix E) and in the appropriate eCRF.

All endoscopies will be reviewed by a central reviewer who is blinded. Endoscopies completed at Week 12 and Week 24, for those subjects who undergo blinded therapy in Induction Period 2, will use the local reader results for stratification for Study M16-000.

There will be a window of ± 7 days to conduct the ileocolonoscopy. This window may be extended as necessary after consultation with the AbbVie TA MD in case of external circumstances.

The endoscopies performed at the time points described above will be used to provide the endoscopy subscores to calculate the SES-CD. All attempts should be made by the endoscopist to explore all segments of the colon and terminal ileum, including intubation of the terminal ileum, at every endoscopy visit. The endoscopy subscores by segment will be noted in the subject's source documents and in the database but the central reviewer's endoscopy subscore will be used for the efficacy analyses.

Biopsy During Endoscopy

Appropriate documentation of biopsy results consistent with the diagnosis of CD, in the assessment of the Investigator, must be available in order to confirm the subject's eligibility for the study. If this documentation is not available a diagnostic biopsy from the most affected area of the colon must be performed during the Screening endoscopy and read by a qualified local pathologist and the results reviewed by the Investigator. Biopsies to rule out dysplasia and colon cancer may be taken per the Investigator's discretion during any endoscopy performed during this study and evaluated by the local pathologist.

If any biopsy sample(s) are obtained, it should also be recorded on the video.

Any biopsy sample(s) will be collected from the respective bowel segment during the withdrawal of the endoscope and after sufficient recording for the central reader to calculate the SES-CD.

The signed pathology report will be monitored by the responsible CRA and kept with the subject's source documents onsite. Subjects should not be enrolled if high grade colonic dysplasia or colon cancer is discovered at Screening endoscopy or endoscopy performed within 45 days prior to Baseline visit. Subjects may be enrolled if low grade colonic dysplasia is discovered during endoscopy and is completely removed.

If a diagnosis of high grade colonic dysplasia or colon cancer is discovered during any subsequent endoscopic evaluation during the course of the study, the findings should be recorded as an AE and the subject should be discontinued from the study. If low grade colonic dysplasia is discovered during any subsequent endoscopic evaluation during the course of the study, the findings should be entered as an AE and the subject can continue in the study if the lesion has been completely removed.

Subject Diary

Subjects will be dispensed an electronic diary at Screening and will be trained on how to complete the diary by site staff during the Screening visit. All subjects should complete their subject diary on a daily basis throughout the entire study. The diary will be reviewed by site personnel with the subject at each visit and collected at the Final/PD visit, unless the subject continues into Study M16-000. Subjects should also be dispensed the patient information card at Screening.

Completion will be reinforced during study visits as necessary.

Outcomes and Questionnaires

Subjects will be asked to complete the following electronic questionnaires/outcomes at the time points indicated in Appendix C.

- Inflammatory Bowel Disease Questionnaire (IBDQ)
- Work Productivity and Impairment Questionnaire – CD (WPAI-CD)
- Crohn's Symptom Severity (CSS)
- Patient Global Impression of Change (PGIC)
- Patient Global Impression of Severity (PGIS)
- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)
- European Quality of Life 5 Dimensions (EQ-5D-5L)
- 36-Item Short Form Health Survey (SF-36)

Due to the COVID-19 pandemic and any local restrictions, sites may administer PRO instruments over the phone as needed. Sites may read the PRO questions and response options to the subject and record the subject's responses. Sites may send the questionnaires (email or hard copy) to the subjects to allow them to read/understand the questions and responses when the subject is providing responses over the phone. The date and time of PRO data collection should be recorded along with who collected the information.

Study Drug Dispensing/Administration

Intravenous and SC study drug will be administered to all subjects on-site. For WOCBP subjects, the urine pregnancy test needs to be negative prior to receiving study drug. The site will be provided administration instructions. Also, the initial 20 subjects enrolled between the Phase 3 induction trials will be monitored on site for 2 hours after completion of each infusion. Subjects should be observed after study drug administration until judged clinically stable by the study personnel. If an anaphylactic reaction or other serious allergic reaction occurs, administration of study drug should be discontinued immediately, appropriate laboratory testing samples drawn and appropriate therapy initiated.

Study drug kits are assigned by the IRT following the subjects randomized treatment schedule. (Refer to Section 5.5 for additional information).

During the Study Drug Dosing Period, a subject with confirmed (viral test positive) or suspected COVID-19 infection can only be dosed with study drug if the following COVID-19 viral clearance criteria are met:

- Symptomatic subjects: At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since recovery, defined as resolution of fever without use of antipyretics and improvement in respiratory symptoms (e.g., cough, shortness of breath)
- Asymptomatic subjects: At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since prior positive result (note:

subjects who develop symptoms will follow guidance above for symptomatic subjects)

5.3.1.2 Collection and Handling of Optional Exploratory Research/Validation Studies Samples

Subjects will have the option to provide samples for exploratory research and validation studies. Subjects may still participate in the study even if they decide not to participate in the optional exploratory research/validation. The procedures for obtaining and documenting informed consent are discussed in Section 9.3.

Exploratory research can help to improve our understanding of how individuals respond to drugs and our ability to predict which patients would benefit from receiving specific therapies. In addition, exploratory research may help to improve our understanding of how to diagnose and assess/monitor CD by assessing associations between disease characteristics, outcomes data and biomarkers of interests.

Validation studies, including those related to the development of potential in vitro diagnostic tests, may be carried out retrospectively in order to assess associations between events of interest (i.e., efficacy and/or safety events) and candidate biomarkers.

AbbVie (or people or companies working with AbbVie) will store the biomarker exploratory research/validation studies samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on risankizumab (or drugs of this class) or this disease and related conditions continues, but for no longer than 20 years after study completion.

It is preferred that the subject has fasted (8 hours, except for water) prior to sample collection, however it is not required. It must be recorded whether the subject has fasted or not at the time of collection in the laboratory request, source document, and eCRF. The following samples will be collected according to Appendix D from each subject who consents to provide samples for exploratory research/validation studies:

- DNA samples for pharmacogenetic or epigenetic analyses
- RNA samples for transcriptomic and/or epigenetic analyses
- Serum and plasma samples for systemic analyses including, but not limited to proteomics and metabolomics
- Stool samples for investigations including, but not limited to, proteomics, metabolomics, transcriptomics and metagenomics
- Intestinal biopsies for pathological and biological investigations, including but not limited to transcriptomic analyses.

Samples will be shipped to AbbVie or a designated laboratory for DNA/RNA extraction, if applicable, and/or analyses or long-term storage. Instructions for the preparation and shipment of the samples will be provided in the laboratory manual.

5.3.2 Drug Concentration and Anti-Drug Antibody Measurements

5.3.2.1 Collection of Samples for Analysis

Serum risankizumab concentrations, ADA, and neutralizing antibodies (nAb) will be determined from blood collected by venipuncture just prior to dosing as indicated in Appendix C. The time that each blood sample is collected will be recorded to the nearest minute in the source document and on the appropriate eCRF.

For approximately 20 subjects who consent to participate in the Optional Intensive PK sampling, refer to Appendix H.

5.3.2.2 Handling/Processing of Samples

Specific instructions for collection of blood/serum samples and subsequent preparation and storage of the samples for the assays will be provided by the central laboratory, AbbVie, or its designee.

Refer to the study specific laboratory manual for detailed instructions on sample collection, processing, and shipment.

5.3.2.3 Disposition of Samples

Frozen samples will be packed in dry ice (pellet form) sufficient to last 3 days during transport. Samples will be shipped pursuant to instructions from the onsite CRA. An inventory of the samples will be included in the package for shipment. Arrangements will be made with the central lab for the transfer of samples.

5.3.2.4 Measurement Methods

Serum concentrations of risankizumab and relative titers of risankizumab ADA will be determined using validated methods under the supervision of the Bioanalysis department at AbbVie. Any additional analytes may be analyzed using non-validated methods.

Serum samples collected for risankizumab and risankizumab ADA and risankizumab nAb analysis may be used for future assay development or validation activities.

The nAb samples upon request may be used for the analysis of neutralizing anti-drug antibodies in a validated assay.

5.3.3 Efficacy Variables

Endpoint definitions:

- **Clinical remission:** average daily SF $\leq$ 2.8 and not worse than Baseline AND average daily AP score $\leq$ 1 and not worse than Baseline
- **Enhanced clinical response:** $\geq$ 60% decrease in average daily SF and/or $\geq$ 35% decrease in average daily AP score and both not worse than Baseline, and/or clinical remission
- **Clinical response:** $\geq$ 30% decrease in average daily SF and/or $\geq$ 30% decrease in average daily AP score and both not worse than Baseline
- **Endoscopic response:** decrease in SES-CD > 50% from Baseline (or for subjects with isolated ileal disease and a Baseline SES-CD of 4, at least a 2 point reduction from Baseline), as scored by central reviewer

- **Ulcer-free endoscopy:** SES-CD ulcerated surface subscore of 0 in subjects with SES-CD ulcerated surface subscore ≥ 1 at Baseline, as scored by a central reviewer
- **Endoscopic remission:** SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable, as scored by a central reviewer
- **CDAI clinical response:** reduction of CDAI ≥ 100 points from baseline
- **CDAI clinical remission:** CDAI < 150
- **SF remission:** average daily SF ≤ 2.8 and not worse than baseline
- **AP remission:** average daily AP score ≤ 1 and not worse than baseline

5.3.3.1 Primary Variable

Co-Primary Endpoints:

- Proportion of subjects with CDAI clinical remission at Week 12
- Proportion of subjects with endoscopic response at Week 12

5.3.3.2 Secondary Variables

Ranked Secondary Endpoints:

1. Proportion of subjects with clinical remission at Week 12
2. Proportion of subjects with CDAI clinical response at Week 4
3. Proportion of subjects with CDAI clinical response at Week 12
4. Change from baseline of Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT fatigue) at Week 12
5. Proportion of subjects with CDAI clinical remission at Week 4
6. Proportion of subjects with CDAI clinical response and endoscopic response at Week 12

7. Proportion of subjects with SF remission at Week 12
8. Proportion of subjects with AP remission at Week 12
9. Proportion of subjects with endoscopic remission at Week 12
10. Proportion of subjects with enhanced clinical response at Week 4
11. Proportion of subjects with ulcer-free endoscopy at Week 12
12. Proportion of subjects with enhanced clinical response at Week 12
13. Proportion of subjects with resolution of extra-intestinal manifestations (EIMs) at Week 12, in subjects with any EIMs at Baseline
14. Proportion of subjects with CD-related hospitalization through Week 12
15. Proportion of subjects without draining fistulas at Week 12 in subjects with draining fistulas at Baseline

5.3.3.3 Other Endpoints

Non-Ranked endpoints are:

- Change from Baseline in IBDQ over time
- Change from Baseline in individual IBDQ domain scores (bowel, emotional, social, systemic) over time
- Proportion of subjects with IBDQ remission (IBDQ $\geq$ 170 points) over time
- Proportion of subjects with IBDQ response (increase in IBDQ $\geq$ 16 points from Baseline) over time
- Change from Baseline in WPAI-CD over time
- Change from Baseline in EQ-5D-5L over time
- Change from Baseline in FACIT-Fatigue total score and individual item score over time
- Change from Baseline in Short Form-36 overtime
- Change from Baseline in FCP over time

- Change from Baseline in hs-CRP over time
- Change from Baseline in average daily AP score over time
- Change from Baseline in average daily SF over time
- Proportion of subjects with clinical remission over time
- Proportion of subjects with enhanced clinical response over time
- Proportion of subjects with clinical response over time
- Change from Baseline in SES-CD at Week 12
- Proportion of subjects with a SES-CD ulcerated surface subscore ≤ 1 in each segment at Week 12 in subjects with a SES-CD ulcerated surface subscore ≥ 2 at Baseline
- Change from baseline in PGIS over time
- PGIC over time
- Proportion of subjects with endoscopic remission over time
- Proportion of subjects with endoscopic response over time
- Proportion of subjects with CD-related surgeries through Week 12
- Proportion of subjects with any reduction in SES-CD at Week 12
- Proportion of subjects with CDAI clinical remission over time
- Proportion of subjects with CDAI clinical response over time
- Change from Baseline in CDAI over time
- Change from Baseline in CSS over time

  Of note, over time will be measured at each study visit as specified in the study activity table

5.3.4 Safety Variables

Safety analyses will be performed on safety set which includes all subjects who receive at least one dose of study drug. Incidence of AEs, changes in vital signs, physical examination results, and clinical laboratory data will be assessed throughout the study.

5.3.5 Pharmacokinetic Variables

Serum risankizumab concentrations will be determined during the treatment period and at the follow-up visit as outlined in Appendix C. Serum risankizumab concentrations will be summarized at each time point for each dosing regimen using descriptive statistics. Population pharmacokinetic analyses combining the data from this study and other studies may be performed. Relationships between risankizumab exposures and efficacy and safety variables of interest may be explored.

5.3.6 Optional Exploratory Research/Validation Variables

Optional samples may be collected to conduct exploratory investigations into known and novel biomarkers. The types of biomarkers to be analyzed may include, but are not limited to, nucleic acids, proteins, lipids or metabolites. Biomarker assessments may be used to assess and generate prognostic, predictive, pharmacodynamic, or surrogate biomarker signatures. These assessments may be explored in the context of CD or related conditions and/or risankizumab or drugs of similar classes.

The samples may also be used to develop new diagnostic tests, therapies, research methods or technologies. In addition, samples from this study may be banked for future use. Samples may then be used to validate putative biomarker signatures obtained from a prospective study, leading to the development of diagnostic tests. The results from these analyses are exploratory in nature and may not be included with the study report.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

A subject may withdraw from the study at any time. The Investigator may discontinue any subject's participation for any reason, including an AE, safety concerns or failure to comply with the protocol.

Subjects will be withdrawn from the study immediately if any one of the following occurs:

- Clinically significant abnormal laboratory result(s) or AEs, which rule out continuation of the study drug, as determined by the Investigator in consultation with the AbbVie TA MD.
- The Investigator believes it is in the best interest of the subject, including subjects with no improvement to study drug at Week 12 for whom the investigator believes it is in the best interest of the subject not to enter Induction Period 2.
- Subjects who experience a severe systemic hypersensitivity infusion/injection reaction or anaphylaxis
- The subject requests withdrawal from the study.
- Inclusion and exclusion criteria violation was noted after the subject started study drug, when continuation of the study would place the subject at risk as determined by the AbbVie TA MD.
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk as determined by the AbbVie TA MD.
- The subject becomes pregnant while on study drug.
- Subject has a malignancy, except for localized non-melanoma skin cancer. Discontinuation for carcinoma in-situ of the cervix is at the discretion of the Investigator.
- Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation in the study, as determined by the Investigator, in consultation with the AbbVie TA MD.
- Occurrence of following hepatic test abnormalities considered by the Investigator to be related to study drug (retesting for ALT, AST, and TBL may be needed to confirm):
  - Confirmed ALT or AST > 8 × Upper Limit of Normal (ULN)
  - Confirmed ALT or AST > 5 × ULN for more than 2 weeks
  - Confirmed ALT or AST > 3 × ULN and (TBL > 2 × ULN or INR > 1.5)
  - Confirmed ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

If, during the course of study drug administration, the subject prematurely discontinues study drug use, the procedures outlined for the PD visit must be completed within 2 weeks of the last dose of study drug, and preferably prior to the initiation of another therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subject's condition. Following discontinuation of the study drug, the subject will be treated in accordance with the Investigator's best clinical judgment.

A final visit will occur for all subjects, approximately 140 days after the last dose of study drug to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs, except for those who are rolled over to the Study M16-000.

All attempts must be made to determine the date of the last dose of study drug and the primary reason for premature discontinuation. The information will be recorded on the appropriate eCRF page.

For subjects who are considered lost to follow-up, reasonable attempts must be made to obtain information on the final status of the subject. At a minimum, two phone calls must be made and one certified letter must be sent and documented in the subject's source documentation.

Subjects who discontinue the study prematurely will not be replaced.

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The Investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the Investigator by telephone and subsequently provide written instructions for study termination.

5.5 Treatments

5.5.1 Treatments Administered

Each dose of blinded study drug (1200 mg risankizumab, 600 mg risankizumab, or placebo) will be administered intravenously to the subject during 12-Week Induction Period.

Each dose of blinded study drug (1200 mg risankizumab, 360 mg risankizumab, or 180 mg risankizumab) will be administered intravenously or subcutaneously in Induction Period 2.

If the 1200 mg dose is discontinued due to any reason, subjects will continue to enroll into the study and be randomized to either 600 mg risankizumab or placebo at 2:1 ratio. In this case, the randomization ratio and sample size may be further updated in an amendment to the protocol. In addition, for subjects already randomized and for future randomization, 600 mg will be administered during Induction Period 2.

Subjects should not be routinely pre-medicated prior to infusion of study drug. If in the Investigator's judgment the subject requires pre-medication based on prior medical history or symptoms with prior infusions of study drug in the current study, the AbbVie TA MD should be contacted regarding possible permitted pre-medication with diphenhydramine hydrochloride and acetaminophen (or equivalents). Individual dosage, timing, and route of administration would be determined by the Investigator. Any pre-medications administered must be recorded on the appropriate eCRF.

Subjects who do not achieve clinical response at Week 12 will be eligible for Induction Period 2 with blinded risankizumab. Blinded risankizumab will be administered either intravenously at Weeks 12, 16, and 20 or subcutaneously at Weeks 12 and 20.

5.5.2 Identity of Investigational Product

The individual study drug information is presented in Table 2.

Table 2. Identity of Investigational Product

Study Drug	Strength	Route of Administration	Manufacturer
Risankizumab (ABBV-066)	90 mg/mL	IV	Boehringer Ingelheim Pharma GmbH & Co. KG
Placebo for Risankizumab (ABBV-066)	N/A	IV	Boehringer-Ingelheim Pharma GmbH & Co. KG
Risankizumab (ABBV-066)	90 mg/mL	SC	Boehringer-Ingelheim Pharma GmbH & Co. KG
Placebo for Risankizumab (ABBV-066)	N/A	SC	Boehringer-Ingelheim Pharma GmbH & Co. KG

AbbVie will not provide 5% dextrose to be used as a diluent for administration for risankizumab or placebo and it should be sourced locally from approved marketed products from various commercial manufacturers depending on availability.

5.5.2.1 Packaging and Labeling

Risankizumab or placebo will be provided as one (1) vial per carton or one (1) prefilled syringe per carton to accommodate the study design.

Each kit label will contain a unique kit number. This kit number is assigned to a subject via IRT and encodes the appropriate study drug to be dispensed at the subjects corresponding study visit. Each kit will be labeled as required per country requirements. Labels must remain affixed to the kits. All blank spaces on the label will be completed by site staff prior to dispensing to the subjects.

5.5.2.2 Storage and Disposition of Study Drug

Study drug must be kept protected from light in the original packaging, in a refrigerator between 2° to 8°C (36° to 46°F). Study drug must not be frozen at any time.

The investigational products are for investigational use only and are to be used only within context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until

dispensed for subject use or destroyed as appropriate. A temperature log must be maintained for documentation.

The refrigerator temperature must be recorded each business day. Malfunctions or any temperature excursion must be reported to the Sponsor immediately. Sites are responsible to report temperature excursions into the AbbVie Temperature Excursion Management System (ATEMS). Study drug should be quarantined and not dispensed until AbbVie or ATEMS deems the drug as acceptable.

Upon receipt of the study drugs, the site will acknowledge receipt within the IRT system.

5.5.2.3 Preparation/Reconstitution of Dosage Form

Administration Instructions and Dose Preparation Instructions will be provided as separate documents outside of this protocol. Dose preparation will be performed by a licensed unblinded pharmacist or qualified designee, as appropriate.

5.5.3 Method of Assigning Subjects to Treatment Groups

All subjects will be assigned a unique identification number by the IRT at the Screening visit and will keep the same unique subject identification number throughout the study. Subjects who meet the inclusion and none of the exclusion criteria defined in Section 5.2.1 and Section 5.2.2 will be centrally randomized in a 2:2:1 ratio to one of the three treatment groups at Baseline during the 12-Week Induction Period of the study. The randomization will be stratified by number of prior biologics failed (0, 1, > 1), Baseline steroid use (yes, no), and Baseline SES-CD (original, alternative). The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule generated by the Statistics Department at AbbVie.

IRT will provide the appropriate medication kit number(s) to dispense to each subject. Study drug will be administered at the study visits as summarized in Section 5.5. Returned study drug should not be re-dispensed to any subject.

At Week 12, subjects who do not achieve clinical response will be eligible for Induction Period 2 where subjects receiving blinded IV risankizumab will be re-randomized 1:1:1 to receive blinded risankizumab in one of three groups and subjects who are receiving blinded placebo will receive blinded IV risankizumab as summarized in Section 5.5.

5.5.4 Selection and Timing of Dose for Each Subject

Subject will be administered study drug at the clinical site as outlined in Section 5.5.1.

5.5.5 Blinding

All AbbVie personnel with direct oversight of the conduct and management of the study (with the exception of AbbVie's Drug Supply Management Team and unblinded CRA/monitor (as applicable)), as well as the Investigator, the blinded study site personnel (with the exception of the unblinded site staff), and the subject will remain blinded to each subject's treatment throughout the study. The IRT will provide access to blinded subject treatment information in the case of medical emergency.

In the event of a medical emergency in which the Investigator believes that knowledge of study drug treatment is required, reasonable efforts must be made to contact the AbbVie TA MD (see Section 6.1.5) prior to breaking the blind, as long as it does not compromise subject safety. However, if an urgent therapeutic intervention is necessary which warrants breaking the blind prior to contacting AbbVie TA MD, the Investigator can directly access the IRT system to break the blind without AbbVie agreement. In the event that the blind is broken before notification to AbbVie TA MD, it is requested that the AbbVie TA MD be notified within 24 hours of the blind being broken. Also, the date and reason that the blind was broken must be recorded in the source documents and eCRF, as applicable.

5.5.5.1 Blinding of Investigational Product

In order to maintain the blind, it is necessary to have unblinded site staff (unblinded licensed pharmacist or qualified designee) to prepare the IV solutions and blind the doses. Study personnel who administer the infusions to the subjects must remain blinded.

The Administration Instructions and Dose Preparation Instructions are to be checked for the staff requirements for all activities concerning handling of study kits, including IRT transactions.

5.5.5.2 Data Monitoring Committee

An external independent DMC will review unblinded safety data on a cohort level, at a minimum of 6-month intervals throughout the course of the study launch.

A separate DMC charter will be prepared outside of the protocol and approved by AbbVie and the DMC members before a subject is initiated into the study. The DMC charter will describe the composition of the DMC, the roles and responsibilities of the DMC members, frequency and triggers of data reviews, relevant safety data to be assessed, meeting occasions, and communication with AbbVie as well as relevant competent authorities, if necessary. The DMC is responsible for monitoring safety data, alerting AbbVie to possible safety concerns related to the conduct of the study, and recommending appropriate actions for study conduct and management.

At the timing of this amendment, the DMC has provided recommendation that the study may continue without modification and allowed enrollment to begin for 16 - 17 year-olds. A patient information card with information of the symptoms and signs of hypersensitivity reactions, infusion related reactions as well as late stage reactions will be provided to the patients at Screening so that any such events once occurred will be reported immediately by the patients to the investigator.

The DMC will review safety data at a minimum of 6-month intervals throughout the course of the study. The DMC will determine if more frequent DMC meetings are required based on review of the accumulating safety data. In addition, ad-hoc DMC meetings will be scheduled in the event of any significant safety concerns. Based on these reviews, the DMC will make recommendations, as appropriate, regarding the conduct and management of the study.

The CAC and AAC adjudicate blinded data and the DMC reviews the data in an unblinded manner. Unblinded adjudicated cardio-cerebrovascular events and anaphylactic reactions will be presented to the DMC for review on a periodic basis.

Communications from the DMC to the Study Teams will not contain information that could potentially unblind the team to subject treatment assignments.

5.5.6 Treatment Compliance

The Investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

5.5.7 Drug Accountability

The Investigator or designee (blinded or unblinded as applicable) will verify that study drug supplies are received intact, at the appropriate temperature, and in the correct amounts from the depot. This will be accomplished by documenting the condition of the shipment, verifying the kit numbers in the package against the Proof of Receipt (POR) or similar document included with each drug shipment, and documenting this verification by signing and dating the POR or similar document and via direct reporting in IRT. The original POR note or similar document will be kept in the site files as a record of what was received.

In addition, IRT will be used to document investigational product accountability including date received, the lot number, kit number(s), date and number of vials and syringes dispensed and subject number. For this study, unless otherwise prohibited locally, these records will be maintained electronically as part of the IRT system.

An overall accountability of the study drug will be performed by the site and reconciliation will be performed by the CRA/monitor (blinded or unblinded according to the monitoring plan) throughout the study and at the site close-out visit. After verification

of drug accountability, used study drug must be destroyed at the site according to local regulations governing biohazardous waste. Destruction of used study supplies must be completed and documented in such a way that blinding is maintained for all blinded study personnel. All unused supplies must be inventoried, accounted for and destroyed on site according to local procedures or regulation or returned to a destruction facility. A copy of the, Return Consignment Form from IRT, in accordance with instructions provided by the monitor/CRA (blinded or unblinded according to the monitoring plan), will be included in the return shipments.

The use of a third party vendor for drug destruction must be pre-approved by AbbVie. For sites performing on-site drug destruction or using a third party vendor for drug destruction, a copy of the destruction methodology and date of destruction should be maintained at the site's facility.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

Risankizumab is a selective IL-23 inhibitor that may provide improved clinical benefit to risk profile in CD patients. The proposed study is a Phase 3, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of risankizumab compared to placebo in subjects with moderately to severely active CD, who have had inadequate response or intolerance to aminosalicylates, oral locally acting corticosteroids, oral and/or IV systemic corticosteroids, immunomodulators, and/or biologic therapies.

The study consists of a 12 week induction period to evaluate the efficacy and safety of two different IV risankizumab doses (IV, 600 mg or 1200 mg, Q4w) versus placebo. For subjects not in clinical response at Week 12, an optional blinded Induction Period 2 (IV, 1200 mg, Q4w; SC 360 mg, Q8w; SC 180 mg, Q8w) for an additional 12 weeks will be offered. Subjects with clinical response at the end of induction or Induction Period 2 can enter Study M16-000 for an additional 52 weeks of treatment, with additional OL treatment with risankizumab being offered through approval.

At this time, a 12-week placebo controlled study is necessary for registrational purposes. A comparative study utilizing placebo provides an unbiased assessment of the efficacy and safety profile of risankizumab. To ensure all subjects are given the opportunity to receive potentially efficacious therapy, all subjects not responding after 12 weeks can participate in the blinded Induction Period 2 with risankizumab.

5.6.2 Appropriateness of Measurements

Standard statistical, clinical, endoscopy-related and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in subjects with CD. All clinical and laboratory procedures in this study are standard and generally accepted. Central reading of endoscopy will increase study rigor and ensure enrollment of subjects with moderately to severely active CD.

5.6.3 Suitability of Subject Population

Adult male and female subjects, and 16 to 17 years old where locally permitted, with moderately to severely active CD who meet all of the inclusion criteria and none of the exclusion criteria are eligible for enrollment in this study. The specific population chosen was based on the unmet medical need of those subjects with a history of inadequate response or intolerance to immunomodulators (AZA, 6-MP, or MTX), corticosteroids, and/or biologic therapies.

5.6.4 Selection of Doses in the Study

AbbVie plans to evaluate two doses of risankizumab (600 mg and 1200 mg) via IV administration every 4 weeks (Q4w; Weeks 0, 4, 8) through induction (12-Week Induction Period) and an additional three doses of 1200 mg of risankizumab via IV administration (Q4w; Weeks 12, 16, 20) or two doses of 180 or 360 mg SC (Q8w, Weeks 12 and 20; Induction Period 2) for subjects who do not achieve clinical response at Week 12. The selection of the doses in this study is informed by the analysis of the safety and efficacy data, as well as the exposure-response relationship of efficacy, of a Phase 2

study in subjects with CD (Study 1311.6) and the pharmacokinetic data from the completed studies in subjects with psoriasis (Studies 1311.1 and 1311.2).

Results from the placebo controlled Study 1311.6 that evaluated 200 mg and 600 mg IV doses of risankizumab at Weeks 0, 4, 8 for induction suggests increasing trend of clinical response and remission (for both CDAI and PRO-2 based measures) at Week 12 with increasing risankizumab dose and exposure, indicating a potential for further improvement in proportion of subjects with response and remission with evaluation of higher doses. Preliminary model predictions suggest further incremental benefit in CDAI remission in subjects with CD at 1200 mg IV Q4w dose compared to 600 mg IV Q4w dose. The evaluation of higher dose data (1200 mg IV Q4w) will facilitate a more robust characterization of the dose-response and exposure-response relationship for these efficacy endpoints. Inclusion of 1200 mg IV dose in this study is further supported by the safety results from the 12 week blinded induction period in Study 1311.6. The safety profile of the 600 mg risankizumab group compared favorably with the placebo group and no overall safety concerns were identified which would preclude evaluation of IV induction doses higher than 600 mg risankizumab in patients with CD. Furthermore, the projected steady state exposures for the 1200 mg IV risankizumab Q4w regimen in subjects with CD are covered by safety margins of ~1.6 and ~3.6 for C_{max} and $AUC_{0\text{-}28\ days}$ respectively (relative to NOAEL identified in the 26 week GLP toxicology study).

Induction Period 2 will evaluate IV (1200 mg Q4w) or SC (180 mg or 360 mg Q8w) risankizumab. The purpose of Induction Period 2 is to evaluate the efficacy and safety of re-induction of risankizumab versus starting maintenance dosing on clinical response. Data from the Phase 2 study in subjects with CD suggested that re-induction with 600 mg IV increased both clinical response and clinical remission. The selection of the SC doses is informed by the analysis of the safety and efficacy data, as well as the exposure-response relationship of efficacy, of the maintenance period during the Phase 2 study in subjects with CD that evaluated 180 mg SC risankizumab for maintenance. The results from the Phase 2 study suggest a potential for increased benefit with 360 mg SC administration for maintenance regimen.

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

The investigational product in this study contains:

- Biologic compound(s)

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1 through 6.1.7. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The Investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The Investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the Investigator will provide an "Other" cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention and/or if the Investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

Supplemental study case report forms should be completed in the event of COVID-19 related missed/virtual visits, study drug interruptions or discontinuations, or adverse events (including capture of specific signs/symptoms of infection and testing results).

COVID-19 infections should be captured as adverse events. If the event meets the criteria for a serious adverse event (SAE), then follow the SAE reporting directions per the

protocol and above. The following COVID-19 related supplemental eCRFs should be completed:

- COVID-19 Supplemental Signs/Symptoms
- COVID-19 Status Form

If a subject has a confirmed or suspected COVID-19 infection and study drug was interrupted, the investigator should contact the sponsor emergency medical contact listed above before reintroducing study drug.

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) within 24 hours of the site being made aware of the serious adverse event.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the Investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate eCRF.

6.1.1.3 Areas of Safety Interest

Additional information may be collected for the following events.

Hepatic Events

In the case of any of the following AEs, the appropriate supplemental eCRFs should be completed:

- Discontinuation or interruption of study drug due to any hepatic related AE
- Any hepatic related SAE
- A subject experiencing an ALT/AST > 8 × ULN
- A subject experiencing an ALT/AST > 3 × ULN in conjunction with a total bilirubin > 2 × ULN.

Systemic Hypersensitivity/Anaphylactic Reactions

Therapeutic protein products, such as biologics, may elicit a range of acute effects, from symptomatic discomfort to sudden, fatal reactions that have often been grouped as 'infusion reactions' in the past. Although the term implies a certain temporal relationship, infusion reactions are otherwise not well defined and may encompass a wide range of clinical events, including anaphylaxis and other event that may not be directly related to antibody responses, such as cytokine release syndrome.

In the event of a suspected systemic hypersensitivity/anaphylactic reaction, in addition to the standard AE eCRF, a supplemental eCRF should also be completed by the site. The clinical criterion for diagnosing anaphylaxis is provided in Appendix I for reference; symptoms of anaphylactic reaction usually occur within 24 hours after exposure to an allergen. These are guidelines that are used to help diagnose anaphylaxis. The investigator is encouraged to report any suspected reactions.

All intravenous and subcutaneous doses of risankizumab will be administered by study-site personnel under the direction of the Investigator. Subjects will be monitored throughout the study for signs and symptoms suggestive of hypersensitivity reactions, including allergic reactions and anaphylaxis. A medical person qualified in the treatment of acute hypersensitivity reactions must be present during the infusions. All appropriate medical support measures (e.g., diphenhydramine, steroids, epinephrine, oxygen) for the treatment of suspected hypersensitivity reactions should be available for immediate use in the event that a suspected hypersensitivity reaction occurs. Subjects who manifest any new signs or symptoms during the infusion should be monitored for appropriate resolution prior to leaving the site. Subjects are encouraged to report any symptoms related to a possible infusion related reactions or local injection site reaction or late phase reactions to the site any time during the study. A patient information card listing the symptoms of these reactions will be provided to the participants.

Cardiac Events/Procedures

In the case of any of the following reported MACE, the appropriate supplemental eCRFs should be completed:

- Cardiac events;
- Myocardial infarction or unstable angina;
- Cerebral vascular accident and transient ischemic attack;
- Cardiovascular procedures

Tuberculosis (TB)

In the case of any positive TB test or diagnosis of active TB, the appropriate supplemental eCRFs should be completed.

6.1.2 Adverse Event Severity

When criteria are available, events should be graded as described in the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03,[20] which can be accessed at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

If no specific criteria are provided to grade the reported event, the event should be graded as follows:

Mild (Grade 1)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Moderate (Grade 2)	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
Severe (Grade 3)	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Severe (Grade 4)	Life-threatening consequences; urgent intervention indicated.

Severe (Grade 5)	Death related to AE

Use the following guidelines when entering the severity grading criteria into the electronic data capture (EDC) system.

Grade 1 as Mild; Grade 2 as Moderate; and Grade 3 to 5 as Severe.

6.1.3 Relationship to Study Drug

The Investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

Reasonable Possibility	After consideration of factors including timing of the event biologic plausibility, clinical judgment and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event biologic plausibility, clinical judgment and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the Investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

If an Investigator's opinion of no reasonable possibility of being related to study drug is given, an "Other" cause of event must be provided by the Investigator for the serious adverse event.

6.1.3.1 Lack of Efficacy or Worsening of Disease

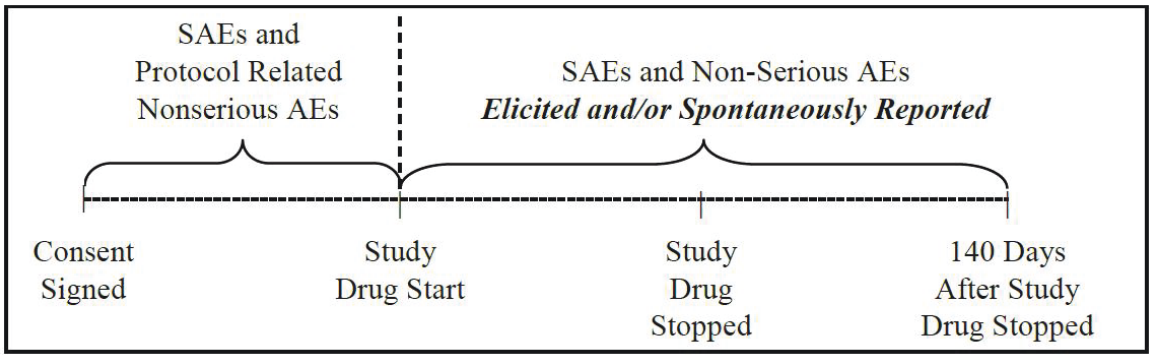
Events that are clearly consistent with progression of the underlying disease (CD) are considered an expected outcome for this study and will not be subject to expedited reporting.

6.1.4 Adverse Event Collection Period

All adverse events reported from the time of study drug administration until 140 days from the last dose of study drug have elapsed will be collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events and protocol-related nonserious adverse events will be collected from the time the subject signed the study-specific informed consent.

Adverse event information will be collected as shown in Figure 2.

Figure 2. Adverse Event Collection



6.1.5 Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the electronic data capture (EDC) system. Serious adverse events that occur prior to the site

having access to the RAVE® system, or if RAVE® is not operable, should be documented on the SAE Non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event.

Email: PPDINDPharmacovigilance@abbvie.com

FAX to: +1 (847) 938-0660

For safety concerns, contact the Immunology Safety Team at:

Immunology Safety Team
Dept. R48S, Bldg. AP31-2
1 North Waukegan Road
North Chicago, IL 60064

Safety Hotline: +1 847-938-8737
Email: GPRD_SafetyManagement_Immunology@abbvie.com

For any subject safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director:

[redacted]
100 Research Drive, Suite 3009
Worcester, MA 01605

Telephone Contact Information:
Office:
Mobile:
Email: [redacted]

In emergency situations involving study subjects when the primary AbbVie TA MD is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie TA MD:

Phone: +1 (973)-784-6402

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the investigational medicinal product (IMP) in accordance with global and local guidelines and Appendix A of the Investigator Brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a DSUR reporting period serves as the RSI during the reporting period. For follow up report, the RSI in place at the time of occurrence of the suspected Serious Adverse Reaction will be used to assess expectedness.

In Japan, the principal Investigator will provide documentation of all serious adverse events to the Director of the investigative site and the Sponsor.

6.1.5.1 Adverse Events Commonly Associated with CD in Study Population

Certain events are anticipated to occur in the study population as known consequences of CD (e.g., as symptoms or due to disease progression) independent of drug exposure. These events are listed in Table 3. These AEs, which should be captured on the appropriate eCRF, are considered expected for reporting purposes for this protocol. Although exempt from expedited reporting to certain Health Authorities and ECs/IRBs as individual cases, if any of these events meets seriousness criteria, it must be reported to AbbVie within 24 hours of the site being made aware of the SAE (as defined in Section 6.1.5).

Events commonly associated with CD population hence considered expected for reporting.

Table 3. Common Events Associated with CD

Fistulae	Abscesses	Stenoses/Obstruction
• Anal fistula • Colovaginal fistula • Colovesical fistula • Enterocolonic fistula • Enterocutaneous fistula • Enterovaginal fistula • Female genital-digestive tract fistula • Ileal fistula • Ileorectal fistula • Ileovaginal fistula • Perineal fistula • Rectal fistula • Rectovaginal fistula	• Anal abscess • Anorectal abscess • Rectal abscess **Others** • Anal fissure • Worsening of Crohn's disease • Intestinal perforation	1. Anal stenosis 2. Ileal stenosis 3. Intestinal obstruction 4. Small intestine obstruction

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 24 hours of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued from study drug (Section 5.4.1).

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected.

Pregnancy in a study subject is not considered an adverse event. The medical outcome for either mother or infant, meeting any serious criteria including an elective or spontaneous abortion, is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.1.7 Cardiac Adjudication Committee

The independent external CAC will be adjudicating observed cardio- and cerebro-vascular events and will remain blinded to treatment allocation. The events that are adjudicated

and the adjudication process will be detailed in the Cardiac Adjudication Committee Charter. Dedicated eCRFs will be used for events of myocardial infarction-unstable angina, stroke-transient ischemic attack, and death. In addition, the site may be contacted for additional source documentation for relevant events.

6.1.8 Anaphylaxis Adjudication Committee

The independent external AAC will be adjudicating observed potential anaphylactic events and will remain blinded to treatment allocation. The events that are adjudicated and the adjudication process will be detailed in the Anaphylaxis Adjudication Committee Charter. A supplemental eCRF will be used to collect information pertinent to the events. In addition, the site may be contacted for additional source documentation for relevant events.

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product.

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, or packaging issues.

Any information available to help in the determination of causality to the events outlined directly above should be captured.

6.2.2 Reporting

Product Complaints concerning the investigational product must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a

satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition. In instances where a return is requested, every effort should be made by the Investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects. The principal Investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic) after a subject has been enrolled, the principal Investigator is responsible for notifying IEC/IRB regulatory authorities (as applicable), and AbbVie.

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

In Japan, the Investigator will record all protocol deviations in the appropriate medical records at site.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

The objective of the statistical analyses is to evaluate the efficacy and safety of risankizumab versus placebo in subjects with moderately to severely active CD who had baseline eligibility SES-CD of ≥ 6 (≥ 4 for isolated ileal disease).

When all patients complete their Week 12/PD visit, the database will be locked and un-blinded for the 12-week induction period. The planned analysis for the 12-week induction period will be performed. This is the only and final analysis for co-primary endpoints of the 12-week induction period. When all the patients who enter the induction Period 2 finish Week 24/PD visit, the database will be locked for the whole study and all the planned analyses for the induction Period 2 will be performed.

Complete, specific details of the statistical analyses will be described and fully documented in the study Statistical Analysis Plan (SAP). The SAP will be finalized prior to the study database lock.

The impact of missing data due to COVID-19 will be monitored and appropriate modifications to the analysis of primary and key secondary endpoints for handling such missing data will be reflected and incorporated in the final SAP.

8.1.1 Datasets for Analysis

8.1.1.1 Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set includes all randomized subjects who received at least one dose of study drug. The primary population for efficacy analysis are the subjects in the intent-to-treat set who had baseline eligibility SES-CD of ≥ 6 (≥ 4 for isolated ileal disease). The ITT subjects will be analyzed as randomized.

8.1.1.2 Safety Analysis Set

The safety analysis set consists of all subjects who received at least one dose of the study drug. The safety set will be analyzed as treated, according to treatment the subject actually received. The safety set will be used for safety analysis.

8.1.2 Definition of Missing Data Imputation

Missing data will be imputed using one or more of the following methods:

Non-Responder Imputation (NRI): In NRI analyses, subjects who prematurely discontinue the study prior to efficacy assessment at Week 12 will be considered non-responders with respect to the efficacy endpoint.

Observed Cases (OC): The OC analysis will not impute values for missing evaluations, and thus a subject who does not have an evaluation on a scheduled visit will be excluded from the OC analysis for that visit.

8.1.3 Subject Disposition

The number and percentage of subjects who are enrolled, randomized and received at least one dose of study drug, and the number of subjects who prematurely discontinued and the reason for premature discontinuation will be summarized by treatment group. Premature discontinuation of study drug will be summarized for each treatment group, as well as for all subjects combined, with frequencies and percentages overall and by reason for discontinuation for all randomized subjects who received at least one dose of study drug. Subjects may have multiple reasons for prematurely discontinuing study drug, but will be counted no more than once for the total ("Any Reason").

8.1.4 Demographics and Baseline Characteristics

Demographics (where collection is allowed) and Baseline characteristics of the study subjects will be summarized using descriptive statistics. Summary statistics for continuous variables will include the number of observations, mean, standard deviation,

median, and range for each treatment group. For other categorical or discrete variables, frequencies and percentages will be computed in each category for each treatment group, as well as for all subjects combined.

8.1.5 Prior and Concomitant Medications

Prior therapy and medications will include all therapies and medications administered prior to the date of the first dose of study drug. Prior therapy and medication will be summarized for all randomized subjects. No statistical test will be performed.

Concomitant medications will be summarized for all randomized subjects. Concomitant medications will be summarized using the World Health Organization Drug Dictionary with frequencies and percentages for each treatment group. No statistical test will be performed.

8.1.6 Efficacy Analysis

8.1.6.1 Primary Efficacy Variables

The co-primary endpoints are the proportion of subjects who achieve CDAI clinical remission at Week 12 and proportion of subjects with endoscopic response at Week 12.

The comparisons between each risankizumab dose versus placebo for the primary efficacy variable will be performed using the Cochran-Mantel-Haenszel (CMH) test adjusted by number of prior biologics failed (0, 1, > 1) and steroid use at Baseline (yes, no). A multiple testing procedure will be used to provide strong control of the type 1 error rate at alpha = 0.05 (2-sided) across analyses comparing each risankizumab dose level to placebo with respect to the co-primary endpoints, and ranked secondary endpoints. Specifically, testing will utilize a sequence of hypothesis testing for the co-primary endpoints followed by the ranked secondary endpoints, and will begin with testing each of the co-primary endpoints using α of 0.025 (2-sided) for each dose compared to placebo. If both co-primary endpoints achieve statistical significance within a dose level, continued testing will follow a pre-specified weight of α allocation between the single hypothesis within the family, as well as between the families of hypotheses across the doses. Details will be

provided in the Statistical Analysis Plan. A CMH based two-sided 95% confidence interval for the difference between treatment groups will be calculated. Subjects who discontinue prior to Week 12 for any reason will be considered as "not-achieved" for CDAI clinical remission and endoscopic response endpoints.

The analysis of co-primary efficacy endpoints will be performed in bio-IR and non-bio-IR population. Additional subgroup analyses will be outlined in the SAP. Sensitivity analyses for missing data handling using MI, PMM and OC will be performed for co-primary endpoints and details will be outlined in the SAP.

8.1.6.2 Secondary Efficacy Variables

The secondary efficacy variables are divided into two groups. The first group includes ranked secondary endpoints, which are ranked by clinical importance. Statistical significance is assessed at the pre-specified alpha level (two-sided) in ranked endpoint order until the significant level exceeds the pre-specified alpha level. No additional statistically significant treatment differences could be declared if the preceding ranked endpoint fails to achieve the pre-specified alpha level. The second group includes all other additional secondary variables. All analyses of secondary endpoints will be performed using the ITT analysis set.

In general, continuous secondary efficacy variables will be analyzed using a Mixed-Effect Model Repeated Measure (MMRM) model including factors for treatment group, visit, visit by treatment interaction, and stratification variables, for the longitudinal continuous endpoints. The MMRM analysis is considered primary for inferential purposes.

Categorical secondary efficacy variables will be analyzed using the CMH test controlling for stratification variables. Non-responder imputation for missing data will be used for categorical secondary endpoints.

Analysis of Pattern Mixture Model (PMM) will be performed as sensitivity analyses for ranked secondary endpoints.

8.1.7 Safety Analysis

Safety analyses will be carried out using the safety analysis sets, which includes all subjects who receive at least one dose of study drug. Incidence of AEs, including those related to study drug, changes in vital signs, physical examination results, and clinical laboratory values will be analyzed.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Treatment-emergent AEs are defined as AEs that began or worsened in severity after initiation of study drug and within 140 days after the last dose of the study drug. An overview of treatment-emergent AEs, including AEs leading to death and AEs leading to premature discontinuation (see details in the SAP), AEs by MedDRA preferred term and system organ class, AEs by maximum relationship to study drug, and AEs by maximum severity will be summarized by number and percentage.

Continuous laboratory and vital sign parameters will be summarized for each treatment group by visit. Treatment group differences between each of the risankizumab dosing groups and the placebo group for changes from Baseline may be analyzed using a one-way Analysis of Variance (ANOVA). Vital signs and laboratory data will be described by statistical characteristics and frequency of abnormal values. In addition, shift tables and listings will be provided for abnormal values, whereby the normal range of the analyzing laboratory will be used. Analysis details will be specified in the SAP.

8.1.8 Analysis of Optional Exploratory Variables

For exploratory biomarkers that are measured, including but not limited to pharmacogenetic, epigenetic, transcriptomic, proteomic, and metabolomic biomarkers, the association of biomarkers to the efficacy and safety endpoints may be explored for each biomarker one at a time, and also for combinations of biomarkers via some multivariate predictive modeling algorithms. Optimal multivariate combinations of biomarkers that associate with efficacy endpoints, subject response/non-response (with respect to appropriate clinical endpoints), and also with safety endpoints may be explored via a variety of statistical predictive modeling algorithms. Cut-points for individual biomarkers

and optimal combinations of biomarkers that differentiate the subject response with respect to efficacy/safety endpoints may be explored using the in-house developed subgroup identification algorithms: Sequential BATTing, PRIM, AIM BATTing, and AIM Rule. The significance of these multivariate combinations of biomarkers may be assessed via at least 20 iterations of 5-fold cross-validation.[21,22]

8.1.9 Analysis of Pharmacokinetic and Pharmacodynamic Variables

Serum risankizumab concentrations will be summarized at each time point for each dosing regimen using descriptive statistics. In addition, ADA incidence will be summarized by cohorts and study visits. ADA titers will be tabulated for each subject at the respective study visits. Data from this study may be combined with data from other studies for the population pharmacokinetic and exposure-response analyses and may not be part of the clinical study report. Population pharmacokinetic and exposure-response analyses of only data from this study may not be conducted. The following general methodology will be used for the population pharmacokinetic analysis.

Population pharmacokinetic analyses of risankizumab will be performed using the actual sampling time relative to dosing. Pharmacokinetic models will be build using a non-linear mixed-effects modeling approach with NONMEM software (Version 7, or a higher version). The structure of the starting pharmacokinetic model will be based on the pharmacokinetic analysis data from previous studies. Systemic Clearance and volume of distribution of risankizumab will be the pharmacokinetic parameters of major interest in the NONMEM analyses. If necessary, other parameters, including the parameters describing absorption characteristics, may be estimated if useful in the analysis.

The evaluation criteria described below will be used to examine the performance of different models:

1. The objective function of the best model is significantly smaller than the alternative model(s).

2. The observed and predicted concentrations from the preferred model are more randomly distributed across the line of unity (a straight line with zero intercept and a slope of one) than the alternative model(s).
3. Visual inspection of model fit, standard errors of model parameters, and change in inter-subject and intra-subject error.

Once an appropriate base pharmacokinetic model (including inter- and intra-subject error structure) is developed, empirical Bayesian estimates of individual model parameters will be calculated by the posterior conditional estimation technique using NONMEM. The relationship between these conditional estimates CL/F or Vss/F values with only potentially physiologically relevant or clinically meaningful covariates (such as ADA classification, subject age, sex, body weight, concomitant medications, possibly baseline inflammatory and disease markers) may be explored using stepwise forward selection method, or another suitable regression/smoothing method at a significance level of 0.01.

After identification of all relevant covariates, a stepwise backward elimination of covariates from the full model will be employed to evaluate the significance (at $P < 0.001$, corresponding to a decrease in objective function > 10.83 for one degree of freedom) of each covariate in the full model.

Linear or non-linear relationships of primary pharmacokinetic parameters with various covariates may also be explored.

Relationships between exposure and clinical observations (primary or secondary efficacy or safety variables of interest) may be explored. Additional analyses will be performed if useful and appropriate.

8.2 Determination of Sample Size

The co-primary endpoints are the proportion of subjects with CDAI clinical remission at Week 12 and proportion of subjects with endoscopic response at Week 12.

A total of approximately 855 subjects will be randomized into two risankizumab treatment groups and the placebo group in a 2:2:1 ratio (342 subjects for risankizumab 600 mg dose group, 342 subjects for risankizumab 1200 mg dose group, and 171 subjects for placebo group). Assuming the Week 12 CDAI clinical remission rate will be 37% for one of the risankizumab dose groups and 17% for the placebo group, a sample size of 342 subjects for each of the risankizumab dose groups and 171 for the placebo group will have 99% power to detect the treatment difference between the risankizumab dose groups and placebo in CDAI clinical remission rates at Week 12 using Fisher's exact test at alpha of 0.025 (two-sided). Assuming the Week 12 endoscopic response rate will be 25.5% for one of the risankizumab dose groups and 8% for the placebo group, this sample size will have 99% power to detect the treatment difference between the risankizumab dose groups and placebo in endoscopic response rates at Week 12 using a Fisher's exact test at alpha of 0.025 (two-sided).

In addition, with sample size of approximately 540 bio-IR subjects, this study will have approximately 92% power for the bio-IR population to detect the treatment difference between one of the risankizumab dose groups and placebo in CDAI clinical remission rates at Week 12 using Fisher's exact test at alpha of 0.025 (two-sided) for the bio-IR population, assuming the Week 12 CDAI clinical remission rate will be 34% for the risankizumab dose groups and 15% for the placebo group. Similarly, with sample size of approximately 315 non-bio-IR subjects, this study will have 70% power to detect the treatment difference between one of the risankizumab dose groups and placebo in CDAI clinical remission rates at Week 12 using Fisher's exact test at alpha of 0.025 (two-sided) for the non-bio-IR population, assuming the Week 12 CDAI clinical remission rate will be 42% for the risankizumab dose groups and 21% for the placebo group for non-bio-IR subjects.

8.3 Randomization Methods

A total of approximately 855 subjects will be randomized into two risankizumab dose groups and the placebo group in a 2:2:1 ratio (342 subjects for risankizumab 600 mg dose group, 342 subjects for risankizumab 1200 mg dose group, and 171 subjects for placebo

group). Randomization will be stratified by number of prior biologics failed (0, 1, > 1), the steroid use at Baseline (yes, no), and Baseline SES-CD (original, alternative), where the stratum of "original" includes the patients with baseline SES-CD of ≥ 6 (or ≥ 4 for subjects with isolated ileal disease), and the stratum of "alternative" includes the patients with baseline SES-CD of ≥ 3 to < 6 for ileocolonic or colonic disease or SES-CD of 3 for isolated ileal disease.

Subjects with clinical non-response to risankizumab at Week 12 will be re-randomized in a 1:1:1 ratio to 1200 mg IV dose group, 360 mg SC dose group, or 180 mg SC dose group. Subjects with clinical non-response to placebo at Week 12 will blindly receive 1200 mg risankizumab IV dose.

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Following local regulation, substantial amendments may also be reviewed and approved by the national competent authority.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The Investigator will be required to submit, maintain and archive study essential documents according to International Conference on Harmonization (ICH) GCP and all other applicable regulatory requirements.

Any SAEs that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the Investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical Investigator are specified in Appendix A.

In the event of a state of emergency due to the COVID-19 pandemic leading to difficulties in performing protocol-specified procedures, AbbVie will engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local lab instead of a central lab). In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

9.3 Subject Information and Consent

For adult subjects the Investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject and the

original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

The optional samples for intensive PK analyses will only be collected if the subject has voluntarily signed and dated the intensive PK section of the main ICF, approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions.

Samples for exploratory research/validation studies will only be collected if the subject has voluntarily signed and dated the separate written consent for exploratory research/validation studies, approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The separate written consent must be signed before the exploratory research/validation studies samples are collected and testing is performed. If the subject does not consent to the exploratory research/validation studies, it will not impact the subject's participation in the study.

For adolescent subjects, the investigator or his/her representative will explain the nature of the study to the subject and the subject's parent/legal guardian, and answer all questions regarding this study. Adolescent subjects will be included in all discussions in order to obtain verbal or written assent. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject's parent/legal guardian, the person who administered the informed consent, and any other signatories according to local requirements. Additionally, in keeping with each institution's IRB/IEC requirements, an informed assent form may also be obtained by each subject prior to any study-related procedures being performed. If a subject becomes of legal age during the course of the study, that subject will need to be re-consented. A copy of the informed consent form and the assent form will be given to

the subject and the subject's parent/legal guardian and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Genetic and non-genetic biomarker analysis will only be performed if the subject's parent/legal guardian has voluntarily signed and dated a separate genetic and non-genetic biomarker informed consent, approved by an IRB/IEC, after the nature of the testing has been explained and the subject and subject's parent/legal guardian has had an opportunity to ask questions. The separate genetic and non-genetic biomarker informed consent must be signed before the genetic and non-genetic biomarker testing is performed. If the subject's parent/legal guardian does not consent to the genetic and non-genetic biomarker testing, it will not impact the subject's participation in the study.

In the event a subject withdraws from the main study, optional exploratory research samples will continue to be stored and analyzed unless the subject specifically withdraws consent for the optional samples. If consent is withdrawn for the optional sampling, the subject must inform their study doctor, and once AbbVie is informed, the optional samples will be destroyed. However, if the subject withdraws his/her consent and the samples have already been tested, those results will still remain as part of the overall research data.

9.3.1 Informed Consent Form and Explanatory Material

In Japan, the principal Investigator will prepare the consent form and explanatory material required to obtain subject's consent to participate in the study with the cooperation of the sponsor and will revise these documents as required. The prepared or revised consent forms and explanatory material will be submitted to the sponsor. Approval of the IRB will be obtained prior to use in the study.

9.3.2 Revision of the Consent Form and Explanatory Material

In Japan, when important new information related to the subject's consent becomes available, the principal Investigator will revise the consent form and explanatory material based on the information without delay and will obtain the approval of the IRB prior to use in the study. The Investigator will provide the information, without delay, to each subject already participating in the study, and will confirm the intention of each subject to continue the study or not. The Investigator shall also provide a further explanation using the revised form and explanatory material and shall obtain written consent from each subject of their own free will to continue participating in the study.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, ECGs, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. IRT may also be the source for drug accountability. Data collected during this study must be recorded on the appropriate source documents. The Investigator Awareness Date (SAE eCRF) may serve as the source for this data point. This AE data point required for eCRF completion can be entered directly in the eCRF.

The Investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

During the COVID-19 pandemic, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10.2 Case Report Forms

Electronic case report forms (eCRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The eCRF data for this study are being collected with an EDC system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific eCRFs will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The Investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

The Investigator or an authorized member of the Investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The principal Investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the study through a password-protected method of internet access. Such access will be removed from Investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the

Investigator at that time as a durable record of the site's eCRF data. It will be possible for the Investigator to make paper printouts from that media.

10.3 Electronic Patient Reported Outcomes (ePRO)

Patient reported data must be completed for each subject screened/enrolled in this study. Some of these data are being collected with an ePRO system called Trialmax, provided by the technology vendor CRF Health of Plymouth Meeting, PA, USA. The ePRO system is in compliance with Title 21 CFR Part 11. The documentation related to the system validation of the ePRO system is available through the vendor, CRF Health, while the user acceptance testing of the study specific PRO design will be conducted and maintained at AbbVie.

The subject will be entering the data on an electronic device; these data will be uploaded to a server. The data on the server will be considered source, and maintained and managed by CRF Health.

Internet access to the ePRO data will be provided by CRF Health for the duration of the study. This access will be available for the duration of the study to the site Investigator, as well as delegated personnel. Such access will be removed from Investigator sites following the receipt of the study archive. Data from the ePRO system will be archived on appropriate data media (CD-ROM, etc.) and provided to the Investigator at that time as a durable record of the site's ePRO data. It will be possible for the Investigator to make paper print-outs from that media.

The ePRO data will be collected by the following methods:

Diary Based

The ePRO data (number of liquid or very soft stools, use of medications used for endoscopy preparation, abdominal pain, and general well-being) will be collected electronically via a handheld device into which the subject will record the required pieces of information on a daily basis. The electronic device will be programmed to allow data

entry once per day. All data entered on the device will be immediately stored to the device itself and manually/automatically uploaded to a central server administrated by CRF Health. The investigational site staff will be able to access all uploaded subject entered data via a password protected website, up until the generation, receipt and confirmation of the study archive.

Tablet Based

The PROs listed below will be collected electronically via a Tablet device into which the subject will directly enter the required pieces of information while at the site. The electronic device will be programmed to allow data entry for only the visits specified in the protocol and will not allow for subjects to complete more than one of the same assessment at any one visit. All data entered on the device will be immediately stored to the device itself and (manually/automatically) uploaded to a central server administrated by CRF Health. The investigational site staff will be able to access all uploaded subject entered data via a password protected website, up until the generation, receipt and confirmation of the study archive.

- CSS
- PGIC
- PGIS
- EQ-5D-5L
- FACIT-F
- IBDQ
- SF-36
- WPAI-CD

11.0 Data Quality Assurance

To ensure data integrity and subject safety, a study monitor will, throughout the study, verify that all subjects signed agreement of informed consent prior to any study-specific procedures being conducted. The study monitor will confirm that the Investigator is

conducting the study in compliance with the protocol, GCP and applicable regulations, and verify that the information reported in the eCRF is complete, accurate, and supported by information in source documents.

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

12.0 Use of Information

All information concerning risankizumab and AbbVie operations, such as AbbVie patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of risankizumab. This information may be disclosed as deemed necessary by AbbVie to other clinical Investigators, other pharmaceutical companies, to the Food and Drug Administration (FDA) and to other governmental agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the Investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to source data/documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection.

This confidential information shall remain the sole property of AbbVie, shall not be disclosed to others without the written consent of AbbVie, and shall not be used except in the performance of this study.

If this protocol or the information gained from the conduct of this study will be made public (disclosed/published), AbbVie will determine the information that is not yet in the public domain and if the disclosure of such information may undermine AbbVie's interests, will remain confidential at the time of disclosure/publication.

The Investigator will maintain a confidential subject identification code list of all subjects enrolled in the study (by name and subject number). This list will be maintained at the site and will not be retrieved by AbbVie.

Any exploratory research/validation studies that may be done using the samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management, hence, neither the Investigator, the subject, nor the subject's physician (if different from the Investigator) will be informed of individual subject results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate data from exploratory research/validation studies from this study may be used in scientific publications or presented at medical conventions. Exploratory research/validation studies data will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

The Investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the Investigator (Director of the Site in Japan) and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the Investigator (Director of the Site in Japan) and AbbVie. The Investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The Investigator (Director of the Site in Japan) must submit, maintain, and archive any records related to the study according to ICH GCP and all other applicable regulatory requirements. If the Investigator (Director of the Site in Japan) is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory Investigator from the Investigators who participate in the study. Selection criteria for this Investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory Investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last visit.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for risankizumab.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study of the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Crohn's Disease
Protocol Date:	01 September 2020

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

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Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the Investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee/competent authority reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.

10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]		Clinical Development, Immunology
		Clinical Development, Immunology
		Statistics
		Statistics
		Clinical Pharmacology and Pharmacometrics
		Bioanalysis
		Clinical Operations

Appendix C. Study Activities for Efficacy, Safety, and PK/PD

Activity	Screening Period (35 Days)[a]	12-Week Double-Blind Induction				Induction Period 2			Unsch[b]	140-Day Follow-Up[c]
	Screening	Baseline	Week 4	Week 8	Week 12/PD	Week 16	Week 20	Week 24		
Informed consent	X									
Inclusion/Exclusion	X	X[d]								
Medical/Surgery History	X	X[d]								
Previous and Concomitant Medication	X	X[d]	X	X	X	X	X	X	X	
Physical Exam[e]/Vital Signs[f]	X	X	X	X	X	X	X	X	X	
Adverse Event Assessment[g]	X	X	X	X	X	X	X	X	X	X
TB Screening[h]	X[y]									
ECG[i]	X[y]									
Hepatitis B, Hepatitis C Screening[j], and HIV Test[l]	X[y]				X[k]			X[k]		
C. difficile toxin	X[x]									
Urinalysis[m,n]	X[x]	X[o]			X			X		
Pregnancy Test[p]	X[x]	X	X	X	X	X	X	X		
Chemistry and Hematology[n]	X[x]	X[o]	X	X	X	X	X	X		
Optional Blood Sample for Biologic Drug Level	X									
COVID-19 Assessment[z]	X									
hs-CRP[n]		X	X	X	X			X		
Serum Risankizumab[q]			X	X	X			X	X	

Activity	Screening Period (35 Days)[a]	12-Week Double-Blind Induction				Induction Period 2			Unsch[b]	140-Day Follow-Up[c]
	Screening	Baseline	Week 4	Week 8	Week 12/PD	Week 16	Week 20	Week 24		
Serum Anti-Drug Antibody (ADA)[q,w] and Neutralizing Anti-Drug Antibodies (nAb)[q]		X	X	X	X			X	X	
Fecal calprotectin (FCP)[n, r]		X	X		X			X		
Crohn's Disease Activity Index (CDAI)		X[t]	X	X	X	X	X	X	X	
Endoscopy/SES-CD[u]	X				X			X		
Intestinal Biopsies[v]	X				X			X		
Dispense Subject Diary[s]	X									
Subject Diary Review		X	X	X	X	X	X	X	X	
Subject Questionnaire: CSS		X	X	X	X	X	X	X	X	
Subject Questionnaire: PGIC and PGIS		X (PGIS only)	X	X	X	X	X	X	X	
Subject Questionnaires: EQ-5D-5L FACIT-F IBDQ SF-36 WPAI-CD		X	X		X			X		
Study Drug Administration[w]		X	X	X	X[w]	X	X			

a. The Screening period should be a minimum of 4 days, preferably 7 days for CDAI calculation, (refer to Section 5.3.1.1). The Baseline CDAI will be calculated using the data collected during the Screening period. Baseline visit date will serve as the reference for all subsequent visits. A ± 7 day window is permitted around all study visits.

b. Visits to retest a lab will not be considered an Unscheduled visit. Unscheduled visits according to this table are for purposes when the subject is coming in a visit for evaluation and assessment.

c. Subjects will be contacted 140 days following last dose of study drug for an assessment of any new or ongoing AEs, except those subjects who roll-over into Study M16-000 after the end of study participation.

d. Update inclusion/exclusion, prior and concomitant therapy, and medical/surgical history information to assure subject eligibility.

e. Physical examinations are full physical examinations at Screening and Week 12 and Week 24 if the subject receives treatment in Induction Period 2. Physical examinations at all other visits (including unscheduled visits) are symptom based and should include the assessment of EIMs and a count of the number of cutaneous fistulas as part of calculating the CDAI.

f. Blood pressure, pulse rate, temperature, respiratory rate and weight should be performed before blood draws are performed. Height will be measured at Screening only (with shoes off and then adding 1 inch or 2.5 cm) for subjects ≥ 18 years of age. Height will be re-measured at Week 12 and Week 24 (if applicable) for subjects < 18 years of age at Baseline.

g. Collection of SAEs and protocol-related nonserious AEs begins the day the subject signs the informed consent.

h. Subjects with negative QuantiFERON-TB Gold test and/or PPD test within 90 days of Screening will not require a repeat test (documentation must be available). PPD skin test is to be read 48 to 72 hours after placement. In case of positive PPD/positive or repeat indeterminate IGRA testing, subjects may participate in the study if further work up (according to local practice/guidelines) is negative for active TB.

i. For subjects with a normal ECG taken within 90 days of Screening, a repeat ECG at Screening will not be required, provided source documentation is available. Subjects can have a repeat ECG at any time during the study as warranted based on the opinion of the Investigator.

j. Subjects will be tested for the presence of the HBV and HCV at Screening. A positive result for the hepatitis B surface antigen (HBs Ag) or hepatitis C (HCV RNA detectable in any subject with anti-HCV Ab) will be exclusionary. For subjects who are negative for HBs Ag but are positive for core antibodies (HBc Ab), HBV DNA PCR will be performed and any result that meets or exceeds detection sensitivity will be exclusionary.

k. For Japan only: for subjects with HBs Ab (+) and/or HBc Ab (+) at Screening, the HBV-DNA PCR test should be performed again at Week 12 and Week 24. Retesting at Week 12 and Week 24 is not necessary with subjects that have a history of HBV vaccine and are HBs Ab (+).

l. HIV testing will be performed at the central laboratory, which will report the results directly to the sites. AbbVie will not receive results from the testing.

m. Dipstick urinalysis will be completed by the sites at required visits. A microscopic analysis will be performed by the central laboratory, in the event the dipstick results show leukocytes, nitrite, protein, ketones or blood greater than negative or glucose greater than normal.

n. Urinalysis, chemistry and hematology, hs-CRP, and FCP may be collected at other scheduled and unscheduled visits than indicated in the table if they are warranted by the Investigator.

o. Lab assessments will only need to be repeated at Baseline if the time between Screening and Baseline is greater than 14 days, or if the subject's health status has changed to warrant a repeat test.

p. Serum pregnancy test will be performed on all WOCBP at Screening. Urine pregnancy test will be performed locally as indicated in the table for all WOCBP. The urine pregnancy test must be negative to receive study drug. If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory. FSH will be performed in all female subjects < 55 years old with no menses for 12 months.

q. Serum risankizumab concentrations and ADA will be determined from samples collected just prior to dosing at every visit. The date and time of sample collection will be captured on the eCRF. If the subject consented to the optional intensive PK sampling, refer to Appendix H.

r. Stool sample will be collected at each time point indicated in the table. For the visit when endoscopy will be conducted, stool sample should be collected prior to bowel prep and should be returned to the site per the instructions provided outside of this protocol. If a sample cannot be obtained during the site visit, the site will give instructions and a stool sample supply kit.

s. Subjects should also be dispensed the patient information card.

t. Diary information collected during Screening will serve to calculate Baseline CDAI. During screening, subjects will be instructed on how to calculate the number of very soft and liquid stools, including a visual depiction. CDAI should be completed at the Baseline visit, just prior to randomization.

u. Endoscopy at/during the screening period or within 45 days of the Baseline visit will be used to calculate the SES-CD score at Baseline. Endoscopic evaluations using SES CD confirmed by central reader will be done at Screening. Endoscopies completed at Week 12 and Week 24, for those subjects who receive treatment in Induction Period 2, will use the local reader results for stratification for Study M16-000.

v. Biopsies may be done when performing the endoscopy to confirm CD diagnosis (if appropriate documentation for confirmation of the diagnosis does not exist), and/or to rule out dysplasia and colon cancer at the Investigator's discretion. These samples will be processed and assessed locally. Histology report should be available in the subject's source records.

w. Administration of drug will be performed after all assessments and examinations scheduled for that day have been completed, including endoscopy. Completion of PROs are permitted during administration of study drug. At Week 12, study drug will only be administered for subjects who are to receive treatment in Induction Period 2. Subjects will also be dispensed a patient information card. In the event of a suspected systemic post-dose hypersensitivity reaction, serum risankizumab, ADA, and nAb should be collected once within 24 hours of the reaction. In addition, tryptase sample should be obtained between 15 minutes to 3 hours of symptom onset, and no later than 6 hours, and another sample is requested a minimum of 2 weeks after the recorded event or at the next study visit. Also, plasma histamine sample should be obtained within 5 to 15 minutes of the onset of symptoms and no later than 1 hour.

x. For Rescreening, if a subject is being rescreened within 14 days (≤ 14 days have passed) from the collection date of the previous screening testing, it is not required to repeat Screening testing for chemistry/hematology, urinalysis, serum pregnancy, and C. *difficile* provided that the subject's health status has not changed to warrant a repeat test.

y. For Rescreening, if the subject had a complete initial screening evaluation including the TB test, hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and electrocardiogram (ECG), these tests will not be required to be repeated for re-screening provided the conditions noted in Section 5.3.1.1 are met and no more than 90 days have passed since the collection date of the testing.

z. Assessment for signs/symptoms of COVID-19 infection. If the investigator suspects the possibility of COVID-19 based on the signs, symptoms and medical complaint (chief complaint, history of exposure, etc.), local laboratory testing must be completed to confirm negative for infection.

Appendix D. Study Activities – Optional Exploratory Research Samples

Samples Collected[a,b]	Screening Period (35 Days)	12-Week Double-Blind Induction	
	Screening	Baseline	Week 12/PD
Pharmacogenetic		X	
Transcriptomic and epigenetic[c]		X	X
Proteomic and targeted protein investigations (plasma)[c]		X	X
Proteomic and targeted protein investigations (serum)[c]		X	X
Stool		X	X
Intestinal biopsies (RNA)[d]	X		X

a. Collections to be performed only if subject provides separate written consent to collect the exploratory research/validation studies samples; if the separate consent is not signed, no samples can be collected.

b. Based on the value of different technologies, samples may also be used to assess other biomarker signatures, including but not limited to metabolomics, lipidomics, and other approaches.

c. It is preferred that the subject has fasted (8 hours, except for water) prior to sample collection, however it is not required. It must be recorded whether the subject has fasted or not at the time of collection.

d. Biopsy may be done when performing the endoscopy.

Appendix E. Sample SES-CD Scoring

SES-CD Scoring[23]

	Rectum	Sigmoid and Left Colon	Transverse Colon	Right Colon	Ileum	Total
Size of Ulcers Enter: 0 if none 1 if aphthous ulcers (Ø 0.1 to 0.5 cm) 2 if large ulcers (Ø 0.5 to 2 cm) 3 if very large ulcers (Ø > 2 cm)						
Ulcerated Surface Enter: 0 if none 1 if < 10% 2 if 10% – 30% 3 if > 30%						
Affected Surface Enter: 0 if unaffected segments 1 if < 50% 2 if 50% – 75% 3 if > 75%						
Presence of Narrowing Enter: 0 if none 1 if single, can be passed 2 if multiple, can be passed 3 if cannot be passed						
					TOTAL =	

Appendix F. Crohn's Disease Activity Index (CDAI)

			Factor	Subtotal
1. Number of liquid or very soft stools (Record the frequency per day)	__+___+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	×	2	
2. Abdominal pain rating: 0 = none, 1 = mild, 2 = moderate, 3 = severe	__+___+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	×	5	
3. General well-being: 0 = generally well, 1 = slightly underpar, 2 = poor, 3 = very poor, 4 = terrible	__+___+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	×	7	
4. Number of 6 listed categories the subject now has **Check all items that apply:** ☐ Arthritis/arthralgia ☐ Iritis/uveitis ☐ Erythema nodosum/pyoderma gangrenosum/aphthous stomatitis ☐ Fissure, abscess and/or anal fistula (draining/non-draining) ☐ Other cutaneous fistula (draining/non-draining) Fistula ☐ Fever over 100°F (37.8°C) during past week	_____ _____ Record "0" if no categories checked	×	20	
5. Taking Lomotil/Imodium/ Loperamide/opiates for diarrhea 0 = no, 1 = yes	_____	×	30	
6. Abdominal mass 0 = none, 2 = questionable, 5 = defined	_____	×	10	
7. Hematocrit: ___.__	Male: (47 – hematocrit) = Female: (42 – hematocrit) = Subtotal If hematocrit > normal, enter "0"	×	6	
8. Body weight: ___.__(kg) Standard weight: ___.__(kg)	100 × [1 – (Body wt/Standard wt)] = Percent below standard weight: _____ If body wt > std. wt, enter "0"	×	1	
			Total	

NOTE: During Screening subjects will be instructed on how to calculate the number of very soft and liquid stools, including a visual depiction.

Appendix G. Standard Weights

Standard Height and Weight Tables – Use to Calculate CDAI Score		
Standard Height cm (Inches)	**Standard Weight (Men) kg (Pounds)**	**Standard Weight (Women) kg (Pounds)**
121.9 (48.0)		40.8 (89.9)
123.2 (48.5)		41.3 (91.0)
124.5 (49.0)		41.8 (92.1)
125.7 (49.5)		42.3 (93.3)
127.0 (50.0)		42.8 (94.4)
128.3 (50.5)		43.4 (95.6)
129.5 (51.0)		43.9 (96.8)
130.8 (51.5)		44.4 (98.0)
132.1 (52.0)	55.5 (122.4)	45.0 (99.2)
133.4 (52.5)	55.7 (122.7)	45.5 (100.4)
134.6 (53.0)	55.8 (123.1)	46.1 (101.6)
135.9 (53.5)	56.0 (123.5)	46.6 (102.8)
137.2 (54.0)	56.2 (123.9)	47.2 (104.1)
138.4 (54.5)	56.4 (124.4)	47.8 (105.3)
139.7 (55.0)	56.7 (124.9)	48.3 (106.6)
141.0 (55.5)	56.9 (125.5)	48.9 (107.9)
142.2 (56.0)	57.2 (126.1)	49.5 (109.1)
143.5 (56.5)	57.4 (126.7)	50.1 (110.4)
144.8 (57.0)	57.7 (127.3)	50.7 (111.7)
146.1 (57.5)	58.1 (128.0)	51.3 (113.0)
147.3 (58.0)	58.4 (128.7)	52.2 (115.0)
148.6 (58.5)	58.7 (129.5)	52.6 (116.0)
149.9 (59.0)	59.1 (130.3)	53.1 (117.0)
151.1 (59.5)	59.5 (131.1)	53.6 (118.3)
152.4 (60.0)	59.9 (132.0)	54.2 (119.5)
153.7 (60.5)	60.3 (132.9)	54.8 (120.8)
154.9 (61.0)	60.7 (133.8)	55.3 (122.0)
156.2 (61.5)	61.1 (134.8)	56.0 (123.5)
157.5 (62.0)	61.7 (136.0)	56.7 (125.0)

Standard Height and Weight Tables – Use to Calculate CDAI Score		
Standard Height cm (Inches)	**Standard Weight (Men) kg (Pounds)**	**Standard Weight (Women) kg (Pounds)**
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)	71.2 (156.9
185.4 (73.0)	75.7 (167.0)	71.9 (158.5)
186.7 (73.5)	76.6 (169.0)	72.6 (160.2)
188.0 (74.0)	77.5 (171.0)	73.4 (161.8)
189.2 (74.5)	78.4 (172.8)	74.1 (163.4)
190.5 (75.0)	79.1 (174.5)	74.9 (165.1)
191.8 (75.5)	80.2 (176.8)	75.6 (166.8)
193.0 (76.0)	81.2 (179.0)	76.4 (168.4)
194.3 (76.5)	82.0 (180.8)	77.2 (170.1)
195.6 (77.0)	82.9 (182.9)	77.9 (171.8)
196.9 (77.5)	83.9 (185.0)	78.7 (173.5)

Standard Height and Weight Tables – Use to Calculate CDAI Score		
Standard Height cm (Inches)	**Standard Weight (Men) kg (Pounds)**	**Standard Weight (Women) kg (Pounds)**
198.1 (78.0)	84.9 (187.2)	79.5 (175.2)
199.4 (78.5)	85.9 (189.4)	80.3 (177.0)
200.7 (79.0)	86.9 (191.6)	81.0 (178.7)
201.9 (79.5)	87.9 (193.9)	81.8 (180.5)
203.2 (80.0)	89.0 (196.2)	82.6 (182.2)
204.5 (80.5)	90.0 (198.6)	*Standard height is calculated using actual height obtained at screening (without shoes) plus one inch
205.7 (81.0)	91.1 (200.9)	*Indoor clothing weighing 5 pounds for men and 3 pounds for women
207.0 (81.5)	92.2 (203.3)	*Centimeters × 0.3937 = inches
208.3 (82.0)	93.3 (205.8)	*Pounds × 0.4535 = kilograms

Appendix H. Optional Intensive PK Subjects

Samples for pharmacokinetics (PK) analysis will be collected in all subjects as described in Appendix C (Prior to dose at the specified weeks). For the subjects who consent to the optional intensive PK sampling, in addition to the time points in Appendix C, blood samples for PK evaluation will be collected per the schedule shown below. All other study procedures should be conducted as outlined in Section 5.0.

- Week 8: immediately after completion of infusion and 2 hours post completion of infusion
- Weeks 9, 10, 11: a visit window of ± 3 days would be applicable for these visits

PK samples should be processed according to the guidelines in Section 5.3.2.2 and Section 5.3.2.3. Subjects will follow all other protocol-specified procedures (as outlined in Appendix C)

NOTE: The date and time of site-administered dose and blood sample collection will be recorded to the nearest minute in the source documents and will be recorded to the nearest minute on the eCRF.

Appendix I. Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis[24] is highly likely when any one of the following 3 criteria are fulfilled:

1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING

   a) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

   b) Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

   a) Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips tongue-uvula)

   b) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

   c) Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)

   d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3) Reduced BP after exposure to known allergen for that patient (minutes to several hours):

   a) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*

b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline.

PEF: peak expiratory flow; BP: blood pressure

* low systolic BP for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mg Hg from 11 to 17 years.

Serious Systemic Hypersensitivity Reaction: A hypersensitivity reaction is a clinical sign or symptom, or constellation of signs or symptoms, caused by an inappropriate and excessive immunologic reaction to study drug administration. A systemic hypersensitivity reaction is a hypersensitivity reaction that does not occur at the local site of study drug administration (e.g., not an injection site reaction). A serious systemic hypersensitivity reaction is a systemic hypersensitivity reaction that fulfills criteria for a serious adverse event as specified in Section 6.1.1.2.

In the event of an anaphylactic reaction, blood samples will be drawn per Appendix C after the onset of the reaction. This will include: histamine and tryptase. A blood sample for ADA assessment will also be collected along with 1 hour blood samples for above assessments. Separate instructions for the collection, handling, storage and shipping of these labs will be provided outside of the study protocol.

Appendix J. Tanner Stage 5 for Development

Tanner Stage 5 for Development[25,26]

Puberty and the Tanner Stages – developed by Professor James M Tanner

Introduction

Adolescents experience several types of maturation, including cognitive (the development of formal operational thought), psychosocial (the stages of adolescence), and biologic. The complex series of biologic transitions are known as puberty, and these changes may impact psychosocial factors.

The most visible changes during puberty are growth in stature and development of secondary sexual characteristics.

Equally profound are changes in body composition; the achievement of fertility; and changes in most body systems, such as the neuroendocrine axis, bone size, and mineralization; and the cardiovascular system. As an example, normal cardiovascular changes, including greater aerobic power reserve, electrocardiographic changes, and blood pressure changes, occur during puberty.

The normal sequence of pubertal events and perils of puberty are reviewed here. This is within the normal ranges and does not take into account Precocious Puberty or Delayed Puberty.

Tanner Stages

Conceptually, pubertal maturation can be described in terms of sequence, timing, and tempo (Puberty consists of a series of predictable events, and the sequence of changes in secondary sexual characteristics has been categorized by several groups. The staging system utilized most frequently is that published by Marshall and Tanner and the sequence of changes, commonly referred to as "Tanner stages," is described below.

Boys – development of external genitalia

Stage 1: Prepubertal

Stage 2: Enlargement of scrotum and testes; scrotum skin reddens and changes in texture

Stage 3: Enlargement of penis (length at first); further growth of testes

Stage 4: Increased size of penis with growth in breadth and development of glans; testes and scrotum larger, scrotum skin darker

Stage 5: Adult genitalia

Girls – breast development

Stage 1: Prepubertal

Stage 2: Breast bud stage with elevation of breast and papilla; enlargement of areola

Stage 3: Further enlargement of breast and areola; no separation of their contour

Stage 4: Areola and papilla form a secondary mound above level of breast

Stage 5: Mature stage: projection of papilla only, related to recession of areola

Boys and girls – pubic hair

Stage 1: Prepubertal (can see velus hair similar to abdominal wall)

Stage 2: Sparse growth of long, slightly pigmented hair, straight or curled, at base of penis or along labia

Stage 3: Darker, coarser and more curled hair, spreading sparsely over junction of pubes

Stage 4: Hair adult in type, but covering smaller area than in adult; no spread to medial surface of thighs

Stage 5: Adult in type and quantity, with horizontal distribution ("feminine")

Boys Growth

- Stage 1: 5 – 6 cm/year
- Stage 2: 5 – 6 cm/year
- Stage 3: 7 – 8 cm/year
- Stage 4: 10 cm/year
- Stage 5: No further height increase after 17 years

Girls Growth

- Stage 1: 5 – 6 cm/year
- Stage 2: 7 – 8 cm/year
- Stage 3: 8 cm/year
- Stage 4: 7 cm/year
- Stage 5: No further height after 16 years

Appendix K. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes

Section 1.2 Synopsis
Previously read:

AbbVie Inc.	**Protocol Number:** M16-006
Name of Study Drug: Risankizumab (ABBV-066)	**Phase of Development:** 3
Name of Active Ingredient: Risankizumab	**Date of Protocol Synopsis:** 28 July 2020
Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study of the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Crohn's Disease	
Objective: The objective of Study M16-006 is to evaluate the efficacy and safety of risankizumab versus placebo during induction therapy in subjects with moderately to severely active Crohn's disease (CD).	
Investigators: Multicenter	
Study Sites: Approximately 400 sites	

Study Population: Males and females aged ≥ 18 to ≤ 80 years of age, or minimum age of adult consent according to local regulations at the Baseline visit, or aged 16 to < 18 years of age where locally permitted and who meet the definition of Tanner stage 5 development (refer to Appendix J) at the Baseline visit, with a diagnosis of moderately to severely active CD, defined as:

1. average daily stool frequency (SF) ≥ 4 (when calculating SF, only the number of liquid or very soft stools should be recorded) and/or average daily abdominal pain (AP) score ≥ 2; plus
2. endoscopic evidence of mucosal inflammation as measured by the Simple Endoscopic Score for CD (SES-CD). All eligible scores exclude the presence of narrowing component and are confirmed by a central reader. Endoscopic activity is defined as a SES-CD of ≥ 3.

The number of subjects enrolled with a SES-CD of ≥ 3 to < 6 for ileocolonic or colonic disease or SES-CD of 3 for isolated ileal disease will be no more than 85 subjects. Once cap of no more than 85 subjects is reached, enrollment criterion will be an eligibility SES-CD of ≥ 6 for ileocolonic or colonic disease, or eligibility SES-CD of ≥ 4 for isolated ileal disease.

The study will enroll both subjects who have had an inadequate response (IR) to prior biologic therapy (bio-IR) and subjects who have not (non-bio-IR). The bio-IR enrollment will be approximately 540 subjects and the non-bio-IR enrollment will be approximately 315 subjects.

The **bio-IR** population is defined as subjects with documented intolerance or inadequate response to one or more of the approved anti-TNF or anti-integrin biologics for CD (infliximab, adalimumab, certolizumab, vedolizumab, ustekinumab and/or natalizumab).

The **non-bio-IR** population will include subjects who had an inadequate response or intolerance to conventional therapy. Conventional therapy is defined as one or more of the following: aminosalicylates, oral locally acting steroids (e.g., budesonide, beclomethosone), systemic corticosteroids (prednisone or equivalent), or immunomodulators. This population will also include subjects who have received biologic therapy in the past but stopped therapy based on reasons other than inadequate response or intolerance (e.g., change in reimbursement coverage, well-controlled disease).

The percent of subjects with exposure, including intolerance or inadequate response, to ustekinumab will be no more than 20%.

Number of Subjects to be Enrolled: Approximately 855 for the primary ITT population used for efficacy analysis; additionally, up to 85 subjects with lower SES-CD will be enrolled

Methodology:

Study M16-006 is a randomized, double blind, placebo-controlled 12-week induction study.

Subjects (n = 855) will be randomized 2:2:1 to 1200 mg risankizumab or 600 mg risankizumab or placebo intravenous (IV) given at Baseline, Weeks 4 and 8. The randomization will be stratified by number of prior biologics failed (0, 1, > 1), Baseline steroid use (yes, no), and Baseline SES-CD (original, alternative), where the stratum of "original" includes the patients with baseline SES-CD of ≥ 6 (or ≥ 4 for subjects with isolated ileal disease), and the stratum of "alternative" includes the patients with baseline SES-CD of ≥ 3 to < 6 for ileocolonic or colonic disease or SES-CD of 3 for isolated ileal disease.

Visits during the study will occur at Baseline and Weeks 4, 8, and 12/Premature Discontinuation (PD) to collect clinical and laboratory assessments of disease activity. Subjects who do not achieve clinical response at Week 12 will be offered blinded risankizumab therapy in Induction Period 2 with evaluation for clinical response at Week 24.

All subjects will be provided with a subject diary where they will record CD related symptoms throughout the study. Subjects will also be dispensed a patient information card at Screening. Additionally, subjects will complete symptom, quality of life (QoL) and work productivity questionnaires throughout the study. Clinical labs including, but not limited to, urinalysis, chemistry and hematology, high-sensitivity C-reactive protein (hs-CRP), serum risankizumab concentrations, and serum anti-drug antibody (ADA) levels will be collected throughout the study. In addition, stool samples for calprotectin analysis will be collected and should be taken before starting bowel preparations for endoscopy. All endoscopies will be evaluated using SES-CD and will be confirmed by a central reader. Biopsy to confirm diagnosis (during Screening) or to rule out dysplasia/malignancy may be performed during the same time points as the endoscopy. Optional exploratory research samples may be taken during the study.

At the Week 12/PD visit, all subjects will undergo an endoscopy for evaluation of mucosal inflammation. It is expected that all subjects who remain in the study through at least Week 8 will have a Week 12/PD endoscopy. All subjects achieving clinical response, defined as ≥ 30% decrease in average daily SF and/or ≥ 30% decrease in average daily AP score (both not worse than Baseline) at Week 12 may be eligible to enter Study M16-000. Subjects are not eligible to enter Study M16-000 until endoscopy has been completed (local reader results will be used for stratification for Study M16-000).

All subjects who do not achieve clinical response at Week 12 may be eligible to receive blinded risankizumab treatment in Induction Period 2 as specified below. Subjects are not eligible to enter Induction Period 2 until the Week 12 endoscopy has been completed.

<u>Induction Period 2:</u>

At Week 12, subjects who do not achieve clinical response will be randomized by Interactive Response Technologies (IRT) to Induction Period 2, a double-blind, double-dummy 12-week treatment period.

Subjects who received IV risankizumab induction treatment with inadequate clinical response at Week 12 will be randomized 1:1:1 to:

- Group 1: 1200 mg IV risankizumab
- Group 2: 360 mg SC risankizumab
- Group 3: 180 mg SC risankizumab

Methodology (Continued):

Subjects who received IV placebo induction treatment will receive:

- Group 4: 1200 mg IV risankizumab

The IV risankizumab dose or matching IV placebo will be given at Weeks 12, 16, and 20. The SC risankizumab dose or matching SC placebo will be given at Weeks 12, and 20. At Week 24, subjects who received treatment in Induction Period 2 will be reassessed and undergo a third endoscopy for evaluation of mucosal inflammation. Subjects who achieve clinical response at Week 24 may be eligible to enter Study M16-000. Subjects without clinical response at Week 24, as well as all subjects who terminate the study early (including subjects who are eligible for, but do not enter Induction Period 2), will be discontinued and have a follow-up call 140 days from the last dose of study drug to obtain information on any new or ongoing AEs.

Concomitant aminosalicylates, immunomodulators (azathioprine [AZA], 6-mercaptopurine [6-MP], methotrexate [MTX]), and/or CD-related antibiotics.

Subjects taking aminosalicylates, immunomodulators, and/or CD-related antibiotics at Baseline must continue these treatments for the duration of the study. Initiating and/or increasing doses of aminosalicylates, immunomodulators, and/or CD-related antibiotics during the study is prohibited. Decreasing doses of aminosalicylates, immunomodulators, and/or CD-related antibiotics is prohibited during the study, except in the event of moderate-to-severe treatment related toxicities and after discussion with the AbbVie Therapeutic Area Medical Director (TA MD). CD-related antibiotics may be discontinued in Induction Period 2 at the discretion of the Investigator.

Note: the duration of the study includes Induction Period 2.

Concomitant Corticosteroids

Subjects taking corticosteroids at Baseline must continue their concomitant treatment at the Baseline dose for the duration of the 12-week induction period. Initiation and/or increasing doses of systemic and/or CD related corticosteroids during the entire study is prohibited. Decreasing doses of corticosteroids is prohibited during the 12-week induction period, except in the event of moderate-to-severe treatment related toxicities and after discussion with the AbbVie TA MD.

Subjects who receive Induction Period 2 treatment during Weeks 12 to 24 will be allowed to taper their corticosteroids at the discretion of the Investigator. Increasing doses above the Baseline dose is prohibited.

Dose Selection

This study will evaluate two IV doses of risankizumab (600 mg and 1200 mg) during induction. The selection of the doses in this study is informed by the analysis of the safety and efficacy data, as well as the exposure-response relationship of efficacy, of a Phase 2 study in subjects with CD that explored 200 mg and 600 mg doses. The results from the Phase 2 study suggest a potential for increased benefit with 1200 mg administration.

Methodology (Continued):

Induction Period 2 will evaluate IV (1200 mg Q4w) or SC (180 mg or 360 mg Q8w; maintenance dosing regimen) risankizumab. The purpose of Induction Period 2 is to evaluate the efficacy and safety of re-induction of risankizumab (1200 mg IV at Weeks 12, 16, and 20) versus initiating maintenance dosing on clinical response status. Data from the Phase 2 study in subjects with CD suggested that re-induction with 600 mg IV increased both clinical response and clinical remission in subjects with inadequate response at Week 12. The selection of the SC doses is informed by the analysis of the safety and efficacy data, as well as the exposure-response relationship of efficacy, of the maintenance period during the Phase 2 study in subjects with CD that evaluated 180 mg SC risankizumab for maintenance. The results from the Phase 2 study suggest a potential for increased benefit with 360 mg SC administration for maintenance regimen.

Data Monitoring Committee (DMC)

An external independent DMC will review unblinded safety data on a cohort level, at a minimum of 6-month intervals throughout the course of the study. At the timing of this amendment, the DMC has provided recommendation that the study may continue without modification and allowed enrollment to begin for 16 - 17 year-olds. A patient information card with information of the symptoms and signs of hypersensitivity reactions, infusion related reactions as well as late stage reactions will be provided to the patients at Screening so that any such events once occurred will be reported immediately by the patients to the investigator.

A separate DMC charter will be prepared outside of the protocol and will describe the roles and responsibilities of the DMC member, frequency and triggers of data reviews, and relevant safety data to be assessed. The cardiac adjudication committee (CAC) and anaphylaxis adjudication committee (AAC) adjudicates blinded data and the DMC reviews the data in an unblinded manner. Unblinded adjudicated cardio-cerebrovascular events and anaphylactic reactions will be presented to the DMC for review on a periodic basis. Communications from the DMC to the Study Teams will not contain information that could potentially unblind the team to subject treatment assignments.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Males or females ≥ 18 and ≤ 80 years of age or minimum age of adult consent according to local regulations at the Baseline Visit. Where locally permissible, subjects 16 to < 18 years of age who meet the definition of Tanner stage 5 for development (refer to Appendix J), at the Baseline Visit (sites will be notified when adolescents may enroll).
2. Confirmed diagnosis of CD for at least 3 months prior to Baseline. Appropriate documentation of biopsy results consistent with the diagnosis of CD, in the assessment of the Investigator, must be available.
3. Crohn's disease activity index (CDAI) score 220 – 450 at Baseline.
4. Endoscopic evidence of mucosal inflammation as documented by an SES-CD of ≥ 3. All eligible scores exclude the presence of narrowing component and are confirmed by a central reader. (Once cap of no more than 85 subjects is reached, enrollment criterion will be an SES-CD of ≥ 6 for ileocolonic or colonic disease or SES-CD of ≥ 4 for isolated ileal disease.)
5. Average daily SF ≥ 4 and/or average daily AP score ≥ 2 at Baseline.
6. Demonstrated intolerance or inadequate response to one or more of the following categories of drugs: aminosalicylates, oral locally acting steroids, systemic steroids (prednisone or equivalent), immunomodulators, and/or biologic therapies
    - Demonstration of intolerance requires no minimum dose or duration of use (intolerance includes patients with a known TPMT genetic mutation or low activity).
    - Inadequate response is defined as outlined below:
        - Oral aminosalicylates (e.g., mesalamine, sulfasalazine, olsalazine, balsalazide):
            - Signs and symptoms of persistently active disease, in the opinion of the Investigator, during a current or prior course of at least 4 weeks of treatment with 2.4 g/day mesalamine, 4 g/day sulfasalazine, 1 g/day olsalazine, or 6.75 g/day balsalazide,
        - Oral locally acting steroids (e.g., budesonide, beclomethasone):
            - Signs and symptoms of persistently active disease, in the opinion of the Investigator, during or after a course of at least 4 weeks of treatment with 9 mg/day budesonide or 5 mg/day beclomethasone,

              or
            - Inability to taper oral budesonide to at or below 6 mg/day without recurrent active disease,
        - IV or Oral systemic steroids (prednisone or equivalent):
            - Signs and symptoms of persistently active disease, in the opinion of the Investigator, during or after tapering of at least one regimen consisting of a dose equivalent to prednisone ≥ 40 mg/day orally for 3 weeks or intravenously for 1 week,

              or
            - Inability to taper oral systemic steroids to at or below a dose equivalent to prednisone 10 mg/day without recurrent active disease,

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

- Immunomodulators:
  - Signs and symptoms of persistently active disease, in the opinion of the Investigator, during a current or prior course of at least 90 days of treatment with one or more of the following:
    - AZA: ≥ 2.0 mg/kg/day rounded to the nearest available tablet or half tablet formulation (≥ 1 mg/kg/day for subjects in Japan, Korea, Hong Kong, Taiwan, Singapore, or China) (or a documented 6-TGN level of ≥ 230 pmol/8 × 10^8 RBC)
    - 6-MP: ≥ 1 mg/kg/day rounded to the nearest available tablet or half tablet formulation (≥ 0.6 mg/kg/day for subjects in Japan, Korea, Hong Kong, Taiwan, Singapore, or China) (or a 6-TGN level of ≥ 230 pmol/8 × 10^8 RBC)
    - MTX: ≥ 15 mg/week subcutaneous (SC) or intramuscular (IM)
      - *Note:* Oral MTX use is allowed during the study, however prior or current use of oral MTX is not sufficient for inclusion into the study
- Biologic Therapies for CD:
  - Signs and symptoms of persistently (in the opinion of the Investigator) active disease despite a history of one or more of the following:
    - At least one 6-week induction regimen of infliximab (≥ 5 mg/kg IV at Weeks 0, 2, and 6),
    - At least one 4-week induction regimen of adalimumab (one 160 mg SC dose at Week 0, followed by one 80 mg SC dose at Week 2 [or one 80 mg SC dose at Week 0, followed by one 40 mg SC dose at Week 2, in countries where this dosing regimen is approved]),
    - At least one 4-week induction regimen of certolizumab pegol (400 mg SC at Weeks 0, 2, and 4),
    - At least one 6-week induction regimen of vedolizumab (300 mg IV at Weeks 0, 2, and 6)
    - At least one 12-week induction regimen of natalizumab (300 mg IV every 4 weeks)
    - At least one 8-week induction regimen of ustekinumab [260 mg (≤ 55 kg) or 390 mg (> 55 to ≤ 85 kg) or 520 mg (> 85 kg) IV, followed by 90 mg SC at Week 8] (Once cap of no more than 20% ustekinumab exposed subjects is reached, subjects with prior ustekinumab exposure will not be allowed to enroll.)

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

- Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit of the above biologics
- Note: Subjects who discontinued biologics for reasons other than inadequate response as defined above or intolerance (e.g., change of insurance) must meet the criteria for intolerance or inadequate response to aminosalicylates, oral locally acting steroids, systemic steroids (prednisone or equivalent), and/or immunomodulators as defined above

7. If female, subject must meet the criteria as stated in Section 5.2.4 of this protocol *Contraception Recommendations*. Females of childbearing potential must have a negative serum pregnancy test result during Screening, and a negative urine pregnancy at Baseline. Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) during Screening do not require pregnancy testing at Baseline.

   Note: Subjects with borderline serum pregnancy test at Screening must have a serum pregnancy test ≥ 3 days later to document continued lack of a positive result.
8. Subjects must be able and willing to give written informed consent and to comply with the requirements of this study protocol. In Japan, if the subject is < 20 years old, a subject's parent or legal guardian must be willing to give written informed consent.

Main Exclusion:

1. Subject with a current diagnosis of ulcerative colitis or indeterminate colitis.

<u>Concomitant Medications and Treatments</u>

2. Subject on CD-related antibiotics who has not been on stable doses for greater than, or discontinued within, 14 days prior to Baseline.
3. Subject on oral aminosalicylates who has not been on stable doses for greater than, or discontinued within, at least 14 days prior to Baseline.
4. Subject taking oral corticosteroids:
   - Budesonide > 9 mg/day
   - Beclomethasone > 5 mg/day
   - Prednisone or equivalent > 20 mg/day
   - Or has not been on the current course for ≥ 14 days prior to Baseline and on a stable dose for ≥ 7 days prior to Baseline
5. Subject on immunomodulators (AZA, 6-MP, MTX) who:
   - Has not been on the current course for ≥ 42 days prior to Baseline, and
   - Has not been on a stable dose for ≥ 35 days prior to Baseline

<u>Medications and Treatments During the Screening Period</u>

6. Subject who received IV anti-infectives within 35 days prior to Baseline visit or oral/intramuscular anti-infectives (non-CD-related) within 14 days prior to the Baseline visit. This does not apply to TB prophylaxis.
7. Subject who received exclusive enteral nutrition or any parenteral nutrition within 35 days prior to Baseline.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

Medications and Treatments During the Screening Period (Continued)

8. Subject who received any live bacterial or viral vaccination within 30 days (8 weeks for Japan) prior to Screening or during the Screening Period.
9. Subject who received cyclosporine, tacrolimus, or mycophenolate mofetil within 35 days prior to Baseline.
10. Subject who received fecal microbial transplantation within 35 days prior to Baseline.

Prior Medications and Treatments

11. Subject who received any:
    - Approved biologics: infliximab, adalimumab, certolizumab, vedolizumab, natalizumab) within 8 weeks prior to Baseline, or ustekinumab within 12 weeks prior to Baseline

      Note: If there is proper documentation of an undetectable drug level measured by a commercially available assay for any of the approved biologics above, there is no minimum washout prior to Baseline.
    - Any investigational biologic or other agent or procedure within 35 days or 5 half-lives prior to Baseline, whichever is longer.
12. Subject with prior exposure to p19 inhibitors (e.g., risankizumab).
13. Subject has been taking combination of two or more of the following: oral budesonide, or oral beclomethasone and/or oral prednisone (or equivalent) simultaneously, with the exception of inhalers, within 14 days prior to Screening or during the Screening period.
14. Subject who received IV/intramuscular corticosteroids within 14 days prior to Screening or during the Screening period.
15. Subject who received therapeutic enema or suppository, other than required for endoscopy, within 14 days prior to endoscopy used for Screening or during the Screening period.
16. Subject who received apheresis (e.g., Adacolumn apheresis) ≤ 60 days prior to Screening or during the Screening period.
17. Subject who has concomitant cannabis use either recreational or for medical reasons within 14 days prior to Baseline or any history of clinically significant drug, or alcohol abuse in the last 12 months.

CD Related

18. Subject with currently known complications of CD such as:
    - abscess (abdominal or perianal),
    - symptomatic bowel strictures,
    - > 2 missing segments of the following 5 segments: terminal ileum, right colon, transverse colon, sigmoid and left colon, and rectum
    - fulminant colitis,
    - toxic megacolon,
    - or any other manifestation that might require surgery while enrolled in the study.
19. Subject with ostomy or ileoanal pouch.
20. Subject diagnosed with short gut or short bowel syndrome.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

21. Subject with surgical bowel resection within the past 3 months prior to Baseline, or a history of ≥ 3 bowel resections.

Safety

22. Subject who has a known hypersensitivity to risankizumab or the excipients of any of the study drugs or the ingredients of Chinese hamster ovary (CHO).
23. Subjects with the following chronic or active infections:
    - Active, chronic, or recurrent infection that based on the Investigator's clinical assessment makes the subject unsuitable candidate for the study,
    - Infection with C. *difficile* toxin or other intestinal pathogen during Screening,
    - Are infected with human immunodeficiency virus (HIV),
    - QuantiFERON®-TB test or Purified Protein Derivative (PPD) skin test, or both, according to local guidelines, will be performed during Screening. QuantiFERON®-TB test is preferred for subjects who received BCG vaccination or were exposed to other Mycobacteria species. Subjects with a positive test result (or indeterminate results that have been repeated) may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active tuberculosis. Subjects with a history of active TB who have documented completion of a full course of anti-TB therapy may be allowed to enter the study after consultation with the AbbVie TA MD. If latent TB is established, TB prophylaxis/treatment should be initiated and maintained according to local country guidelines.
    - Have active hepatitis B or hepatitis C defined as:
        - HBV: hepatitis B surface antigen (HBs Ag) positive (+), or detected sensitivity on the HBV deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) qualitative test for hepatitis B core antibody (HBc Ab) positive subjects;
        - HCV: HCV ribonucleic acid (RNA) detectable in any subject positive with anti-HCV antibody (HCV Ab)
24. Subject with a previous history of dysplasia of the gastrointestinal tract or found to have dysplasia, other than completely removed low-grade dysplastic lesions, in any biopsy performed during the Screening endoscopy.
25. Subject with a known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly.
26. Subject with current or previous history of malignancy other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix.
27. Subject who has severe, progressive, or uncontrolled renal, hepatic, hematological, endocrine, disorder or symptoms thereof.
28. Female subjects who is pregnant, breastfeeding, or is considering becoming pregnant during the study or for approximately 140 days after the last dose of study drug.
29. Subject who has any condition, including any physical, psychological, or psychiatric condition, which in the opinion of the Investigator, would compromise the safety of the subject or the quality of the data and renders the subject an unsuitable candidate for the study.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

Safety (Continued):

30. Screening laboratory and other analyses show any of the following abnormal results:
    - Aspartate transaminase (AST), alanine transaminase (ALT) > 2 × upper limit of the reference range;
    - White blood cell (WBC) count < 3.0×10^9/L;
    - Total bilirubin ≥ 2 mg/dL; except for subjects with isolated elevation of indirect bilirubin relating to Gilbert syndrome;
    - Estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula < 30 ml/min/1.73 m^2.
    - Hemoglobin < 8 g/dL
    - Platelets < 100,000/µL
    - Positive serum pregnancy test at the Screening visit or positive urine pregnancy test at the Baseline visit.

    Laboratory values can be re-tested once during the screening period after discussion and clearance with the TAMD. If the re-tested lab value(s) remain(s) exclusionary, the subject will be considered a screen failure. Redrawing samples if previous samples were unable to be analyzed would not count as a retest since previous result was never obtained.
31. No known active COVID-19 infection. Subject must not have signs/symptoms associated with COVID-19 infection.

    Subjects who do not meet COVID-19 eligibility criteria must be screen failed and may only rescreen after they meet the following COVID-19 viral clearance criteria:
    - Symptomatic subjects: At least 2 negative viral tests in a row completed locally, ≥ 24 hours apart after at least 10 days have passed since recovery, defined as resolution of fever without use of antipyretics and improvement in respiratory symptoms (e.g., cough, shortness of breath)
    - Asymptomatic subjects: At least 2 negative viral tests in a row completed locally, ≥ 24 hours apart after at least 10 days have passed since prior positive result (Note: subjects who develop symptoms will follow guidance above for symptomatic subjects)

    Frequency or timing of COVID-19 testing and interval between testing for the above viral clearance criteria may be adjusted to account for epidemiological trends, updated information regarding infectivity and local/institutional guidelines.

Investigational Product:	Risankizumab
Doses:	Risankizumab 1200 mg IV Q4W* Risankizumab 600 mg IV Q4W Risankizumab 180 mg SC Q8W Risankizumab 360 mg SC Q8W * If the 1200 mg dose is discontinued due to any reason, subjects will continue to enroll into the study and be randomized to either 600 mg risankizumab or placebo at 2:1 ratio. The randomization ratio and sample size may be further updated in an amendment to the protocol. Subjects already randomized to treatment arms, including Induction Period 2, will receive blinded 600 mg risankizumab IV.
Mode of Administration:	Risankizumab solution for infusion (IV) Risankizumab solution for injection (SC)
Reference Therapy:	Placebo for risankizumab
Dose:	N/A
Mode of Administration:	Placebo solution for infusion (IV) Placebo solution for injection (SC)

Duration of Treatment: 12 or 24 weeks

The study will include a Screening period of up to 35 days and a double-blind induction period of 12 weeks. All subjects who do not achieve clinical response at Week 12 will be eligible to receive treatment in Induction Period 2 with risankizumab over a subsequent 12 week period. There will be a follow up call 140 days from the last dose of study drug to obtain information on any new or ongoing AEs for those subjects who do not roll over into Study M16-000 or discontinue from the study prematurely.

Criteria for Evaluation:

Endpoint Definitions:

- **Clinical remission:** average daily SF $\leq$ 2.8 and not worse than Baseline AND average daily AP score $\leq$ 1 and not worse than Baseline
- **Enhanced clinical response:** $\geq$ 60% decrease in average daily SF and/or $\geq$ 35% decrease in average daily AP score and both not worse than Baseline, and/or clinical remission
- **Clinical response:** $\geq$ 30% decrease in average daily SF and/or $\geq$ 30% decrease in average daily AP score and both not worse than Baseline
- **Endoscopic response:** decrease in SES-CD > 50% from Baseline (or for subjects with isolated ileal disease and a Baseline SES-CD of 4, at least a 2 point reduction from Baseline), as scored by central reviewer
- **Ulcer-free endoscopy:** SES-CD ulcerated surface subscore of 0 in subjects with SES-CD ulcerated surface subscore $\geq$ 1 at Baseline, as scored by a central reviewer
- **Endoscopic remission:** SES-CD $\leq$ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable, as scored by a central reviewer

Criteria for Evaluation (Continued):

Endpoint Definitions (Continued):

- **CDAI clinical response:** reduction of CDAI ≥ 100 points from baseline
- **CDAI clinical remission:** CDAI < 150

Efficacy:

Co-Primary Endpoints:

- Proportion of subjects with clinical remission at Week 12
- Proportion of subjects with endoscopic response at Week 12

Ranked Secondary Endpoints:

1. Proportion of subjects with CDAI clinical remission at Week 12
2. Proportion of subjects with CDAI clinical response at Week 4
3. Proportion of subjects with clinical remission at Week 4
4. Proportion of subjects with CDAI clinical response at Week 12
5. Mean change from baseline of induction in FACIT fatigue at Week 12
6. Mean change from baseline of induction in IBDQ total score at Week 12
7. Proportion of subjects with enhanced clinical response and endoscopic response at Week 12
8. Proportion of subjects with endoscopic remission at Week 12
9. Proportion of subjects with enhanced clinical response at Week 4
10. Proportion of subjects with ulcer-free endoscopy at Week 12
11. Enhanced clinical response at Week 12
12. Proportion of subjects with resolution of extra-intestinal manifestations (EIMs) at Week 12, in subjects with any EIMs at Baseline
13. Proportion of subjects with CD-related hospitalization through Week 12
14. Proportion of subjects without draining fistulas at Week 12 in subjects with draining fistulas at Baseline

For further information, including non-ranked endpoints, refer to protocol

Pharmacokinetics:

Serum risankizumab concentrations will be determined from samples collected just prior to dosing at Weeks 4, 8, and 12/PD, and at Week 24 for subjects who receive treatment in Induction Period 2.

Additionally, intensive pharmacokinetic assessment will be performed in 20 subjects after the 3rd induction dose (Week 8 to 12). For Subjects who consent to the intensive pharmacokinetic assessment, in addition to the time points above, blood samples will be collected at Week 8 immediately after completion of infusion and 2 hours post completion of infusion, and at Weeks 9, 10, and 11. Refer to Appendix H for more details.

Immunogenicity:

Serum ADAs will be determined from samples collected just prior to dosing at Baseline and Weeks 4, 8, and 12/PD, and at Week 24 for subjects who receive treatment in Induction Period 2.

Criteria for Evaluation (Continued):

Safety:

Safety analyses will be performed on safety set which includes all subjects who receive at least one dose of study drug. Incidence of adverse events (AEs), changes in vital signs, physical examination results, and clinical laboratory data will be assessed throughout the study.

Exploratory Research Variables and Validation Studies (Optional):

Prognostic, surrogate, predictive and pharmacodynamics biomarkers signatures may be investigated. Samples for different applications, including but not limited to, pharmacogenetic, epigenetic, transcriptomic, proteomic, metabolomics, metagenomic and targeted investigations will be collected at various time points. Assessments will include but may not be limited to nucleic acids, proteins, metabolites or lipids.

Statistical Methods:

Efficacy:

The co-primary endpoints are the proportion of subjects with clinical remission at Week 12 and proportion of subjects with endoscopic response at Week 12. A total of approximately 855 subjects will be randomized into two risankizumab treatment groups and the placebo group in a 2:2:1 ratio (342 subjects for risankizumab 600 mg dose group, 342 subjects for risankizumab 1200 mg dose group, and 171 subjects for placebo group). When all patients complete their Week 12/PD visit, the database will be locked for the final analysis of 12-week induction period. When all the patients who enter the induction Period 2 finish Week 24/PD visit, the database will be locked for the whole study and all the planned analysis for the induction Period 2 will be performed.

Sample size calculation is based on the larger sample size needed to detect treatment difference for each of the co-primary endpoints. Since historical data show slightly lower event rate and similar treatment difference versus placebo for the endoscopic response rate than the clinical remission rate at Week 12, clinical remission rates at Week 12 are used for power calculation. Assuming the Week 12 clinical remission rate will be 27.8% for one of the risankizumab dose groups and 12% for the placebo group, a sample size of 342 subjects for each of the risankizumab dose groups and 171 for the placebo group will have 97% power to detect the treatment difference between the risankizumab dose groups and placebo in clinical remission rates at Week 12 using Fisher's exact test at alpha of 0.025 (two-sided).

The bio-IR population is approximately 540 subjects. The study will have 80% power to detect the treatment difference between one of the risankizumab dose groups and placebo in clinical remission rates at Week 12 using Fisher's exact test at alpha of 0.025 (two-sided) for the bio-IR population, assuming the Week 12 clinical remission rate will be 24.2% for the risankizumab dose groups and 10% for the placebo group for bio-IR subjects. The non-bio-IR population is approximately 315 subjects. The study will have 72% power to detect the treatment difference between one of the risankizumab dose groups and placebo in clinical remission rates, at Week 12 using Fisher's exact test at alpha of 0.025 (two-sided) for the non-bio-IR sub-population, assuming the Week 12 clinical remission rate will be 35% for the risankizumab dose groups and 15% for the placebo group for non-bio-IR subjects.

The comparisons between each risankizumab dose versus placebo for the primary efficacy variable will be performed using the Cochran-Mantel-Haenszel (CMH) test adjusted by prior biologic use (0, 1, > 1) and Baseline steroid use (yes, no). Both of the co-primary efficacy endpoints will be tested at statistically significant of 0.025 for each of the risankizumab dose groups versus placebo to adjust for multiplicity. A CMH based two-sided 95% confidence interval for the difference between treatment groups will be calculated.

Statistical Methods (Continued):

Efficacy (Continued):

The intent-to-treat (ITT) set includes all randomized subjects who have taken at least one dose of study drug. The primary population for efficacy analysis are the subjects in the intent-to-treat analysis set who had baseline eligibility SES-CD of ≥ 6 (≥ 4 for isolated ileal disease). If the average daily SF or average daily AP score data at Week 12 are missing, the non-responder imputation (NRI) approach will be applied. Subjects who discontinue prior to Week 12 for any reason will be considered as "not-achieved" for clinical remission and endoscopic response endpoints.

In general, continuous secondary efficacy variables will be analyzed using a Mixed-Effect Model Repeated Measure (MMRM) model including factors for treatment group, visit, visit by treatment interaction, and stratification variables, for the longitudinal continuous endpoints. The MMRM analysis is considered primary for inferential purposes.

Pharmacokinetics and Immunogenicity:

Serum risankizumab concentrations will be summarized at each time point for each dosing regimen using descriptive statistics. Population pharmacokinetic analyses combining the data from this study and other studies may be performed. Relationships between risankizumab exposures and efficacy and safety variables of interest may be explored.

ADA incidence will be summarized by cohorts and study visits. ADA titers will be tabulated for each subject at the respective study visits. The effect of ADAs on risankizumab pharmacokinetics, efficacy and/or safety variable(s) and/or any additional analyses will be explored.

Safety:

Adverse events, laboratory data and vital signs are the primary safety parameters in this study. All safety comparisons will be performed between treatment groups using the safety set. Treatment emergent AEs are defined as events that begin or worsen either on or after the first dose of the study drug and within 140 days after the last dose of the study drug for subjects who do not participate in Study M16-000 or until first dose of study drug in Study M16-000 if the subject is enrolled in Study M16-000.

An overview of treatment-emergent AEs, AEs leading to death and AEs leading to premature discontinuation (see details in the statistical analysis plan [SAP]), AEs by Medical Dictionary for Drug Regulatory Activities (MedDRA version) preferred term and system organ class, AEs by maximum relationship to study drug, and AEs by maximum severity will be summarized by number and percentage.

Changes in laboratory data will be described using statistical characteristics and compared between treatment groups will be performed using a one-way Analysis of Variance (ANOVA). In addition, shift tables and listings will be provided for abnormal values, whereby the normal range of the analyzing laboratory will be used. Vital signs will be analyzed similarly.

Has been changed to read:

AbbVie Inc.	**Protocol Number:** M16-006
Name of Study Drug: Risankizumab (ABBV-066)	**Phase of Development:** 3
Name of Active Ingredient: Risankizumab	**Date of Protocol Synopsis:** 01 September 2020
Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study of the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Crohn's Disease	
Objective: The objective of Study M16-006 is to evaluate the efficacy and safety of risankizumab versus placebo during induction therapy in subjects with moderately to severely active Crohn's disease (CD).	
Investigators: Multicenter	
Study Sites: Approximately 400 sites	
Study Population: Males and females aged ≥ 18 to ≤ 80 years of age, or minimum age of adult consent according to local regulations at the Baseline visit, or aged 16 to < 18 years of age where locally permitted and who meet the definition of Tanner stage 5 development (refer to Appendix J) at the Baseline visit, with a diagnosis of moderately to severely active CD, defined as: 1. average daily stool frequency (SF) ≥ 4 (when calculating SF, only the number of liquid or very soft stools should be recorded) and/or average daily abdominal pain (AP) score ≥ 2; plus 2. endoscopic evidence of mucosal inflammation as measured by the Simple Endoscopic Score for CD (SES-CD). All eligible scores exclude the presence of narrowing component and are confirmed by a central reader. Endoscopic activity is defined as a SES-CD of ≥ 3. The number of subjects enrolled with a SES-CD of ≥ 3 to < 6 for ileocolonic or colonic disease or SES-CD of 3 for isolated ileal disease will be no more than 85 subjects. Once cap of no more than 85 subjects is reached, enrollment criterion will be an eligibility SES-CD of ≥ 6 for ileocolonic or colonic disease, or eligibility SES-CD of ≥ 4 for isolated ileal disease. The study will enroll both subjects who have had an inadequate response (IR) to prior biologic therapy (bio-IR) and subjects who have not (non-bio-IR). The bio-IR enrollment will be approximately 540 subjects and the non-bio-IR enrollment will be approximately 315 subjects. The **bio-IR** population is defined as subjects with documented intolerance or inadequate response to one or more of the approved anti-TNF or anti-integrin biologics for CD (infliximab, adalimumab, certolizumab, vedolizumab, ustekinumab and/or natalizumab). The **non-bio-IR** population will include subjects who had an inadequate response or intolerance to conventional therapy. Conventional therapy is defined as one or more of the following: aminosalicylates, oral locally acting steroids (e.g., budesonide, beclomethosone), systemic corticosteroids (prednisone or equivalent), or immunomodulators. This population will also include subjects who have received biologic therapy in the past but stopped therapy based on reasons other than inadequate response or intolerance (e.g., change in reimbursement coverage, well-controlled disease). The percent of subjects with exposure, including intolerance or inadequate response, to ustekinumab will be no more than 20%.	
Number of Subjects to be Enrolled: Approximately 855 for the primary ITT population used for efficacy analysis; additionally, up to 85 subjects with lower SES-CD will be enrolled	

Methodology:

Study M16-006 is a randomized, double blind, placebo-controlled 12-week induction study.

Subjects (n = 855) will be randomized 2:2:1 to 1200 mg risankizumab or 600 mg risankizumab or placebo intravenous (IV) given at Baseline, Weeks 4 and 8. The randomization will be stratified by number of prior biologics failed (0, 1, > 1), Baseline steroid use (yes, no), and Baseline SES-CD (original, alternative), where the stratum of "original" includes the patients with baseline SES-CD of ≥ 6 (or ≥ 4 for subjects with isolated ileal disease), and the stratum of "alternative" includes the patients with baseline SES-CD of ≥ 3 to < 6 for ileocolonic or colonic disease or SES-CD of 3 for isolated ileal disease.

Visits during the study will occur at Baseline and Weeks 4, 8, and 12/Premature Discontinuation (PD) to collect clinical and laboratory assessments of disease activity. Subjects who do not achieve clinical response at Week 12 will be offered blinded risankizumab therapy in Induction Period 2 with evaluation for clinical response at Week 24.

All subjects will be provided with a subject diary where they will record CD related symptoms throughout the study. Subjects will also be dispensed a patient information card at Screening. Additionally, subjects will complete symptom, quality of life (QoL) and work productivity questionnaires throughout the study. Clinical labs including, but not limited to, urinalysis, chemistry and hematology, high-sensitivity C-reactive protein (hs-CRP), serum risankizumab concentrations, and serum anti-drug antibody (ADA) levels will be collected throughout the study. In addition, stool samples for calprotectin analysis will be collected and should be taken before starting bowel preparations for endoscopy. All endoscopies will be evaluated using SES-CD and will be confirmed by a central reader. Biopsy to confirm diagnosis (during Screening) or to rule out dysplasia/malignancy may be performed during the same time points as the endoscopy. Optional exploratory research samples may be taken during the study.

At the Week 12/PD visit, all subjects will undergo an endoscopy for evaluation of mucosal inflammation. It is expected that all subjects who remain in the study through at least Week 8 will have a Week 12/PD endoscopy. All subjects achieving clinical response, defined as ≥ 30% decrease in average daily SF and/or ≥ 30% decrease in average daily AP score (both not worse than Baseline) at Week 12 may be eligible to enter Study M16-000. Subjects are not eligible to enter Study M16-000 until endoscopy has been completed (local reader results will be used for stratification for Study M16-000).

All subjects who do not achieve clinical response at Week 12 may be eligible to receive blinded risankizumab treatment in Induction Period 2 as specified below. Subjects are not eligible to enter Induction Period 2 until the Week 12 endoscopy has been completed.

<u>Induction Period 2:</u>

At Week 12, subjects who do not achieve clinical response will be randomized by Interactive Response Technologies (IRT) to Induction Period 2, a double-blind, double-dummy 12-week treatment period.

Subjects who received IV risankizumab induction treatment with inadequate clinical response at Week 12 will be randomized 1:1:1 to:

- Group 1: 1200 mg IV risankizumab
- Group 2: 360 mg SC risankizumab
- Group 3: 180 mg SC risankizumab

Methodology (Continued):

Subjects who received IV placebo induction treatment will receive:

- Group 4: 1200 mg IV risankizumab

The IV risankizumab dose or matching IV placebo will be given at Weeks 12, 16, and 20. The SC risankizumab dose or matching SC placebo will be given at Weeks 12, and 20. At Week 24, subjects who received treatment in Induction Period 2 will be reassessed and undergo a third endoscopy for evaluation of mucosal inflammation. Subjects who achieve clinical response at Week 24 may be eligible to enter Study M16-000. Subjects without clinical response at Week 24, as well as all subjects who terminate the study early (including subjects who are eligible for, but do not enter Induction Period 2), will be discontinued and have a follow-up call 140 days from the last dose of study drug to obtain information on any new or ongoing AEs.

Concomitant aminosalicylates, immunomodulators (azathioprine [AZA], 6-mercaptopurine [6-MP], methotrexate [MTX]), and/or CD-related antibiotics.

Subjects taking aminosalicylates, immunomodulators, and/or CD-related antibiotics at Baseline must continue these treatments for the duration of the study. Initiating and/or increasing doses of aminosalicylates, immunomodulators, and/or CD-related antibiotics during the study is prohibited. Decreasing doses of aminosalicylates, immunomodulators, and/or CD-related antibiotics is prohibited during the study, except in the event of moderate-to-severe treatment related toxicities and after discussion with the AbbVie Therapeutic Area Medical Director (TA MD). CD-related antibiotics may be discontinued in Induction Period 2 at the discretion of the Investigator.

Note: the duration of the study includes Induction Period 2.

Concomitant Corticosteroids

Subjects taking corticosteroids at Baseline must continue their concomitant treatment at the Baseline dose for the duration of the 12-week induction period. Initiation and/or increasing doses of systemic and/or CD related corticosteroids during the entire study is prohibited. Decreasing doses of corticosteroids is prohibited during the 12-week induction period, except in the event of moderate-to-severe treatment related toxicities and after discussion with the AbbVie TA MD.

Subjects who receive Induction Period 2 treatment during Weeks 12 to 24 will be allowed to taper their corticosteroids at the discretion of the Investigator. Increasing doses above the Baseline dose is prohibited.

Dose Selection

This study will evaluate two IV doses of risankizumab (600 mg and 1200 mg) during induction. The selection of the doses in this study is informed by the analysis of the safety and efficacy data, as well as the exposure-response relationship of efficacy, of a Phase 2 study in subjects with CD that explored 200 mg and 600 mg doses. The results from the Phase 2 study suggest a potential for increased benefit with 1200 mg administration.

Methodology (Continued):

Induction Period 2 will evaluate IV (1200 mg Q4w) or SC (180 mg or 360 mg Q8w; maintenance dosing regimen) risankizumab. The purpose of Induction Period 2 is to evaluate the efficacy and safety of re-induction of risankizumab (1200 mg IV at Weeks 12, 16, and 20) versus initiating maintenance dosing on clinical response status. Data from the Phase 2 study in subjects with CD suggested that re-induction with 600 mg IV increased both clinical response and clinical remission in subjects with inadequate response at Week 12. The selection of the SC doses is informed by the analysis of the safety and efficacy data, as well as the exposure-response relationship of efficacy, of the maintenance period during the Phase 2 study in subjects with CD that evaluated 180 mg SC risankizumab for maintenance. The results from the Phase 2 study suggest a potential for increased benefit with 360 mg SC administration for maintenance regimen.

Data Monitoring Committee (DMC)

An external independent DMC will review unblinded safety data on a cohort level, at a minimum of 6-month intervals throughout the course of the study. At the timing of this amendment, the DMC has provided recommendation that the study may continue without modification and allowed enrollment to begin for 16 - 17 year-olds. A patient information card with information of the symptoms and signs of hypersensitivity reactions, infusion related reactions as well as late stage reactions will be provided to the patients at Screening so that any such events once occurred will be reported immediately by the patients to the investigator.

A separate DMC charter will be prepared outside of the protocol and will describe the roles and responsibilities of the DMC member, frequency and triggers of data reviews, and relevant safety data to be assessed. The cardiac adjudication committee (CAC) and anaphylaxis adjudication committee (AAC) adjudicates blinded data and the DMC reviews the data in an unblinded manner. Unblinded adjudicated cardio-cerebrovascular events and anaphylactic reactions will be presented to the DMC for review on a periodic basis. Communications from the DMC to the Study Teams will not contain information that could potentially unblind the team to subject treatment assignments.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Males or females ≥ 18 and ≤ 80 years of age or minimum age of adult consent according to local regulations at the Baseline Visit. Where locally permissible, subjects 16 to < 18 years of age who meet the definition of Tanner stage 5 for development (refer to Appendix J), at the Baseline Visit (sites will be notified when adolescents may enroll).
2. Confirmed diagnosis of CD for at least 3 months prior to Baseline. Appropriate documentation of biopsy results consistent with the diagnosis of CD, in the assessment of the Investigator, must be available.
3. Crohn's disease activity index (CDAI) score 220 – 450 at Baseline.
4. Endoscopic evidence of mucosal inflammation as documented by an SES-CD of ≥ 3. All eligible scores exclude the presence of narrowing component and are confirmed by a central reader. (Once cap of no more than 85 subjects is reached, enrollment criterion will be an SES-CD of ≥ 6 for ileocolonic or colonic disease or SES-CD of ≥ 4 for isolated ileal disease.)
5. Average daily SF ≥ 4 and/or average daily AP score ≥ 2 at Baseline.
6. Demonstrated intolerance or inadequate response to one or more of the following categories of drugs: aminosalicylates, oral locally acting steroids, systemic steroids (prednisone or equivalent), immunomodulators, and/or biologic therapies
    - Demonstration of intolerance requires no minimum dose or duration of use (intolerance includes patients with a known TPMT genetic mutation or low activity).
    - Inadequate response is defined as outlined below:
        - Oral aminosalicylates (e.g., mesalamine, sulfasalazine, olsalazine, balsalazide):
            - Signs and symptoms of persistently active disease, in the opinion of the Investigator, during a current or prior course of at least 4 weeks of treatment with 2.4 g/day mesalamine, 4 g/day sulfasalazine, 1 g/day olsalazine, or 6.75 g/day balsalazide,
        - Oral locally acting steroids (e.g., budesonide, beclomethasone):
            - Signs and symptoms of persistently active disease, in the opinion of the Investigator, during or after a course of at least 4 weeks of treatment with 9 mg/day budesonide or 5 mg/day beclomethasone,

              or
            - Inability to taper oral budesonide to at or below 6 mg/day without recurrent active disease,
        - IV or Oral systemic steroids (prednisone or equivalent):
            - Signs and symptoms of persistently active disease, in the opinion of the Investigator, during or after tapering of at least one regimen consisting of a dose equivalent to prednisone ≥ 40 mg/day orally for 3 weeks or intravenously for 1 week,

              or
            - Inability to taper oral systemic steroids to at or below a dose equivalent to prednisone 10 mg/day without recurrent active disease,

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

- Immunomodulators:
  - Signs and symptoms of persistently active disease, in the opinion of the Investigator, during a current or prior course of at least 90 days of treatment with one or more of the following:
    - AZA: ≥ 2.0 mg/kg/day rounded to the nearest available tablet or half tablet formulation (≥ 1 mg/kg/day for subjects in Japan, Korea, Hong Kong, Taiwan, Singapore, or China) (or a documented 6-TGN level of ≥ 230 pmol/8 × 10^8 RBC)
    - 6-MP: ≥ 1 mg/kg/day rounded to the nearest available tablet or half tablet formulation (≥ 0.6 mg/kg/day for subjects in Japan, Korea, Hong Kong, Taiwan, Singapore, or China) (or a 6-TGN level of ≥ 230 pmol/8 × 10^8 RBC)
    - MTX: ≥ 15 mg/week subcutaneous (SC) or intramuscular (IM)
      - *Note:* Oral MTX use is allowed during the study, however prior or current use of oral MTX is not sufficient for inclusion into the study
- Biologic Therapies for CD:
  - Signs and symptoms of persistently (in the opinion of the Investigator) active disease despite a history of one or more of the following:
    - At least one 6-week induction regimen of infliximab (≥ 5 mg/kg IV at Weeks 0, 2, and 6),
    - At least one 4-week induction regimen of adalimumab (one 160 mg SC dose at Week 0, followed by one 80 mg SC dose at Week 2 [or one 80 mg SC dose at Week 0, followed by one 40 mg SC dose at Week 2, in countries where this dosing regimen is approved]),
    - At least one 4-week induction regimen of certolizumab pegol (400 mg SC at Weeks 0, 2, and 4),
    - At least one 6-week induction regimen of vedolizumab (300 mg IV at Weeks 0, 2, and 6)
    - At least one 12-week induction regimen of natalizumab (300 mg IV every 4 weeks)
    - At least one 8-week induction regimen of ustekinumab [260 mg (≤ 55 kg) or 390 mg (> 55 to ≤ 85 kg) or 520 mg (> 85 kg) IV, followed by 90 mg SC at Week 8] (Once cap of no more than 20% ustekinumab exposed subjects is reached, subjects with prior ustekinumab exposure will not be allowed to enroll.)

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

- Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit of the above biologics
- Note: Subjects who discontinued biologics for reasons other than inadequate response as defined above or intolerance (e.g., change of insurance) must meet the criteria for intolerance or inadequate response to aminosalicylates, oral locally acting steroids, systemic steroids (prednisone or equivalent), and/or immunomodulators as defined above

7. If female, subject must meet the criteria as stated in Section 5.2.4 of this protocol *Contraception Recommendations*. Females of childbearing potential must have a negative serum pregnancy test result during Screening, and a negative urine pregnancy at Baseline. Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) during Screening do not require pregnancy testing at Baseline.

   Note: Subjects with borderline serum pregnancy test at Screening must have a serum pregnancy test ≥ 3 days later to document continued lack of a positive result.
8. Subjects must be able and willing to give written informed consent and to comply with the requirements of this study protocol. In Japan, if the subject is < 20 years old, a subject's parent or legal guardian must be willing to give written informed consent.

Main Exclusion:

1. Subject with a current diagnosis of ulcerative colitis or indeterminate colitis.

<u>Concomitant Medications and Treatments</u>

2. Subject on CD-related antibiotics who has not been on stable doses for greater than, or discontinued within, 14 days prior to Baseline.
3. Subject on oral aminosalicylates who has not been on stable doses for greater than, or discontinued within, at least 14 days prior to Baseline.
4. Subject taking oral corticosteroids:
   - Budesonide > 9 mg/day
   - Beclomethasone > 5 mg/day
   - Prednisone or equivalent > 20 mg/day
   - Or has not been on the current course for ≥ 14 days prior to Baseline and on a stable dose for ≥ 7 days prior to Baseline
5. Subject on immunomodulators (AZA, 6-MP, MTX) who:
   - Has not been on the current course for ≥ 42 days prior to Baseline, and
   - Has not been on a stable dose for ≥ 35 days prior to Baseline

<u>Medications and Treatments During the Screening Period</u>

6. Subject who received IV anti-infectives within 35 days prior to Baseline visit or oral/intramuscular anti-infectives (non-CD-related) within 14 days prior to the Baseline visit. This does not apply to TB prophylaxis.
7. Subject who received exclusive enteral nutrition or any parenteral nutrition within 35 days prior to Baseline.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

Medications and Treatments During the Screening Period (Continued)

8. Subject who received any live bacterial or viral vaccination within 30 days (8 weeks for Japan) prior to Screening or during the Screening Period.
9. Subject who received cyclosporine, tacrolimus, or mycophenolate mofetil within 35 days prior to Baseline.
10. Subject who received fecal microbial transplantation within 35 days prior to Baseline.

Prior Medications and Treatments

11. Subject who received any:
    - Approved biologics: infliximab, adalimumab, certolizumab, vedolizumab, natalizumab) within 8 weeks prior to Baseline, or ustekinumab within 12 weeks prior to Baseline

      Note: If there is proper documentation of an undetectable drug level measured by a commercially available assay for any of the approved biologics above, there is no minimum washout prior to Baseline.
    - Any investigational biologic or other agent or procedure within 35 days or 5 half-lives prior to Baseline, whichever is longer.
12. Subject with prior exposure to p19 inhibitors (e.g., risankizumab).
13. Subject has been taking combination of two or more of the following: oral budesonide, or oral beclomethasone and/or oral prednisone (or equivalent) simultaneously, with the exception of inhalers, within 14 days prior to Screening or during the Screening period.
14. Subject who received IV/intramuscular corticosteroids within 14 days prior to Screening or during the Screening period.
15. Subject who received therapeutic enema or suppository, other than required for endoscopy, within 14 days prior to endoscopy used for Screening or during the Screening period.
16. Subject who received apheresis (e.g., Adacolumn apheresis) ≤ 60 days prior to Screening or during the Screening period.
17. Subject who has concomitant cannabis use either recreational or for medical reasons within 14 days prior to Baseline or any history of clinically significant drug, or alcohol abuse in the last 12 months.

CD Related

18. Subject with currently known complications of CD such as:
    - abscess (abdominal or perianal),
    - symptomatic bowel strictures,
    - > 2 missing segments of the following 5 segments: terminal ileum, right colon, transverse colon, sigmoid and left colon, and rectum
    - fulminant colitis,
    - toxic megacolon,
    - or any other manifestation that might require surgery while enrolled in the study.
19. Subject with ostomy or ileoanal pouch.
20. Subject diagnosed with short gut or short bowel syndrome.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

21. Subject with surgical bowel resection within the past 3 months prior to Baseline, or a history of ≥ 3 bowel resections.

Safety

22. Subject who has a known hypersensitivity to risankizumab or the excipients of any of the study drugs or the ingredients of Chinese hamster ovary (CHO).
23. Subjects with the following chronic or active infections:
    - Active, chronic, or recurrent infection that based on the Investigator's clinical assessment makes the subject unsuitable candidate for the study,
    - Infection with C. *difficile* toxin or other intestinal pathogen during Screening,
    - Are infected with human immunodeficiency virus (HIV),
    - QuantiFERON®-TB test or Purified Protein Derivative (PPD) skin test, or both, according to local guidelines, will be performed during Screening. QuantiFERON®-TB test is preferred for subjects who received BCG vaccination or were exposed to other Mycobacteria species. Subjects with a positive test result (or indeterminate results that have been repeated) may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active tuberculosis. Subjects with a history of active TB who have documented completion of a full course of anti-TB therapy may be allowed to enter the study after consultation with the AbbVie TA MD. If latent TB is established, TB prophylaxis/treatment should be initiated and maintained according to local country guidelines.
    - Have active hepatitis B or hepatitis C defined as:
        - HBV: hepatitis B surface antigen (HBs Ag) positive (+), or detected sensitivity on the HBV deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) qualitative test for hepatitis B core antibody (HBc Ab) positive subjects;
        - HCV: HCV ribonucleic acid (RNA) detectable in any subject positive with anti-HCV antibody (HCV Ab)
24. Subject with a previous history of dysplasia of the gastrointestinal tract or found to have dysplasia, other than completely removed low-grade dysplastic lesions, in any biopsy performed during the Screening endoscopy.
25. Subject with a known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly.
26. Subject with current or previous history of malignancy other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix.
27. Subject who has severe, progressive, or uncontrolled renal, hepatic, hematological, endocrine, disorder or symptoms thereof.
28. Female subjects who is pregnant, breastfeeding, or is considering becoming pregnant during the study or for approximately 140 days after the last dose of study drug.
29. Subject who has any condition, including any physical, psychological, or psychiatric condition, which in the opinion of the Investigator, would compromise the safety of the subject or the quality of the data and renders the subject an unsuitable candidate for the study.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

Safety (Continued):

30. Screening laboratory and other analyses show any of the following abnormal results:
    - Aspartate transaminase (AST), alanine transaminase (ALT) > 2 × upper limit of the reference range;
    - White blood cell (WBC) count < 3.0×10^9/L;
    - Total bilirubin ≥ 2 mg/dL; except for subjects with isolated elevation of indirect bilirubin relating to Gilbert syndrome;
    - Estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula < 30 ml/min/1.73 m^2.
    - Hemoglobin < 8 g/dL
    - Platelets < 100,000/µL
    - Positive serum pregnancy test at the Screening visit or positive urine pregnancy test at the Baseline visit.

    Laboratory values can be re-tested once during the screening period after discussion and clearance with the TAMD. If the re-tested lab value(s) remain(s) exclusionary, the subject will be considered a screen failure. Redrawing samples if previous samples were unable to be analyzed would not count as a retest since previous result was never obtained.
31. No known active COVID-19 infection. Subject must not have signs/symptoms associated with COVID-19 infection.

    Subjects who do not meet COVID-19 eligibility criteria must be screen failed and may only rescreen after they meet the following COVID-19 viral clearance criteria:
    - Symptomatic subjects: At least 2 negative viral tests in a row completed locally, ≥ 24 hours apart after at least 10 days have passed since recovery, defined as resolution of fever without use of antipyretics and improvement in respiratory symptoms (e.g., cough, shortness of breath)
    - Asymptomatic subjects: At least 2 negative viral tests in a row completed locally, ≥ 24 hours apart after at least 10 days have passed since prior positive result (Note: subjects who develop symptoms will follow guidance above for symptomatic subjects)

    Frequency or timing of COVID-19 testing and interval between testing for the above viral clearance criteria may be adjusted to account for epidemiological trends, updated information regarding infectivity and local/institutional guidelines.

Investigational Product:	Risankizumab
Doses:	Risankizumab 1200 mg IV Q4W* Risankizumab 600 mg IV Q4W Risankizumab 180 mg SC Q8W Risankizumab 360 mg SC Q8W * If the 1200 mg dose is discontinued due to any reason, subjects will continue to enroll into the study and be randomized to either 600 mg risankizumab or placebo at 2:1 ratio. The randomization ratio and sample size may be further updated in an amendment to the protocol. Subjects already randomized to treatment arms, including Induction Period 2, will receive blinded 600 mg risankizumab IV.
Mode of Administration:	Risankizumab solution for infusion (IV) Risankizumab solution for injection (SC)
Reference Therapy:	Placebo for risankizumab
Dose:	N/A
Mode of Administration:	Placebo solution for infusion (IV) Placebo solution for injection (SC)

Duration of Treatment: 12 or 24 weeks

The study will include a Screening period of up to 35 days and a double-blind induction period of 12 weeks. All subjects who do not achieve clinical response at Week 12 will be eligible to receive treatment in Induction Period 2 with risankizumab over a subsequent 12 week period. There will be a follow up call 140 days from the last dose of study drug to obtain information on any new or ongoing AEs for those subjects who do not roll over into Study M16-000 or discontinue from the study prematurely.

Criteria for Evaluation:

Endpoint Definitions:

- **Clinical remission:** average daily SF $\leq$ 2.8 and not worse than Baseline AND average daily AP score $\leq$ 1 and not worse than Baseline
- **Enhanced clinical response:** $\geq$ 60% decrease in average daily SF and/or $\geq$ 35% decrease in average daily AP score and both not worse than Baseline, and/or clinical remission
- **Clinical response:** $\geq$ 30% decrease in average daily SF and/or $\geq$ 30% decrease in average daily AP score and both not worse than Baseline
- **Endoscopic response:** decrease in SES-CD > 50% from Baseline (or for subjects with isolated ileal disease and a Baseline SES-CD of 4, at least a 2 point reduction from Baseline), as scored by central reviewer
- **Ulcer-free endoscopy:** SES-CD ulcerated surface subscore of 0 in subjects with SES-CD ulcerated surface subscore $\geq$ 1 at Baseline, as scored by a central reviewer
- **Endoscopic remission:** SES-CD $\leq$ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable, as scored by a central reviewer

Criteria for Evaluation (Continued):

Endpoint Definitions (Continued):

- **CDAI clinical response:** reduction of CDAI ≥ 100 points from baseline
- **CDAI clinical remission:** CDAI < 150
- **SF remission:** average daily SF ≤ 2.8 and not worse than baseline
- **AP remission:** average daily AP score ≤ 1 and not worse than baseline

Efficacy:

Co-Primary Endpoints:

- Proportion of subjects with CDAI clinical remission at Week 12
- Proportion of subjects with endoscopic response at Week 12

Ranked Secondary Endpoints:

1. Proportion of subjects with clinical remission at Week 12
2. Proportion of subjects with CDAI clinical response at Week 4
3. Proportion of subjects with CDAI clinical response at Week 12
4. Change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-fatigue) at Week 12
5. Proportion of subjects with CDAI clinical remission at Week 4
6. Proportion of subjects with CDAI clinical response and endoscopic response at Week 12
7. Proportion of subjects with SF remission at Week 12
8. Proportion of subjects with AP remission at Week 12
9. Proportion of subjects with endoscopic remission at Week 12
10. Proportion of subjects with enhanced clinical response at Week 4
11. Proportion of subjects with ulcer-free endoscopy at Week 12
12. Proportion of subjects with enhanced clinical response at Week 12
13. Proportion of subjects with resolution of extra-intestinal manifestations (EIMs) at Week 12, in subjects with any EIMs at Baseline
14. Proportion of subjects with CD-related hospitalization through Week 12
15. Proportion of subjects without draining fistulas at Week 12 in subjects with draining fistulas at Baseline

For further information, including non-ranked endpoints, refer to protocol

Pharmacokinetics:

Serum risankizumab concentrations will be determined from samples collected just prior to dosing at Weeks 4, 8, and 12/PD, and at Week 24 for subjects who receive treatment in Induction Period 2.

Additionally, intensive pharmacokinetic assessment will be performed in 20 subjects after the 3rd induction dose (Week 8 to 12). For Subjects who consent to the intensive pharmacokinetic assessment, in addition to the time points above, blood samples will be collected at Week 8 immediately after completion of infusion and 2 hours post completion of infusion, and at Weeks 9, 10, and 11. Refer to Appendix H for more details.

Criteria for Evaluation (Continued):

Immunogenicity:

Serum ADAs will be determined from samples collected just prior to dosing at Baseline and Weeks 4, 8, and 12/PD, and at Week 24 for subjects who receive treatment in Induction Period 2.

Safety:

Safety analyses will be performed on safety set which includes all subjects who receive at least one dose of study drug. Incidence of adverse events (AEs), changes in vital signs, physical examination results, and clinical laboratory data will be assessed throughout the study.

Exploratory Research Variables and Validation Studies (Optional):

Prognostic, surrogate, predictive and pharmacodynamics biomarkers signatures may be investigated. Samples for different applications, including but not limited to, pharmacogenetic, epigenetic, transcriptomic, proteomic, metabolomics, metagenomic and targeted investigations will be collected at various time points. Assessments will include but may not be limited to nucleic acids, proteins, metabolites or lipids.

Statistical Methods:

Efficacy:

The co-primary endpoints are the proportion of subjects with CDAI clinical remission at Week 12 and proportion of subjects with endoscopic response at Week 12. A total of approximately 855 subjects will be randomized into two risankizumab treatment groups and the placebo group in a 2:2:1 ratio (342 subjects for risankizumab 600 mg dose group, 342 subjects for risankizumab 1200 mg dose group, and 171 subjects for placebo group). When all patients complete their Week 12/PD visit, the database will be locked for the final analysis of 12-week induction period. When all the patients who enter the induction Period 2 finish Week 24/PD visit, the database will be locked for the whole study and all the planned analysis for the induction Period 2 will be performed.

Assuming the Week 12 CDAI clinical remission rate will be 37% for one of the risankizumab dose groups and 17% for the placebo group, a sample size of 342 subjects for each of the risankizumab dose groups and 171 for the placebo group will have 99% power to detect the treatment difference between the risankizumab dose groups and placebo in CDAI clinical remission rates at Week 12 using Fisher's exact test at alpha of 0.025 (two-sided).

The bio-IR population is approximately 540 subjects. The study will have 92% power to detect the treatment difference between one of the risankizumab dose groups and placebo in CDAI clinical remission at Week 12 using a Fisher's exact test a 0.025 significant level (two-sided) for the bio-IR population, assuming the Week 12 CDAI clinical remission rate will be 34% for the risankizumab dose groups and 15% for the placebo group for bio-IR subjects. The non-bio-IR population is approximately 315 subjects. The study will have 70% power to detect the treatment difference between one of the risankizumab dose groups and placebo in CDAI clinical remission, at Week 12 using a Fisher's exact test a 0.025 significant level (two-sided) for the non-bio-IR sub-population, assuming the Week 12 CDAI clinical remission rate will be 42% for the risankizumab dose groups and 21% for the placebo group for non-bio-IR subjects.

Statistical Methods (Continued):

Efficacy (Continued):

The comparisons between each risankizumab dose versus placebo for the primary efficacy variable will be performed using the Cochran-Mantel-Haenszel (CMH) test adjusted by prior biologic use (0, 1, > 1) and Baseline steroid use (yes, no). Both of the co-primary efficacy endpoints will be tested at statistically significant of 0.025 for each of the risankizumab dose groups versus placebo to adjust for multiplicity. A CMH based two-sided 95% confidence interval for the difference between treatment groups will be calculated.

The intent-to-treat (ITT) set includes all randomized subjects who have taken at least one dose of study drug. The primary population for efficacy analysis are the subjects in the intent-to-treat analysis set who had baseline eligibility SES-CD of ≥ 6 (≥ 4 for isolated ileal disease). Subjects who discontinue prior to Week 12 for any reason will be considered as "not-achieved" for CDAI clinical remission and endoscopic response endpoints.

In general, continuous secondary efficacy variables will be analyzed using a Mixed-Effect Model Repeated Measure (MMRM) model including factors for treatment group, visit, visit by treatment interaction, and stratification variables, for the longitudinal continuous endpoints. The MMRM analysis is considered primary for inferential purposes.

Pharmacokinetics and Immunogenicity:

Serum risankizumab concentrations will be summarized at each time point for each dosing regimen using descriptive statistics. Population pharmacokinetic analyses combining the data from this study and other studies may be performed. Relationships between risankizumab exposures and efficacy and safety variables of interest may be explored.

ADA incidence will be summarized by cohorts and study visits. ADA titers will be tabulated for each subject at the respective study visits. The effect of ADAs on risankizumab pharmacokinetics, efficacy and/or safety variable(s) and/or any additional analyses will be explored.

Safety:

Adverse events, laboratory data and vital signs are the primary safety parameters in this study. All safety comparisons will be performed between treatment groups using the safety set. Treatment emergent AEs are defined as events that begin or worsen either on or after the first dose of the study drug and within 140 days after the last dose of the study drug for subjects who do not participate in Study M16-000 or until first dose of study drug in Study M16-000 if the subject is enrolled in Study M16-000.

An overview of treatment-emergent AEs, AEs leading to death and AEs leading to premature discontinuation (see details in the statistical analysis plan [SAP]), AEs by Medical Dictionary for Drug Regulatory Activities (MedDRA version) preferred term and system organ class, AEs by maximum relationship to study drug, and AEs by maximum severity will be summarized by number and percentage.

Changes in laboratory data will be described using statistical characteristics and compared between treatment groups will be performed using a one-way Analysis of Variance (ANOVA). In addition, shift tables and listings will be provided for abnormal values, whereby the normal range of the analyzing laboratory will be used. Vital signs will be analyzed similarly.

Section 3.2 Benefits and Risks
Last paragraph previously read:

Considering the coronavirus (COVID-19) pandemic, the benefit and risk to subjects participating in this study have been re-evaluated. Based on the limited information to date, no additional risk to study participants is anticipated with the use of risankizumab.

Has been changed to read:

In view of the COVID-19 pandemic, the benefit-risk profile of various immunomodulatory therapies on COVID-19 is being evaluated based on real world and clinical trial data. At this time, the effects of risankizumab on the course of COVID-19 are not well defined.

Section 5.2.2 Exclusion Criteria
Subsection <u>Rationale for Exclusion Criteria</u>
Previously read:

1	To avoid medical conditions that may compromise the ability to identify subjects with the correct diagnosis or to interpret medical importance of clinical results
2 – 17	To avoid bias for the evaluation of efficacy and safety by concomitant use of other medications or treatments and to ensure the safety of the subject
18 – 21	To avoid complications of CD that may compromise the evaluations of efficacy and safety
22 – 30	To ensure the safety of the subject and or others

Has been changed to read:

1	To avoid medical conditions that may compromise the ability to identify subjects with the correct diagnosis or to interpret medical importance of clinical results
2 – 17	To avoid bias for the evaluation of efficacy and safety by concomitant use of other medications or treatments and to ensure the safety of the subject

18 – 21	To avoid complications of CD that may compromise the evaluations of efficacy and safety
22 – 31	To ensure the safety of the subject and or others

Section 5.3.3 Efficacy Variables
Add: new ninth and tenth bullet

- **SF remission:** average daily SF ≤ 2.8 and not worse than baseline
- **AP remission:** average daily AP score ≤ 1 and not worse than baseline

Section 5.3.3.1 Primary Variable
First bullet previously read:

Proportion of subjects with clinical remission at Week 12

Has been changed to read:

Proportion of subjects with CDAI clinical remission at Week 12

Section 5.3.3.2 Secondary Variables
First bullet previously read:

Proportion of subjects with CDAI clinical remission at Week 12

Has been changed to read:

Proportion of subjects with clinical remission at Week 12

Section 5.3.3.2 Secondary Variable
Delete: Item 3

Proportion of subjects with clinical remission at Week 4

Section 5.3.3.2 Secondary Variable
Item 5, 6, 7, 8, 9, 10, and 11 previously read:

5. Mean change from baseline of induction in FACIT fatigue at Week 12

6. Mean change from baseline of induction in IBDQ total score at Week 12
7. Proportion of subjects with enhanced clinical response and endoscopic response at Week 12
8. Proportion of subjects with endoscopic remission at Week 12
9. Proportion of subjects with enhanced clinical response at Week 4
10. Proportion of subjects with ulcer-free endoscopy at Week 12
11. Enhanced clinical response at Week 12

Has been changed to read:

4. Change from baseline of Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT fatigue) at Week 12
5. Proportion of subjects with CDAI clinical remission at Week 4
6. Proportion of subjects with CDAI clinical response and endoscopic response at Week 12
7. Proportion of subjects with SF remission at Week 12
8. Proportion of subjects with AP remission at Week 12
9. Proportion of subjects with endoscopic remission at Week 12
10. Proportion of subjects with enhanced clinical response at Week 4
11. Proportion of subjects with ulcer-free endoscopy at Week 12
12. Proportion of subjects with enhanced clinical response at Week 12

Section 5.3.3.3 Other Endpoints
Delete: third bullet

Change from Baseline individual IBDQ item under Bowel Symptom domain (for Q1, Q5, Q9, Q13, Q17, Q20, Q22, Q24, Q26, and Q29) over time

Section 5.3.3.3 Other Endpoints
Eighth bullet previously read:

Change from Baseline in FACIT-Fatigue overtime

Has been changed to read:

Change from Baseline in FACIT-Fatigue total score and individual item score over time

Section 5.3.3.3 Other Endpoints
Last bullet
Add: new last paragraph

Of note, over time will be measured at each study visit as specified in the study activity table

Section 8.1.6.1 Primary Efficacy Variables
First paragraph previously read:

The co-primary endpoints are the proportion of subjects who achieve clinical remission at Week 12 and proportion of subjects with endoscopic response at Week 12.

Has been changed to read:

The co-primary endpoints are the proportion of subjects who achieve CDAI clinical remission at Week 12 and proportion of subjects with endoscopic response at Week 12.

Section 8.1.6.1 Primary Efficacy Variables
Second paragraph, seventh and eighth sentence previously read:

If average daily SF or average daily AP score or endoscopic data at Week 12 are missing, the NRI approach will be applied. Subjects who discontinue prior to Week 12 for any reason will be considered as "not-achieved" for clinical remission and endoscopic response endpoints.

Has been changed to read:

Subjects who discontinue prior to Week 12 for any reason will be considered as "not-achieved" for CDAI clinical remission and endoscopic response endpoints.

Section 8.2 Determination of Sample Size
First paragraph previously read:

The co-primary endpoints are the proportion of subjects with clinical remission at Week 12 and proportion of subjects with endoscopic response at Week 12.

Has been changed to read:

The co-primary endpoints are the proportion of subjects with CDAI clinical remission at Week 12 and proportion of subjects with endoscopic response at Week 12.

Section 8.2 Determination of Sample Size
Second paragraph
Delete: first and second sentence

Sample size calculation is based on the larger sample size needed to detect treatment difference for each of the co-primary endpoints. Since historical data show slightly lower event rate and similar treatment difference versus placebo for the endoscopic response rate than the clinical remission rate at Week 12, clinical remission rates at Week 12 are used for power calculation.

Section 8.2 Determination of Sample Size
Second paragraph, fourth sentence previously read:

Assuming the Week 12 clinical remission rate will be 27.8% for one of the risankizumab dose groups and 12% for the placebo group, a sample size of 342 subjects for each of the risankizumab dose groups and 171 for the placebo group will have 97% power to detect the treatment difference between the risankizumab dose groups and placebo in clinical remission rates at Week 12 using Fisher's exact test at alpha of 0.025 (two-sided).

Has been changed to read:

Assuming the Week 12 CDAI clinical remission rate will be 37% for one of the risankizumab dose groups and 17% for the placebo group, a sample size of 342 subjects for each of the risankizumab dose groups and 171 for the placebo group will have 99% power to detect the treatment difference between the risankizumab dose groups and placebo in CDAI clinical remission rates at Week 12 using Fisher's exact test at alpha of 0.025 (two-sided).

Section 8.2 Determination of Sample Size
Last paragraph previously read:

In addition, with sample size of approximately 540 bio-IR subjects, this study will have approximately 80% power for the bio-IR population to detect the treatment difference between one of the risankizumab dose groups and placebo in clinical remission rates at Week 12 using Fisher's exact test at alpha of 0.025 (two-sided) for the bio-IR population, assuming the Week 12 clinical remission rate will be 24.2% for the risankizumab dose groups and 10% for the placebo group. Similarly, with sample size of approximately 315 non-bio-IR subjects, this study will have 72% power to detect the treatment difference between one of the risankizumab dose groups and placebo in clinical remission rates at Week 12 using Fisher's exact test at alpha of 0.025 (two-sided) for the non-bio-IR population, assuming the Week 12 clinical remission rate will be 35% for the risankizumab dose groups and 15% for the placebo group for non-bio-IR subjects.

Has been changed to read:

In addition, with sample size of approximately 540 bio-IR subjects, this study will have approximately 92% power for the bio-IR population to detect the treatment difference between one of the risankizumab dose groups and placebo in CDAI clinical remission rates at Week 12 using Fisher's exact test at alpha of 0.025 (two-sided) for the bio-IR population, assuming the Week 12 CDAI clinical remission rate will be 34% for the risankizumab dose groups and 15% for the placebo group. Similarly, with sample size of approximately 315 non-bio-IR subjects, this study will have 70% power to detect the

treatment difference between one of the risankizumab dose groups and placebo in CDAI clinical remission rates at Week 12 using Fisher's exact test at alpha of 0.025 (two-sided) for the non-bio-IR population, assuming the Week 12 CDAI clinical remission rate will be 42% for the risankizumab dose groups and 21% for the placebo group for non-bio-IR subjects.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]		Clinical Development, Immunology
		Clinical Development, Immunology
		Statistics
		Statistics
		Clinical Pharmacology and Pharmacometrics
		Bioanalysis
		Clinical Operations

Has been changed to read:

Name	Title	Functional Area
[redacted]		Clinical Development, Immunology
		Clinical Development, Immunology
		Statistics
		Statistics
		Clinical Pharmacology and Pharmacometrics
		Bioanalysis
		Clinical Operations

1.0 Title Page

Clinical Study Protocol M16-006

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study of the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Crohn's Disease

Incorporating Administrative Change 1 and Amendments 1, 2, 3, 4, 5, and 6

AbbVie Investigational Product:	Risankizumab		
Date:	28 July 2020		
Development Phase:	3		
Study Design:	Randomized, Double-Blind, Placebo-Controlled Parallel Group Design		
EudraCT Number:	2016-003123-32		
Investigators:	Multicenter Study (Investigator information is on file at AbbVie)		
Sponsor*:	For non-European countries excluding Japan: AbbVie 1 North Waukegan Road North Chicago, IL 60064 USA	For European Countries: AbbVie Deutschland GmbH & Co KG Knollstrasse 50 Ludwigshafen 67061 Germany	Japan: AbbVie GK 3-5-27, Mita, Minato-ku Tokyo 108-6302, Japan
Sponsor/Emergency Contact:	[redacted] Pharmaceutical Development 100 Research Drive, Suite 3009 Worchester, MA 01605 USA	Phone: Mobile: Fax: Email:	[redacted]

* The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	17 February 2017
Amendment 1	05 July 2017
Amendment 2	29 September 2017
Amendment 3	09 July 2018
Amendment 4	22 February 2019
Amendment 5	19 December 2019

The purpose of this amendment is to:

- Addition of language on the re-evaluation of the benefit and risk in light of the COVID-19 pandemic, to subjects participating in the study in Section 3.2

  Rationale: *To clarify the updated benefit-risk balance to participating subjects*
- Addition of exclusion criteria language in Section 5.2.2

  Rationale: *To exclude subjects with active COVID-19 infection from enrollment into study*
- Addition of study procedure language in Section 5.3.1.1, Section 9.2

  Rationale: *To modify study visits/protocol-specified procedures impacted by changes in local regulations due to the COVID-19 pandemic, as necessary to ensure the safety of subjects, including visit frequency, alternative methods of assessments, locations for data collection permitted by IRB/IEC*
- Addition of protocol language regarding site responsibility in Section 5.5.2.2, Section 5.5.7

  Rationale: *To align with study-related training materials and documented study processes regarding site responsibility for reporting temperature excursions and for drug accountability/destruction*
- Addition of adverse event language in Section 6.1.1.1

Rationale: *To align with AbbVie approved COVID-19 infection adverse event data collection processes*

- Addition of protocol deviation language in Section 7.0

  Rationale: *To clarify that deviations include deviations occurring due to COVID-19*

- Addition of language to address missing data due to COVID-19 in the statistical analysis plan in Section 8.1

  Rationale: *To clarify that modifications to the analysis for missing data due to COVID-19 infection will be incorporated into the statistical analysis plan*

- Addition of protocol modification language regarding data monitoring during COVID-19 in Section 10.1

  Rationale: *To clarify that due to the COVID-19 infection, remote source data verification will be allowed if necessary and permitted by the local regulatory authority, IRB/IEC, and the study site*

- Clarification of HIV results language throughout protocol

  Rationale: *To align with study-related training materials regarding the handling of subject HIV results during screening*

- Addition of event in Study Activities Table in Appendix C

  Rationale: *The addition of COVID-19 testing during subject study screening period*

An itemized list of all changes made to this protocol under this amendment can be found in Appendix K.

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M16-006
Name of Study Drug: Risankizumab (ABBV-066)	**Phase of Development:** 3
Name of Active Ingredient: Risankizumab	**Date of Protocol Synopsis:** 28 July 2020
Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study of the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Crohn's Disease	
Objective: The objective of Study M16-006 is to evaluate the efficacy and safety of risankizumab versus placebo during induction therapy in subjects with moderately to severely active Crohn's disease (CD).	
Investigators: Multicenter	
Study Sites: Approximately 400 sites	
Study Population: Males and females aged ≥ 18 to ≤ 80 years of age, or minimum age of adult consent according to local regulations at the Baseline visit, or aged 16 to < 18 years of age where locally permitted and who meet the definition of Tanner stage 5 development (refer to Appendix J) at the Baseline visit, with a diagnosis of moderately to severely active CD, defined as: 1. average daily stool frequency (SF) ≥ 4 (when calculating SF, only the number of liquid or very soft stools should be recorded) and/or average daily abdominal pain (AP) score ≥ 2; plus 2. endoscopic evidence of mucosal inflammation as measured by the Simple Endoscopic Score for CD (SES-CD). All eligible scores exclude the presence of narrowing component and are confirmed by a central reader. Endoscopic activity is defined as a SES-CD of ≥ 3. The number of subjects enrolled with a SES-CD of ≥ 3 to < 6 for ileocolonic or colonic disease or SES-CD of 3 for isolated ileal disease will be no more than 85 subjects. Once cap of no more than 85 subjects is reached, enrollment criterion will be an eligibility SES-CD of ≥ 6 for ileocolonic or colonic disease, or eligibility SES-CD of ≥ 4 for isolated ileal disease. The study will enroll both subjects who have had an inadequate response (IR) to prior biologic therapy (bio-IR) and subjects who have not (non-bio-IR). The bio-IR enrollment will be approximately 540 subjects and the non-bio-IR enrollment will be approximately 315 subjects. The **bio-IR** population is defined as subjects with documented intolerance or inadequate response to one or more of the approved anti-TNF or anti-integrin biologics for CD (infliximab, adalimumab, certolizumab, vedolizumab, ustekinumab and/or natalizumab). The **non-bio-IR** population will include subjects who had an inadequate response or intolerance to conventional therapy. Conventional therapy is defined as one or more of the following: aminosalicylates, oral locally acting steroids (e.g., budesonide, beclomethosone), systemic corticosteroids (prednisone or equivalent), or immunomodulators. This population will also include subjects who have received biologic therapy in the past but stopped therapy based on reasons other than inadequate response or intolerance (e.g., change in reimbursement coverage, well-controlled disease). The percent of subjects with exposure, including intolerance or inadequate response, to ustekinumab will be no more than 20%.	
Number of Subjects to be Enrolled: Approximately 855 for the primary ITT population used for efficacy analysis; additionally, up to 85 subjects with lower SES-CD will be enrolled	

Methodology:

Study M16-006 is a randomized, double blind, placebo-controlled 12-week induction study.

Subjects (n = 855) will be randomized 2:2:1 to 1200 mg risankizumab or 600 mg risankizumab or placebo intravenous (IV) given at Baseline, Weeks 4 and 8. The randomization will be stratified by number of prior biologics failed (0, 1, > 1), Baseline steroid use (yes, no), and Baseline SES-CD (original, alternative), where the stratum of "original" includes the patients with baseline SES-CD of ≥ 6 (or ≥ 4 for subjects with isolated ileal disease), and the stratum of "alternative" includes the patients with baseline SES-CD of ≥ 3 to < 6 for ileocolonic or colonic disease or SES-CD of 3 for isolated ileal disease.

Visits during the study will occur at Baseline and Weeks 4, 8, and 12/Premature Discontinuation (PD) to collect clinical and laboratory assessments of disease activity. Subjects who do not achieve clinical response at Week 12 will be offered blinded risankizumab therapy in Induction Period 2 with evaluation for clinical response at Week 24.

All subjects will be provided with a subject diary where they will record CD related symptoms throughout the study. Subjects will also be dispensed a patient information card at Screening. Additionally, subjects will complete symptom, quality of life (QoL) and work productivity questionnaires throughout the study. Clinical labs including, but not limited to, urinalysis, chemistry and hematology, high-sensitivity C-reactive protein (hs-CRP), serum risankizumab concentrations, and serum anti-drug antibody (ADA) levels will be collected throughout the study. In addition, stool samples for calprotectin analysis will be collected and should be taken before starting bowel preparations for endoscopy. All endoscopies will be evaluated using SES-CD and will be confirmed by a central reader. Biopsy to confirm diagnosis (during Screening) or to rule out dysplasia/malignancy may be performed during the same time points as the endoscopy. Optional exploratory research samples may be taken during the study.

At the Week 12/PD visit, all subjects will undergo an endoscopy for evaluation of mucosal inflammation. It is expected that all subjects who remain in the study through at least Week 8 will have a Week 12/PD endoscopy. All subjects achieving clinical response, defined as ≥ 30% decrease in average daily SF and/or ≥ 30% decrease in average daily AP score (both not worse than Baseline) at Week 12 may be eligible to enter Study M16-000. Subjects are not eligible to enter Study M16-000 until endoscopy has been completed (local reader results will be used for stratification for Study M16-000).

All subjects who do not achieve clinical response at Week 12 may be eligible to receive blinded risankizumab treatment in Induction Period 2 as specified below. Subjects are not eligible to enter Induction Period 2 until the Week 12 endoscopy has been completed.

<u>Induction Period 2:</u>

At Week 12, subjects who do not achieve clinical response will be randomized by Interactive Response Technologies (IRT) to Induction Period 2, a double-blind, double-dummy 12-week treatment period.

Subjects who received IV risankizumab induction treatment with inadequate clinical response at Week 12 will be randomized 1:1:1 to:

- Group 1: 1200 mg IV risankizumab
- Group 2: 360 mg SC risankizumab
- Group 3: 180 mg SC risankizumab

Methodology (Continued):

Subjects who received IV placebo induction treatment will receive:

- Group 4: 1200 mg IV risankizumab

The IV risankizumab dose or matching IV placebo will be given at Weeks 12, 16, and 20. The SC risankizumab dose or matching SC placebo will be given at Weeks 12, and 20. At Week 24, subjects who received treatment in Induction Period 2 will be reassessed and undergo a third endoscopy for evaluation of mucosal inflammation. Subjects who achieve clinical response at Week 24 may be eligible to enter Study M16-000. Subjects without clinical response at Week 24, as well as all subjects who terminate the study early (including subjects who are eligible for, but do not enter Induction Period 2), will be discontinued and have a follow-up call 140 days from the last dose of study drug to obtain information on any new or ongoing AEs.

Concomitant aminosalicylates, immunomodulators (azathioprine [AZA], 6-mercaptopurine [6-MP], methotrexate [MTX]), and/or CD-related antibiotics.

Subjects taking aminosalicylates, immunomodulators, and/or CD-related antibiotics at Baseline must continue these treatments for the duration of the study. Initiating and/or increasing doses of aminosalicylates, immunomodulators, and/or CD-related antibiotics during the study is prohibited. Decreasing doses of aminosalicylates, immunomodulators, and/or CD-related antibiotics is prohibited during the study, except in the event of moderate-to-severe treatment related toxicities and after discussion with the AbbVie Therapeutic Area Medical Director (TA MD). CD-related antibiotics may be discontinued in Induction Period 2 at the discretion of the Investigator.

Note: the duration of the study includes Induction Period 2.

Concomitant Corticosteroids

Subjects taking corticosteroids at Baseline must continue their concomitant treatment at the Baseline dose for the duration of the 12-week induction period. Initiation and/or increasing doses of systemic and/or CD related corticosteroids during the entire study is prohibited. Decreasing doses of corticosteroids is prohibited during the 12-week induction period, except in the event of moderate-to-severe treatment related toxicities and after discussion with the AbbVie TA MD.

Subjects who receive Induction Period 2 treatment during Weeks 12 to 24 will be allowed to taper their corticosteroids at the discretion of the Investigator. Increasing doses above the Baseline dose is prohibited.

Dose Selection

This study will evaluate two IV doses of risankizumab (600 mg and 1200 mg) during induction. The selection of the doses in this study is informed by the analysis of the safety and efficacy data, as well as the exposure-response relationship of efficacy, of a Phase 2 study in subjects with CD that explored 200 mg and 600 mg doses. The results from the Phase 2 study suggest a potential for increased benefit with 1200 mg administration.

Methodology (Continued):

Induction Period 2 will evaluate IV (1200 mg Q4w) or SC (180 mg or 360 mg Q8w; maintenance dosing regimen) risankizumab. The purpose of Induction Period 2 is to evaluate the efficacy and safety of re-induction of risankizumab (1200 mg IV at Weeks 12, 16, and 20) versus initiating maintenance dosing on clinical response status. Data from the Phase 2 study in subjects with CD suggested that re-induction with 600 mg IV increased both clinical response and clinical remission in subjects with inadequate response at Week 12. The selection of the SC doses is informed by the analysis of the safety and efficacy data, as well as the exposure-response relationship of efficacy, of the maintenance period during the Phase 2 study in subjects with CD that evaluated 180 mg SC risankizumab for maintenance. The results from the Phase 2 study suggest a potential for increased benefit with 360 mg SC administration for maintenance regimen.

Data Monitoring Committee (DMC)

An external independent DMC will review unblinded safety data on a cohort level, at a minimum of 6-month intervals throughout the course of the study. At the timing of this amendment, the DMC has provided recommendation that the study may continue without modification and allowed enrollment to begin for 16 - 17 year-olds. A patient information card with information of the symptoms and signs of hypersensitivity reactions, infusion related reactions as well as late stage reactions will be provided to the patients at Screening so that any such events once occurred will be reported immediately by the patients to the investigator.

A separate DMC charter will be prepared outside of the protocol and will describe the roles and responsibilities of the DMC member, frequency and triggers of data reviews, and relevant safety data to be assessed. The cardiac adjudication committee (CAC) and anaphylaxis adjudication committee (AAC) adjudicates blinded data and the DMC reviews the data in an unblinded manner. Unblinded adjudicated cardio-cerebrovascular events and anaphylactic reactions will be presented to the DMC for review on a periodic basis. Communications from the DMC to the Study Teams will not contain information that could potentially unblind the team to subject treatment assignments.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Males or females ≥ 18 and ≤ 80 years of age or minimum age of adult consent according to local regulations at the Baseline Visit. Where locally permissible, subjects 16 to < 18 years of age who meet the definition of Tanner stage 5 for development (refer to Appendix J), at the Baseline Visit (sites will be notified when adolescents may enroll).
2. Confirmed diagnosis of CD for at least 3 months prior to Baseline. Appropriate documentation of biopsy results consistent with the diagnosis of CD, in the assessment of the Investigator, must be available.
3. Crohn's disease activity index (CDAI) score 220 – 450 at Baseline.
4. Endoscopic evidence of mucosal inflammation as documented by an SES-CD of ≥ 3. All eligible scores exclude the presence of narrowing component and are confirmed by a central reader. (Once cap of no more than 85 subjects is reached, enrollment criterion will be an SES-CD of ≥ 6 for ileocolonic or colonic disease or SES-CD of ≥ 4 for isolated ileal disease.)
5. Average daily SF ≥ 4 and/or average daily AP score ≥ 2 at Baseline.
6. Demonstrated intolerance or inadequate response to one or more of the following categories of drugs: aminosalicylates, oral locally acting steroids, systemic steroids (prednisone or equivalent), immunomodulators, and/or biologic therapies
    - Demonstration of intolerance requires no minimum dose or duration of use (intolerance includes patients with a known TPMT genetic mutation or low activity).
    - Inadequate response is defined as outlined below:
        - Oral aminosalicylates (e.g., mesalamine, sulfasalazine, olsalazine, balsalazide):
            - Signs and symptoms of persistently active disease, in the opinion of the Investigator, during a current or prior course of at least 4 weeks of treatment with 2.4 g/day mesalamine, 4 g/day sulfasalazine, 1 g/day olsalazine, or 6.75 g/day balsalazide,
        - Oral locally acting steroids (e.g., budesonide, beclomethasone):
            - Signs and symptoms of persistently active disease, in the opinion of the Investigator, during or after a course of at least 4 weeks of treatment with 9 mg/day budesonide or 5 mg/day beclomethasone,

              or
            - Inability to taper oral budesonide to at or below 6 mg/day without recurrent active disease,
        - IV or Oral systemic steroids (prednisone or equivalent):
            - Signs and symptoms of persistently active disease, in the opinion of the Investigator, during or after tapering of at least one regimen consisting of a dose equivalent to prednisone ≥ 40 mg/day orally for 3 weeks or intravenously for 1 week,

              or
            - Inability to taper oral systemic steroids to at or below a dose equivalent to prednisone 10 mg/day without recurrent active disease,

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

- Immunomodulators:
  - Signs and symptoms of persistently active disease, in the opinion of the Investigator, during a current or prior course of at least 90 days of treatment with one or more of the following:
    - AZA: ≥ 2.0 mg/kg/day rounded to the nearest available tablet or half tablet formulation (≥ 1 mg/kg/day for subjects in Japan, Korea, Hong Kong, Taiwan, Singapore, or China) (or a documented 6-TGN level of ≥ 230 pmol/8 × 10^8 RBC)
    - 6-MP: ≥ 1 mg/kg/day rounded to the nearest available tablet or half tablet formulation (≥ 0.6 mg/kg/day for subjects in Japan, Korea, Hong Kong, Taiwan, Singapore, or China) (or a 6-TGN level of ≥ 230 pmol/8 × 10^8 RBC)
    - MTX: ≥ 15 mg/week subcutaneous (SC) or intramuscular (IM)
      - *Note:* Oral MTX use is allowed during the study, however prior or current use of oral MTX is not sufficient for inclusion into the study
- Biologic Therapies for CD:
  - Signs and symptoms of persistently (in the opinion of the Investigator) active disease despite a history of one or more of the following:
    - At least one 6-week induction regimen of infliximab (≥ 5 mg/kg IV at Weeks 0, 2, and 6),
    - At least one 4-week induction regimen of adalimumab (one 160 mg SC dose at Week 0, followed by one 80 mg SC dose at Week 2 [or one 80 mg SC dose at Week 0, followed by one 40 mg SC dose at Week 2, in countries where this dosing regimen is approved]),
    - At least one 4-week induction regimen of certolizumab pegol (400 mg SC at Weeks 0, 2, and 4),
    - At least one 6-week induction regimen of vedolizumab (300 mg IV at Weeks 0, 2, and 6)
    - At least one 12-week induction regimen of natalizumab (300 mg IV every 4 weeks)
    - At least one 8-week induction regimen of ustekinumab [260 mg (≤ 55 kg) or 390 mg (> 55 to ≤ 85 kg) or 520 mg (> 85 kg) IV, followed by 90 mg SC at Week 8] (Once cap of no more than 20% ustekinumab exposed subjects is reached, subjects with prior ustekinumab exposure will not be allowed to enroll.)

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

- Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit of the above biologics
- Note: Subjects who discontinued biologics for reasons other than inadequate response as defined above or intolerance (e.g., change of insurance) must meet the criteria for intolerance or inadequate response to aminosalicylates, oral locally acting steroids, systemic steroids (prednisone or equivalent), and/or immunomodulators as defined above

7. If female, subject must meet the criteria as stated in Section 5.2.4 of this protocol *Contraception Recommendations*. Females of childbearing potential must have a negative serum pregnancy test result during Screening, and a negative urine pregnancy at Baseline. Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) during Screening do not require pregnancy testing at Baseline.

   Note: Subjects with borderline serum pregnancy test at Screening must have a serum pregnancy test ≥ 3 days later to document continued lack of a positive result.
8. Subjects must be able and willing to give written informed consent and to comply with the requirements of this study protocol. In Japan, if the subject is < 20 years old, a subject's parent or legal guardian must be willing to give written informed consent.

Main Exclusion:

1. Subject with a current diagnosis of ulcerative colitis or indeterminate colitis.

<u>Concomitant Medications and Treatments</u>

2. Subject on CD-related antibiotics who has not been on stable doses for greater than, or discontinued within, 14 days prior to Baseline.
3. Subject on oral aminosalicylates who has not been on stable doses for greater than, or discontinued within, at least 14 days prior to Baseline.
4. Subject taking oral corticosteroids:
   - Budesonide > 9 mg/day
   - Beclomethasone > 5 mg/day
   - Prednisone or equivalent > 20 mg/day
   - Or has not been on the current course for ≥ 14 days prior to Baseline and on a stable dose for ≥ 7 days prior to Baseline
5. Subject on immunomodulators (AZA, 6-MP, MTX) who:
   - Has not been on the current course for ≥ 42 days prior to Baseline, and
   - Has not been on a stable dose for ≥ 35 days prior to Baseline

<u>Medications and Treatments During the Screening Period</u>

6. Subject who received IV anti-infectives within 35 days prior to Baseline visit or oral/intramuscular anti-infectives (non-CD-related) within 14 days prior to the Baseline visit. This does not apply to TB prophylaxis.
7. Subject who received exclusive enteral nutrition or any parenteral nutrition within 35 days prior to Baseline.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

Medications and Treatments During the Screening Period (Continued)

8. Subject who received any live bacterial or viral vaccination within 30 days (8 weeks for Japan) prior to Screening or during the Screening Period.
9. Subject who received cyclosporine, tacrolimus, or mycophenolate mofetil within 35 days prior to Baseline.
10. Subject who received fecal microbial transplantation within 35 days prior to Baseline.

Prior Medications and Treatments

11. Subject who received any:
    - Approved biologics: infliximab, adalimumab, certolizumab, vedolizumab, natalizumab) within 8 weeks prior to Baseline, or ustekinumab within 12 weeks prior to Baseline

      Note: If there is proper documentation of an undetectable drug level measured by a commercially available assay for any of the approved biologics above, there is no minimum washout prior to Baseline.
    - Any investigational biologic or other agent or procedure within 35 days or 5 half-lives prior to Baseline, whichever is longer.
12. Subject with prior exposure to p19 inhibitors (e.g., risankizumab).
13. Subject has been taking combination of two or more of the following: oral budesonide, or oral beclomethasone and/or oral prednisone (or equivalent) simultaneously, with the exception of inhalers, within 14 days prior to Screening or during the Screening period.
14. Subject who received IV/intramuscular corticosteroids within 14 days prior to Screening or during the Screening period.
15. Subject who received therapeutic enema or suppository, other than required for endoscopy, within 14 days prior to endoscopy used for Screening or during the Screening period.
16. Subject who received apheresis (e.g., Adacolumn apheresis) ≤ 60 days prior to Screening or during the Screening period.
17. Subject who has concomitant cannabis use either recreational or for medical reasons within 14 days prior to Baseline or any history of clinically significant drug, or alcohol abuse in the last 12 months.

CD Related

18. Subject with currently known complications of CD such as:
    - abscess (abdominal or perianal),
    - symptomatic bowel strictures,
    - > 2 missing segments of the following 5 segments: terminal ileum, right colon, transverse colon, sigmoid and left colon, and rectum
    - fulminant colitis,
    - toxic megacolon,
    - or any other manifestation that might require surgery while enrolled in the study.
19. Subject with ostomy or ileoanal pouch.
20. Subject diagnosed with short gut or short bowel syndrome.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

21. Subject with surgical bowel resection within the past 3 months prior to Baseline, or a history of ≥ 3 bowel resections.

Safety

22. Subject who has a known hypersensitivity to risankizumab or the excipients of any of the study drugs or the ingredients of Chinese hamster ovary (CHO).
23. Subjects with the following chronic or active infections:
    - Active, chronic, or recurrent infection that based on the Investigator's clinical assessment makes the subject unsuitable candidate for the study,
    - Infection with C. *difficile* toxin or other intestinal pathogen during Screening,
    - Are infected with human immunodeficiency virus (HIV),
    - QuantiFERON®-TB test or Purified Protein Derivative (PPD) skin test, or both, according to local guidelines, will be performed during Screening. QuantiFERON®-TB test is preferred for subjects who received BCG vaccination or were exposed to other Mycobacteria species. Subjects with a positive test result (or indeterminate results that have been repeated) may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active tuberculosis. Subjects with a history of active TB who have documented completion of a full course of anti-TB therapy may be allowed to enter the study after consultation with the AbbVie TA MD. If latent TB is established, TB prophylaxis/treatment should be initiated and maintained according to local country guidelines.
    - Have active hepatitis B or hepatitis C defined as:
        - HBV: hepatitis B surface antigen (HBs Ag) positive (+), or detected sensitivity on the HBV deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) qualitative test for hepatitis B core antibody (HBc Ab) positive subjects;
        - HCV: HCV ribonucleic acid (RNA) detectable in any subject positive with anti-HCV antibody (HCV Ab)
24. Subject with a previous history of dysplasia of the gastrointestinal tract or found to have dysplasia, other than completely removed low-grade dysplastic lesions, in any biopsy performed during the Screening endoscopy.
25. Subject with a known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly.
26. Subject with current or previous history of malignancy other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix.
27. Subject who has severe, progressive, or uncontrolled renal, hepatic, hematological, endocrine, disorder or symptoms thereof.
28. Female subjects who is pregnant, breastfeeding, or is considering becoming pregnant during the study or for approximately 140 days after the last dose of study drug.
29. Subject who has any condition, including any physical, psychological, or psychiatric condition, which in the opinion of the Investigator, would compromise the safety of the subject or the quality of the data and renders the subject an unsuitable candidate for the study.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

Safety (Continued):

30. Screening laboratory and other analyses show any of the following abnormal results:
    - Aspartate transaminase (AST), alanine transaminase (ALT) > 2 × upper limit of the reference range;
    - White blood cell (WBC) count < 3.0×10^9/L;
    - Total bilirubin ≥ 2 mg/dL; except for subjects with isolated elevation of indirect bilirubin relating to Gilbert syndrome;
    - Estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula < 30 ml/min/1.73 m^2.
    - Hemoglobin < 8 g/dL
    - Platelets < 100,000/µL
    - Positive serum pregnancy test at the Screening visit or positive urine pregnancy test at the Baseline visit.

    Laboratory values can be re-tested once during the screening period after discussion and clearance with the TAMD. If the re-tested lab value(s) remain(s) exclusionary, the subject will be considered a screen failure. Redrawing samples if previous samples were unable to be analyzed would not count as a retest since previous result was never obtained.
31. No known active COVID-19 infection. Subject must not have signs/symptoms associated with COVID-19 infection.

    Subjects who do not meet COVID-19 eligibility criteria must be screen failed and may only rescreen after they meet the following COVID-19 viral clearance criteria:
    - Symptomatic subjects: At least 2 negative viral tests in a row completed locally, ≥ 24 hours apart after at least 10 days have passed since recovery, defined as resolution of fever without use of antipyretics and improvement in respiratory symptoms (e.g., cough, shortness of breath)
    - Asymptomatic subjects: At least 2 negative viral tests in a row completed locally, ≥ 24 hours apart after at least 10 days have passed since prior positive result (Note: subjects who develop symptoms will follow guidance above for symptomatic subjects)

    Frequency or timing of COVID-19 testing and interval between testing for the above viral clearance criteria may be adjusted to account for epidemiological trends, updated information regarding infectivity and local/institutional guidelines.

Investigational Product:	Risankizumab
Doses:	Risankizumab 1200 mg IV Q4W* Risankizumab 600 mg IV Q4W Risankizumab 180 mg SC Q8W Risankizumab 360 mg SC Q8W * If the 1200 mg dose is discontinued due to any reason, subjects will continue to enroll into the study and be randomized to either 600 mg risankizumab or placebo at 2:1 ratio. The randomization ratio and sample size may be further updated in an amendment to the protocol. Subjects already randomized to treatment arms, including Induction Period 2, will receive blinded 600 mg risankizumab IV.
Mode of Administration:	Risankizumab solution for infusion (IV) Risankizumab solution for injection (SC)
Reference Therapy:	Placebo for risankizumab
Dose:	N/A
Mode of Administration:	Placebo solution for infusion (IV) Placebo solution for injection (SC)

Duration of Treatment: 12 or 24 weeks

The study will include a Screening period of up to 35 days and a double-blind induction period of 12 weeks. All subjects who do not achieve clinical response at Week 12 will be eligible to receive treatment in Induction Period 2 with risankizumab over a subsequent 12 week period. There will be a follow up call 140 days from the last dose of study drug to obtain information on any new or ongoing AEs for those subjects who do not roll over into Study M16-000 or discontinue from the study prematurely.

Criteria for Evaluation:

Endpoint Definitions:

- **Clinical remission:** average daily SF $\leq$ 2.8 and not worse than Baseline AND average daily AP score $\leq$ 1 and not worse than Baseline
- **Enhanced clinical response:** $\geq$ 60% decrease in average daily SF and/or $\geq$ 35% decrease in average daily AP score and both not worse than Baseline, and/or clinical remission
- **Clinical response:** $\geq$ 30% decrease in average daily SF and/or $\geq$ 30% decrease in average daily AP score and both not worse than Baseline
- **Endoscopic response:** decrease in SES-CD > 50% from Baseline (or for subjects with isolated ileal disease and a Baseline SES-CD of 4, at least a 2 point reduction from Baseline), as scored by central reviewer
- **Ulcer-free endoscopy:** SES-CD ulcerated surface subscore of 0 in subjects with SES-CD ulcerated surface subscore $\geq$ 1 at Baseline, as scored by a central reviewer
- **Endoscopic remission:** SES-CD $\leq$ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable, as scored by a central reviewer

Criteria for Evaluation (Continued):

Endpoint Definitions (Continued):

- **CDAI clinical response:** reduction of CDAI ≥ 100 points from baseline
- **CDAI clinical remission:** CDAI < 150

Efficacy:

Co-Primary Endpoints:

- Proportion of subjects with clinical remission at Week 12
- Proportion of subjects with endoscopic response at Week 12

Ranked Secondary Endpoints:

1. Proportion of subjects with CDAI clinical remission at Week 12
2. Proportion of subjects with CDAI clinical response at Week 4
3. Proportion of subjects with clinical remission at Week 4
4. Proportion of subjects with CDAI clinical response at Week 12
5. Mean change from baseline of induction in FACIT fatigue at Week 12
6. Mean change from baseline of induction in IBDQ total score at Week 12
7. Proportion of subjects with enhanced clinical response and endoscopic response at Week 12
8. Proportion of subjects with endoscopic remission at Week 12
9. Proportion of subjects with enhanced clinical response at Week 4
10. Proportion of subjects with ulcer-free endoscopy at Week 12
11. Enhanced clinical response at Week 12
12. Proportion of subjects with resolution of extra-intestinal manifestations (EIMs) at Week 12, in subjects with any EIMs at Baseline
13. Proportion of subjects with CD-related hospitalization through Week 12
14. Proportion of subjects without draining fistulas at Week 12 in subjects with draining fistulas at Baseline

For further information, including non-ranked endpoints, refer to protocol

Pharmacokinetics:

Serum risankizumab concentrations will be determined from samples collected just prior to dosing at Weeks 4, 8, and 12/PD, and at Week 24 for subjects who receive treatment in Induction Period 2.

Additionally, intensive pharmacokinetic assessment will be performed in 20 subjects after the 3rd induction dose (Week 8 to 12). For Subjects who consent to the intensive pharmacokinetic assessment, in addition to the time points above, blood samples will be collected at Week 8 immediately after completion of infusion and 2 hours post completion of infusion, and at Weeks 9, 10, and 11. Refer to Appendix H for more details.

Immunogenicity:

Serum ADAs will be determined from samples collected just prior to dosing at Baseline and Weeks 4, 8, and 12/PD, and at Week 24 for subjects who receive treatment in Induction Period 2.

Criteria for Evaluation (Continued):

Safety:

Safety analyses will be performed on safety set which includes all subjects who receive at least one dose of study drug. Incidence of adverse events (AEs), changes in vital signs, physical examination results, and clinical laboratory data will be assessed throughout the study.

Exploratory Research Variables and Validation Studies (Optional):

Prognostic, surrogate, predictive and pharmacodynamics biomarkers signatures may be investigated. Samples for different applications, including but not limited to, pharmacogenetic, epigenetic, transcriptomic, proteomic, metabolomics, metagenomic and targeted investigations will be collected at various time points. Assessments will include but may not be limited to nucleic acids, proteins, metabolites or lipids.

Statistical Methods:

Efficacy:

The co-primary endpoints are the proportion of subjects with clinical remission at Week 12 and proportion of subjects with endoscopic response at Week 12. A total of approximately 855 subjects will be randomized into two risankizumab treatment groups and the placebo group in a 2:2:1 ratio (342 subjects for risankizumab 600 mg dose group, 342 subjects for risankizumab 1200 mg dose group, and 171 subjects for placebo group). When all patients complete their Week 12/PD visit, the database will be locked for the final analysis of 12-week induction period. When all the patients who enter the induction Period 2 finish Week 24/PD visit, the database will be locked for the whole study and all the planned analysis for the induction Period 2 will be performed.

Sample size calculation is based on the larger sample size needed to detect treatment difference for each of the co-primary endpoints. Since historical data show slightly lower event rate and similar treatment difference versus placebo for the endoscopic response rate than the clinical remission rate at Week 12, clinical remission rates at Week 12 are used for power calculation. Assuming the Week 12 clinical remission rate will be 27.8% for one of the risankizumab dose groups and 12% for the placebo group, a sample size of 342 subjects for each of the risankizumab dose groups and 171 for the placebo group will have 97% power to detect the treatment difference between the risankizumab dose groups and placebo in clinical remission rates at Week 12 using Fisher's exact test at alpha of 0.025 (two-sided).

The bio-IR population is approximately 540 subjects. The study will have 80% power to detect the treatment difference between one of the risankizumab dose groups and placebo in clinical remission rates at Week 12 using Fisher's exact test at alpha of 0.025 (two-sided) for the bio-IR population, assuming the Week 12 clinical remission rate will be 24.2% for the risankizumab dose groups and 10% for the placebo group for bio-IR subjects. The non-bio-IR population is approximately 315 subjects. The study will have 72% power to detect the treatment difference between one of the risankizumab dose groups and placebo in clinical remission rates, at Week 12 using Fisher's exact test at alpha of 0.025 (two-sided) for the non-bio-IR sub-population, assuming the Week 12 clinical remission rate will be 35% for the risankizumab dose groups and 15% for the placebo group for non-bio-IR subjects.

The comparisons between each risankizumab dose versus placebo for the primary efficacy variable will be performed using the Cochran-Mantel-Haenszel (CMH) test adjusted by prior biologic use (0, 1, > 1) and Baseline steroid use (yes, no). Both of the co-primary efficacy endpoints will be tested at statistically significant of 0.025 for each of the risankizumab dose groups versus placebo to adjust for multiplicity. A CMH based two-sided 95% confidence interval for the difference between treatment groups will be calculated.

Statistical Methods (Continued):

Efficacy (Continued):

The intent-to-treat (ITT) set includes all randomized subjects who have taken at least one dose of study drug. The primary population for efficacy analysis are the subjects in the intent-to-treat analysis set who had baseline eligibility SES-CD of ≥ 6 (≥ 4 for isolated ileal disease). If the average daily SF or average daily AP score data at Week 12 are missing, the non-responder imputation (NRI) approach will be applied. Subjects who discontinue prior to Week 12 for any reason will be considered as "not-achieved" for clinical remission and endoscopic response endpoints.

In general, continuous secondary efficacy variables will be analyzed using a Mixed-Effect Model Repeated Measure (MMRM) model including factors for treatment group, visit, visit by treatment interaction, and stratification variables, for the longitudinal continuous endpoints. The MMRM analysis is considered primary for inferential purposes.

Pharmacokinetics and Immunogenicity:

Serum risankizumab concentrations will be summarized at each time point for each dosing regimen using descriptive statistics. Population pharmacokinetic analyses combining the data from this study and other studies may be performed. Relationships between risankizumab exposures and efficacy and safety variables of interest may be explored.

ADA incidence will be summarized by cohorts and study visits. ADA titers will be tabulated for each subject at the respective study visits. The effect of ADAs on risankizumab pharmacokinetics, efficacy and/or safety variable(s) and/or any additional analyses will be explored.

Safety:

Adverse events, laboratory data and vital signs are the primary safety parameters in this study. All safety comparisons will be performed between treatment groups using the safety set. Treatment emergent AEs are defined as events that begin or worsen either on or after the first dose of the study drug and within 140 days after the last dose of the study drug for subjects who do not participate in Study M16-000 or until first dose of study drug in Study M16-000 if the subject is enrolled in Study M16-000.

An overview of treatment-emergent AEs, AEs leading to death and AEs leading to premature discontinuation (see details in the statistical analysis plan [SAP]), AEs by Medical Dictionary for Drug Regulatory Activities (MedDRA version) preferred term and system organ class, AEs by maximum relationship to study drug, and AEs by maximum severity will be summarized by number and percentage.

Changes in laboratory data will be described using statistical characteristics and compared between treatment groups will be performed using a one-way Analysis of Variance (ANOVA). In addition, shift tables and listings will be provided for abnormal values, whereby the normal range of the analyzing laboratory will be used. Vital signs will be analyzed similarly.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

6-MP	6-Mercaptopurine
AAC	Anaphylaxis adjudication committee
ADA	Anti-Drug Antibody
AE	Adverse event
ALT	Alanine transaminase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AAC	Anaphylaxis adjudication committee
AP	Abdominal Pain
AST	Aspartate transaminase
ATEMS	AbbVie Temperature Excursion Management System
AZA	Azathioprine
BCG	Bacillus Calmette-Guérin
Bio-IR	Inadequate Response to biologic therapy
BUN	Blood urea nitrogen
CAC	Cardiac Adjudication Committee
CD	Crohn's disease
CDAI	Crohn's disease activity index
CHO	Chinese Hamster Ovary
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease - 2019
CRA	Clinical Research Associate
CSS	Crohn's Symptom Severity
CTCAE	Common Terminology Criteria for Adverse Events
CXR	Chest x-ray
DILI	Drug-induced Liver Injury
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture

EIM	Extra-Intestinal Manifestations
ePRO	Electronic Patient Reported Outcome
EQ-5D-5L	European Quality of Life 5 Dimensions
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FCP	Fecal Calprotectin
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HBc Ab	Hepatitis B core antibody
Hbs Ab	Hepatitis B surface antibody
Hbs Ag	Hepatitis B surface antigen
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
HCT	Hematocrit
HIV	Human immunodeficiency virus
hs-CRP	High-sensitivity C-Reactive Protein
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGRA	Interferon-Gamma Release Assay
IL	Interleukin
IR	Inadequate response
IM	Intramuscular
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technologies
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
MACE	Major Adverse Cardiovascular Events
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Drug Regulatory Activities

MI	Multiple Imputation
MMR	Measles Mumps-Rubella
MMRM	Mixed-Effect Model Repeated Measure
MMRV	Measles Mumps-Rubella Varicella
MTX	Methotrexate
nAb	Neutralizing antibodies
NRI	Non-responder imputation
N/A	Not Applicable
OC	Observed Case
OL	Open-Label
OPV	Oral Polio Vaccine
PCR	Polymerase Chain Reaction
PD	Premature Discontinuation
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetics
PMM	Pattern Mixture Model
POR	Proof of Receipt
PPD	Purified protein derivative
QoL	Quality of Life
Q4w	Every 4 Weeks
Q8w	Every 8 Weeks
RBC	Red blood cell
RNA	Ribonucleic Acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF	Stool Frequency
SF-36	36-Item Short Form Health Status Survey
SUSAR	Suspected Unexpected Serious Adverse Reactions
TA MD	Therapeutic Area Medical Director
TB	Tuberculosis
TNF	Tumor Necrosis Factor

ULN	Upper Limit of Normal
WBC	White blood cell
WOCBP	Women of Childbearing Potential
WPAI-CD	Work Productivity and Impairment Questionnaire – Crohn's disease

2.0 Table of Contents

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3.0 Introduction

Crohn's disease (CD) encompasses a spectrum of clinical and pathological processes manifested by focal asymmetric, transmural, and occasionally granulomatous inflammation that can affect any segment of the gastrointestinal tract and presents with symptoms of fatigue, prolonged diarrhea with or without gross bleeding, abdominal pain, weight loss, and fever.[1] The disease can affect persons of any age, and its onset is most common in the second and third decades. Females are affected slightly more than males, and the risk for disease is higher in some ethnic groups.[2,3] The incidence of CD has steadily increased in developed countries over the past 3 decades[4] with recent estimates varying from 12.7 and 20.2 cases/100,000, and a prevalence of 319 and 322 cases/100,000 in North America and Europe, respectively.[5] In Asia, the incidence of CD is estimated to be 0.5 to 1.0 cases per 100,000 persons, with a prevalence rate ranging from 3.6 to 7.7.[6,7]

The exact cause of CD is still unknown, but is hypothesized to be the result of a dysregulated immune system in the context of a genetically susceptible individual. It is thought that a combination of a patient's genetics, microbiome, immune response, and the environment result in an excessive and abnormal immune response in the gut that results in pathology seen in CD.[2]

The aim of medical treatment in CD has been focused on controlling inflammation and reducing symptoms.[8] In addition to improving symptoms, an emerging goal of therapy is to heal the gut mucosa. Resolution of intestinal ulcers, also known as mucosal healing has been associated with positive clinical benefits, including higher rates of clinical remission, fewer hospitalizations, and fewer abdominal surgeries.[9,10] However, improvement of the appearance of the intestinal mucosa may be more difficult to achieve than symptomatic improvement alone.

Conventional pharmaceutical therapies (e.g., corticosteroids, aminosalicylates, thiopurines, methotrexate) are limited, do not always completely abate the inflammatory process, and have significant adverse effects.[1,11] The advent of anti-TNFα agents

(e.g., adalimumab) and integrin inhibitors (e.g., vedolizumab) have been shown to achieve clinical remission in patients refractory to conventional therapies.[9-13]

Despite the benefits of available biologic therapies, many patients do not respond to initial treatment (primary loss of response) or lose treatment over time (secondary loss of response). Regarding anti-TNF agents, approximately 40% of patients will experience primary non-response and secondary non-response occurs in 38% of patients at 6 months and 50% of patients at 1 year.[12,14-17] Additionally, some patients are not candidates for available biologic therapies. Therefore new therapeutic options are required in order to continue to improve the outcome of patients with CD.

Risankizumab is a fully humanized mAb of the IgG1 subclass directed towards IL-23p19. The antibody has been engineered to reduce Fcγ receptor and complement binding and potential charge heterogeneity. Risankizumab binds with high affinity to human IL-23 and inhibits IL-23 stimulated IL-17 production at inhibitory concentration (IC) 50 concentrations below 10 pM, as compared with 167 pM for ustekinumab in the same system. Risankizumab does not affect IL-12 at a maximum tested concentration (33 nM) and it does not inhibit IL-12 stimulated IFN-γ production.

3.1 Differences Statement

This study is designed to evaluate the efficacy and safety of two risankizumab induction doses versus placebo in subjects with moderately to severely active CD. The primary differences between Study M16-006 and the prior Phase 2 study of risankizumab in CD is that this study will test a higher dosing of 1200 mg. Additionally, the endpoints in this study are different to reflect the changing regulatory requirements for pivotal registrational studies for new agents for the treatment of CD.

3.2 Benefits and Risks

Data suggest that altered immune regulation at the epithelial barrier leads to an overproduction of inflammatory cytokines, tissue destruction, and aberrant tissue repair in CD. Among the cytokines implicated in CD pathogenesis, data at the genetic, human

biology and clinical level strongly implicate IL-23 in this disease.[18,19] The preclinical and clinical profiles of risankizumab suggest that it may have the potential to address unmet medical need in CD. The data observed in the Phase 2 study, suggest that risankizumab will alleviate signs and symptoms of active CD and reduce mucosal inflammation. Participation in this study may help to generate future benefit for subjects with CD.

Though there are no serious adverse drug reactions known to be associated with risankizumab therapy, risks of participating in this study include risk of infection and risks related to the study specific procedures of blood sampling, infusion and injection of study drug, and colonoscopy with biopsy.

Blood sampling, intravenous (IV) infusions and subcutaneous (SC) injections can cause local bruising, inflammation, and pain. Colonoscopy and biopsy, although generally well tolerated, can be associated with diarrhea, abdominal pain, and in more severe cases, perforation, bleeding, effects from anaesthetic medications, and infection.

Local reactions to IV or SC administered biologic therapies are uncommon, and are usually limited to redness, swelling or induration at the injection site. Manifestations of systemic hypersensitivity reactions include anaphylaxis, pruritus, hypotension, and respiratory distress. Both local and systemic hypersensitivity reactions are readily detectable, transient in nature, and manageable with standard medical treatment. Subjects will be closely monitored during drug administration.

As with any immune modulating agent, risankizumab has the potential to impair immune function resulting in a risk of infection. This will be addressed by clinical monitoring for adverse events (AEs) during the treatment and follow up periods. Subjects with positive screening for M. Tuberculosis (TB) (skin/interferon-gamma release assay [IGRA] test positive) will be further worked up for signs and symptoms of active TB (e.g., chest x-ray [CXR]). Subjects with active TB will be excluded from enrolling in the study. Subjects with latent TB will be allowed to enroll in line with local guidelines. If latent TB is established, TB prophylaxis/treatment should be initiated and maintained according to

local country guidelines. Subjects with current signs or symptoms of infection or history of serious infection will not be included in the study.

The role of IL-23 in tumor immunity is not well established at this time, but an increased risk of cancer from an IL-23 antagonist, though considered small, cannot be excluded.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, though there is no known DILI risk with risankizumab, this study requires timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to ensure subjects' safety.

An independent Data Monitoring Committee (DMC) will be assessing all potential safety signals and will be unblinded to treatment allocation. The DMC will review unblinded safety data on a cohort level, at a minimum of 6-month intervals throughout the course of the study. At the timing of this amendment, the DMC has provided recommendation that the study may continue without modification and allowed enrollment to begin for 16 - 17 year-olds. A patient information card with information of the symptoms and signs of hypersensitivity reactions, infusion related reactions as well as late stage reactions will be provided to the patients at Screening so that any such events once occurred will be reported immediately by the patients to the investigator.

Increases in major adverse cardiovascular events (MACE) including myocardial infarction, cerebrovascular accident, and cardiovascular death have been reported in drugs with similar mechanism of action to risankizumab (e.g., p40 inhibitors). However, the incidence of MACE has not been observed in longer term studies. While the likelihood of increased MACE is small, all suspected cardiovascular events (serious or nonserious) observed in this study will be adjudicated by an independent adjudication committee. An independent cardiac adjudication committee (CAC) will be adjudicating observed cardio- and cerebro-vascular events and will remain blinded to treatment allocation. In addition, an independent anaphylaxis adjudication committee (AAC) will be adjudicating observed potential anaphylactic events and will remain blinded to treatment allocation.

The benefit-risk profile is considered appropriate for an experimental therapy at this stage of clinical development.

Considering the coronavirus (COVID-19) pandemic, the benefit and risk to subjects participating in this study have been re-evaluated. Based on the limited information to date, no additional risk to study participants is anticipated with the use of risankizumab.

4.0 Study Objective

The objective of Study M16-006 is to evaluate the efficacy and safety of risankizumab versus placebo during induction therapy in subjects with moderately to severely active CD.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

The study was designed to enroll approximately 855 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled. In addition to the 855 subjects, up to 85 subjects with a lower SES-CD, defined as an eligibility SES-CD of ≥ 3 to < 6 for ileocolonic or colonic disease or SES-CD of 3 for isolated ileal disease will be enrolled in order to inform treatment effect in this patient population, but these subjects will not be included in the primary ITT population for efficacy analysis.

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of risankizumab as an induction therapy in subjects with moderately to severely active CD, defined as:

1. average daily stool frequency (SF) ≥ 4 (when calculating SF, only the number of liquid or very soft stools should be recorded) and/or average daily abdominal pain (AP) score ≥ 2; plus

2. endoscopic evidence of mucosal inflammation as measured by the Simple Endoscopic Score for CD (SES CD). All eligible scores exclude the presence of narrowing component and are confirmed by a central reader. Endoscopic activity is defined as SES-CD of ≥ 3.

The number of subjects enrolled with a SES-CD of ≥ 3 to < 6 for ileocolonic or colonic disease or SES-CD of 3 for isolated ileal disease will be no more than 85 subjects. Once cap of no more than 85 subjects is reached, enrollment criterion will be an eligibility SES-CD of ≥ 6 for ileocolonic or colonic disease, or eligibility SES-CD of ≥ 4 for isolated ileal disease.

All endoscopies will be centrally read to document eligibility and for assessment at the time points indicated in Appendix C.

The study will enroll both subjects who have had an inadequate response (IR) to prior biologic therapy (bio-IR) and subjects who have not (non-bio-IR).

The **bio-IR** population is defined as subjects with documented intolerance or inadequate response to one or more of the approved anti-TNF or anti-integrin biologics for CD (infliximab, adalimumab, certolizumab, vedolizumab, ustekinumab and/or natalizumab). The bio-IR population will be approximately 540 subjects.

The **non-bio-IR** population will include subjects who had an inadequate response or intolerance to conventional therapy. Conventional therapy is defined as one or more of the following: aminosalicylates, oral locally acting steroids (e.g., budesonide, beclomethosone), systemic corticosteroids (prednisone or equivalent), or immunomodulators. This population will also include subjects who have received biologic therapy in the past but stopped therapy based on reasons other than inadequate response or intolerance (e.g., change in reimbursement coverage, well-controlled disease). The non-bio IR population will be approximately 315 subjects.

The percent of subjects with exposure, including intolerance or inadequate response, to ustekinumab will be no more than 20%.

The study duration may be up to 49 weeks, including a Screening period of up to 35 days, a 12-week induction period, a 12-week Induction Period 2 for those subjects who do not achieve clinical response at Week 12, and a 140 day follow up period from the last dose of study drug.

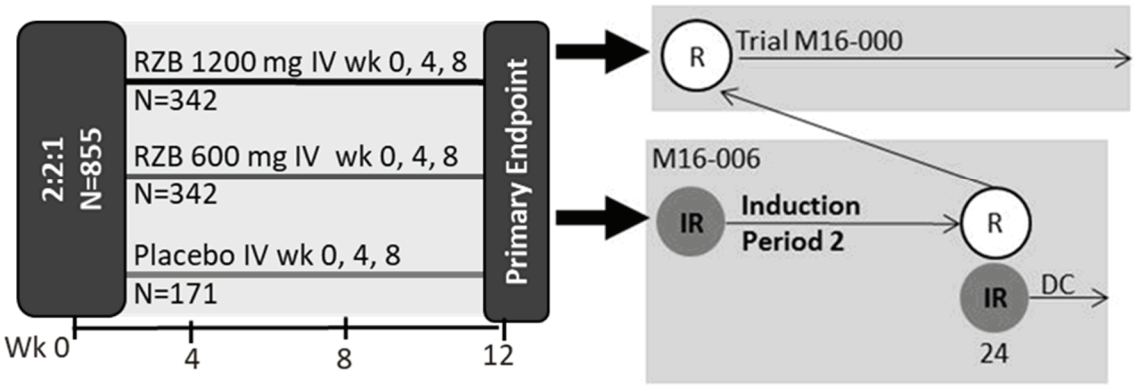
Visits for clinical evaluation will occur at Baseline, Weeks 4, 8, and 12/PD. Subjects, who do not achieve clinical response at Week 12 will be offered blinded induction therapy with risankizumab in Induction Period 2 with additional visits at Weeks 12, 16 and 20 and evaluation for clinical response at Week 24.

At the study visit indicated in Appendix C, all subjects will be provided with a subject diary where they will record CD related symptoms throughout the study. Subjects will also be dispensed the patient information card at Screening. Additionally, subjects will complete symptom, quality of life (QoL) and work productivity questionnaires throughout the study as indicated in Appendix C. Clinical labs including, but not limited to, urinalysis, chemistry and hematology, high sensitivity C-reactive protein (hs-CRP), serum risankizumab concentrations, and serum anti-drug antibody (ADA) levels may be collected. In addition, stool samples for calprotectin analysis will be collected and should be taken before starting bowel preparations for endoscopy. All endoscopies will be evaluated using SES-CD and will be confirmed by a central reader. Biopsy to confirm diagnosis (during Screening) or to rule out dysplasia/malignancy may be performed during the same time points as the endoscopy. Optional exploratory research samples may be taken during the study.

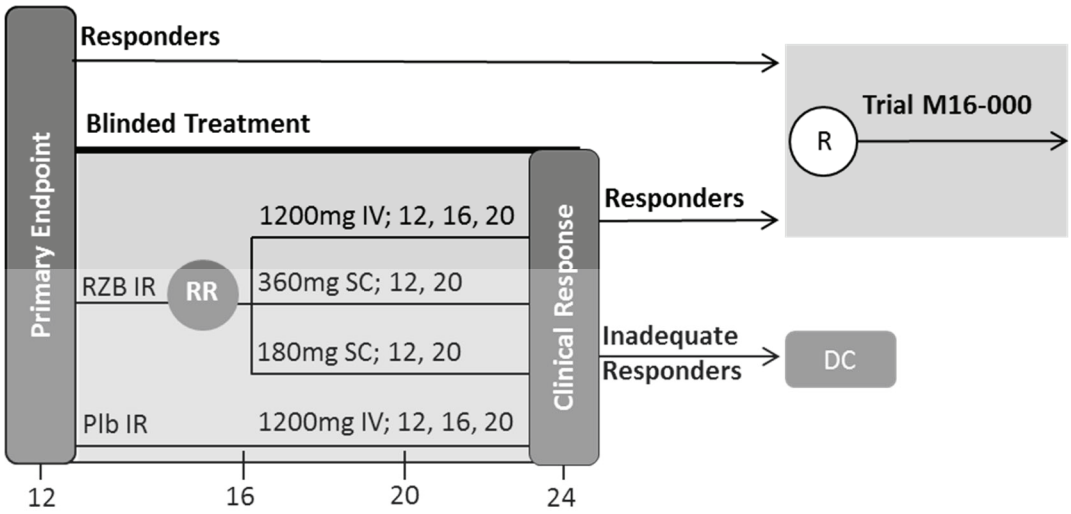
Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the study and randomized in a 2:2:1 ratio as shown in Figure 1. At the timing of this amendment, the DMC has provided recommendation that the study may continue without modification and allowed enrollment to begin for 16 - 17 year-olds.

Figure 1. Study M16-006 Study Schematic

a. 12-Week Induction Period



b. Induction Period 2



DC = discontinued; IR = subjects with inadequate clinical response to induction; IV = intravenous; R = subjects with clinical response; RR = re-randomize

Screening Period

Within 35 days prior to the Baseline visit, subjects will receive a full explanation of the study design and study procedures, provide a written informed consent, and undergo the screening procedures as outlined in Appendix C. Once written informed consent is obtained, subjects will undergo screening procedures.

The length of time between Screening and the Baseline visit must allow time for endoscopy central reading and lab results. The Screening period (35 days ± 7 days is granted around all study visits) may be extended as necessary after consultation with the AbbVie Therapeutic Area Medical Director (TA MD) for subjects who require initiation of prophylactic anti-TB therapy, or in case of external circumstances (e.g., due to the delay of availability of screening test results).

Laboratory values that are exclusionary can be re-tested once during the screening period upon discussion and clearance with TA MD. If the re-tested lab value(s) remain(s) exclusionary, the subject will be considered a screen failure. Redrawing samples if previous samples were unable to be analyzed would not count as a retest since the previous result was never obtained.

Clinical laboratory assessments as specified in Appendix C will only need to be repeated at Baseline if the time between Screening and Baseline is > 14 days, or if the subject's health status has changed to warrant a repeat test.

All subjects need to have their average daily SF, average daily AP, and CDAI calculated and meeting eligibility criteria before randomization at Baseline.

12-Week Induction Period

At the Baseline visit, subjects who meet all the inclusion criteria and none of the exclusion criteria described in Section 5.2.1 and Section 5.2.2 will be enrolled into the study and randomized to the double-blind induction period where they will receive either risankizumab 1200 mg IV, risankizumab 600 mg IV, or placebo, given at Baseline and

Weeks 4 and 8. The randomization at Baseline will be stratified by number of prior biologics failed (0, 1, > 1), steroid use at Baseline (yes, no), and Baseline SES-CD (original, alternative).

During this period of the study, subjects will visit the study site at Weeks 4, 8 and 12/PD. Subjects who do not achieve clinical response at Week 12 and choose to continue in the study will have additional visits at Weeks 16, 20 and 24 for blinded Induction Period 2 with risankizumab. A ± 7-day window is permitted around scheduled study visits. An effort will be made to bring subjects back to their original scheduled visit (calculated from Baseline) if they are out of the visit window.

At the Week 12/PD visit, all subjects will undergo an endoscopy for evaluation of mucosal inflammation. It is expected that all subjects who remain in the study through at least Week 8 will have a Week 12/PD endoscopy. All subjects achieving clinical response, defined as ≥ 30% decrease in average daily SF and/or ≥ 30% decrease in average daily AP score (both not worse than Baseline) at Week 12 may be eligible to enter Study M16-000. Subjects are not eligible to enter Study M16-000 until endoscopy has been completed (local reader results will be used for stratification for Study M16-000).

All subjects who do not achieve clinical response at Week 12 will be able to receive blinded risankizumab in Induction Period 2, as specified below. Subjects are not eligible to receive blinded Induction Period 2 therapy until endoscopy has been completed.

Induction Period 2

At Week 12, subjects who do not achieve clinical response will be randomized by Interactive Response Technologies (IRT) to Induction Period 2, a double-blind, double-dummy 12-week treatment period.

Subjects who received risankizumab induction treatment will be randomized 1:1:1 to:

- Group 1: 1200 mg IV risankizumab

- Group 2: 360 mg SC risankizumab
- Group 3: 180 mg SC risankizumab

Subjects who received placebo induction treatment will receive:

- Group 4: 1200 mg IV risankizumab

The IV risankizumab dose or matching IV placebo will be given at Weeks 12, 16, and 20. The SC risankizumab dose or matching SC placebo will be given at Weeks 12, and 20.

At Week 24, subjects who participated in the blinded Induction Period 2 will be reassessed and undergo a third endoscopy for evaluation of mucosal inflammation. Subjects who achieve clinical response at Week 24 may be eligible to enter Study M16-000. Subjects without clinical response at Week 24, as well as all subjects who terminate the study early (including subjects who are eligible for but do not participate in the blinded Induction Period 2), will be discontinued and have a follow-up call 140 days from the last dose of study drug to obtain information on any new and/or ongoing AEs.

Concomitant aminosalicylates, corticosteroids, immunomodulators (azathioprine [AZA], 6-mercaptopurine [6-MP], methotrexate [MTX]), and/or CD-related antibiotics

Subjects taking aminosalicylates, immunomodulators, and/or CD-related antibiotics at Baseline must continue their concomitant treatment for the duration of the study. Initiating and/or increasing doses of aminosalicylates, immunomodulators, and/or CD-related antibiotics during the study is prohibited. Decreasing doses of aminosalicylates, immunomodulators, and/or CD-related antibiotics is prohibited during the study, except in the event of moderate-to-severe treatment related toxicities and after discussion with the AbbVie Therapeutic Area Medical Director (TA MD). CD-related antibiotics may be discontinued in Induction Period 2 at the discretion of the Investigator.

Note: the duration of the study includes Induction Period 2.

Concomitant Corticosteroids

Subjects taking corticosteroids at Baseline must continue their concomitant treatment at the Baseline dose for the duration of the 12-week induction period. Initiation and/or increasing doses of systemic and/or CD related corticosteroids during the entire study is prohibited. Decreasing doses of corticosteroids is prohibited during the 12-week induction period, except in the event of moderate-to-severe treatment related toxicities and after discussion with the AbbVie Therapeutic Area Medical Director (TA MD).

Subjects who receive blinded therapy in Induction Period 2 during Weeks 12 to 24 will be allowed to taper their corticosteroids at the discretion of the Investigator. While stopping the taper is permitted, increasing doses above the Baseline dose is prohibited.

Follow-Up Period/Premature Discontinuation (PD)

Subjects may discontinue treatment at any time during the study participation (Section 5.4). Subjects who end study participation early will have a PD visit and complete the procedures outlined for the PD visit in Appendix C as soon as possible after the last dose of study drug and preferably prior to the administration of any new therapies.

Subjects who discontinue the study or subjects who complete the Week 12/Week 24 visit and do not roll-over into Study M16-000 will have a follow-up call 140 days from the last dose of study drug to obtain information on any new or ongoing AEs.

Re-Screen

Subjects who initially screen fail for the study may be permitted to re-screen following re-consent. The subject must meet all the inclusion and none of the exclusion criteria at the time of re-screening in order to qualify for the study. There is no minimum period of time a subject must wait to re-screen for the study.

If the subject had a complete initial screening evaluation including the TB test, Hepatitis B virus (HBV), Hepatitis C virus (HCV), human immunodeficiency virus (HIV) and electrocardiogram (ECG), these tests will not be required to be repeated for

re-screening provided the conditions noted in Section 5.3.1.1 are met and no more than 90 days have passed since the collection date of the testing.

If a subject is being rescreened within 14 days (≤ 14 days have passed) from the collection date of the previous screening testing, it is not required to repeat Screening testing for chemistry/hematology, urinalysis, serum pregnancy, and C. *difficile* provided that the subject's health status has not changed to warrant a repeat test. In this case, all Baseline testing should be performed at the Baseline visit.

If rescreening occurs more than 14 days (> 14 days have passed) from the collection date of the previous screening testing then new samples (chemistry/hematology, urinalysis, serum pregnancy, and C. *difficile*) should be collected during Rescreening. In this case, chemistry/hematology, urinalysis do not need to be repeated at the Baseline visit if Baseline occurs within 14 days (≤ 14 days) from the date of rescreening testing provided that the subject's health status has not changed to warrant a repeat test.

All subjects need to have their average daily SF, average daily AP, and CDAI calculated in order to verify eligibility criteria before randomization at Baseline.

An endoscopy with biopsy will not be required to be repeated for re-screening provided the conditions noted in Section 5.3.1.1 are met and the endoscopy is within 45 days of the Baseline visit. Sites may contact the AbbVie TA MD if there are questions on if subjects should or should not be re-screened.

5.2 Selection of Study Population

It is anticipated that approximately 855 subjects with active moderate to severe CD will be enrolled at approximately 400 sites worldwide. Both non-bio-IR and bio-IR subjects will be included. The bio-IR population will be a minimum of approximately 540 subjects and the non-bio-IR population will be a minimum of approximately 315 subjects.

A subject may be enrolled in this study provided that he/she has met all of the inclusion criteria and none of the exclusion criteria specified in this protocol.

5.2.1 Inclusion Criteria

1. Male or female aged ≥ 18 to ≤ 80 years, or minimum age of adult consent according to local regulations, at the Baseline Visit. Where locally permissible, subjects 16 to < 18 years of age who meet the definition of Tanner stage 5 for development (refer to Appendix J) at the Baseline Visit (sites will be notified when adolescents may enroll).
2. Confirmed diagnosis of CD for at least 3 months prior to Baseline. Appropriate documentation of biopsy results consistent with the diagnosis of CD, in the assessment of the Investigator, must be available.
3. Crohn's disease activity index (CDAI) score 220 – 450 at Baseline.
4. Endoscopic evidence of mucosal inflammation as documented by the SES-CD of ≥ 3. All eligible scores exclude the presence of narrowing component and are confirmed by a central reader. (Once cap of no more than 85 subjects is reached, enrollment criterion will be an SES-CD of ≥ 6 for ileocolonic or colonic disease or SES-CD of ≥ 4 for isolated ileal disease.)
5. Average daily SF ≥ 4 and/or average daily AP score ≥ 2 at Baseline.
6. Demonstrated intolerance or inadequate response to one or more of the following categories of drugs: aminosalicylates, oral locally acting steroids, systemic steroids (prednisone or equivalent), immunomodulators, and/or biologic therapies
    - Demonstration of intolerance requires no minimum dose or duration of use (intolerance includes patients with a known TPMT genetic mutation or low activity).
    - Inadequate response is defined as outlined below:
        - Oral aminosalicylates (e.g., mesalamine, sulfasalazine, olsalazine, balsalazide):

- Signs and symptoms of persistently active disease, in the opinion of the Investigator, during a current or prior course of at least 4 weeks of treatment with 2.4 g/day mesalamine, 4 g/day sulfasalazine, 1 g/day olsalazine, or 6.75 g/day balsalazide,

○ Oral locally acting steroids (e.g., budesonide, beclomethasone):

- Signs and symptoms of persistently active disease in the opinion of the Investigator, during or after a course of at least 4 weeks of treatment with 9 mg/day budesonide or 5 mg/day beclomethasone,

  or

- Inability to taper oral budesonide to at or below 6 mg/day without recurrent active disease,

○ IV or Oral systemic steroids (prednisone or equivalent):

- Signs and symptoms of persistently active disease in the opinion of the Investigator, during or after tapering of at least one regimen consisting of a dose equivalent to prednisone ≥ 40 mg/day orally for 3 weeks or intravenously for 1 week,
- or
- Inability to taper oral systemic steroids at or below a dose equivalent to prednisone 10 mg/day without recurrent active disease,

○ Immunomodulators:

- Signs and symptoms of persistently active disease in the opinion of the Investigator, during a current or prior course of at least 90 days of treatment with one or more of the following:
  - AZA: ≥ 2.0 mg/kg/day rounded to the nearest available tablet or half tablet formulation (≥ 1 mg/kg/day for subjects in Japan, Korea, Hong Kong, Taiwan, Singapore, or China) (or a documented 6-TGN level of ≥ 230 pmol/8 × 10^8 RBC)
  - 6-MP: ≥ 1 mg/kg/day rounded to the nearest available tablet or half tablet formulation (≥ 0.6 mg/kg/day for subjects in Japan, Korea, Hong Kong, Taiwan, Singapore, or China) (or a 6 TGN level of ≥ 230 pmol/8 × 10^8 RBC)
  - MTX: ≥ 15 mg/week subcutaneous (SC) or intramuscular (IM)

- *Note:* Oral MTX use is allowed during the study, however prior or current use of oral MTX is not sufficient for inclusion into the study

- Biologic therapies for CD:
  - Signs and symptoms of persistently (in the opinion of the Investigator) active disease despite a history of one or more of the following:
    - At least one 6-week induction regimen of infliximab (≥ 5 mg/kg IV at Weeks 0, 2, and 6),
    - At least one 4-week induction regimen of adalimumab (one 160 mg SC dose at Week 0, followed by one 80 mg SC dose at Week 2 [or one 80 mg SC dose at Week 0, followed by one 40 mg SC dose at Week 2, in countries where this dosing regimen is approved]),
    - At least one 4-week induction regimen of certolizumab pegol (400 mg SC at Weeks 0, 2, and 4),
    - At least one 6-week induction regimen of vedolizumab (300 mg IV at Weeks 0, 2, and 6),
    - At least one 12-week induction regimen of natalizumab (300 mg IV every 4 weeks)
    - At least one 8-week induction regimen of ustekinumab [260 mg (≤ 55 kg) or 390 mg (> 55 to ≤ 85 kg) or 520 mg (> 85 kg) IV, followed by 90 mg SC at Week 8] (Once cap of no more than 20% ustekinumab exposed subjects is reached, subjects with prior ustekinumab exposure will not be allowed to enroll.)
  - Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit of the above biologics
  - Note: Subjects who discontinued biologics for reasons other than inadequate response as defined above or intolerance (e.g., change of insurance) must meet the criteria for intolerance or inadequate response to aminosalicylates, oral locally acting steroids, systemic steroids (prednisone or equivalent), and/or immunomodulators as defined above

7. If female, subject must meet the criteria as stated in Section 5.2.4 of this protocol *Contraception Recommendations.* Females of childbearing potential must have a

negative serum pregnancy test result during Screening, and a negative urine pregnancy at Baseline. Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) during Screening do not require pregnancy testing at Baseline.

Note: Subjects with borderline serum pregnancy test at Screening must have a serum pregnancy test ≥ 3 days later to document continued lack of a positive result.

8. Subject must be able and willing to give written informed consent and to comply with the requirements of this study protocol. In Japan, if the subject is < 20 years old, a subject's parent or legal guardian must be willing to give written informed consent.

Rationale for Inclusion Criteria

1 – 6	To select the adequate subject population with a disease status representative of the target population for evaluation
7	The impact of risankizumab on pregnancy and reproduction is unknown
8	In accordance with harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

1. Subject with a current diagnosis of ulcerative colitis or indeterminate colitis.

Concomitant Medications and Treatments

2. Subject on CD-related antibiotics who has not been on stable doses for greater than, or discontinued within, 14 days prior to Baseline.
3. Subject on oral aminosalicylates who has not been on stable doses for greater than, or discontinued within, at least 14 days prior to Baseline.
4. Subject taking oral corticosteroids:
   - Budesonide > 9 mg/day
   - Beclomethasone > 5 mg/day

- Prednisone or equivalent > 20 mg/day
- Or has not been on the current course for ≥ 14 days prior to Baseline and on a stable dose for ≥ 7 days prior to Baseline

5. Subject on immunomodulators (AZA, 6-MP, MTX) who:
   - Has not been on the current course for ≥ 42 days prior to Baseline, and
   - Has not been on a stable dose for ≥ 35 days prior to Baseline

Medications and Treatments **During** the Screening Period

6. Subject who received IV anti-infectives within 35 days prior to Baseline visit or oral/intramuscular anti-infectives (non-CD-related) within 14 days prior to the Baseline visit. This does not apply to TB prophylaxis.
7. Subject who received exclusive enteral nutrition or any parenteral nutrition within 35 days prior to Baseline.
8. Subject who received any live bacterial or viral vaccination within 30 days (8 weeks for Japan) prior to Screening or during the Screening Period.
9. Subject who received cyclosporine, tacrolimus, or mycophenolate mofetil within 35 days prior to Baseline.
10. Subject who received fecal microbial transplantation within 35 days prior to Baseline.

Prior Medications and Treatments

11. Subject who received any:
    - approved biologic agent: infliximab, adalimumab, certolizumab, vedolizumab, natalizumab within 8 weeks prior to Baseline or ustekinumab within 12 weeks prior to Baseline, or

      Note: If there is proper documentation of an undetectable drug level measured by a commercially available assay for any of the approved biologics above, there is no minimum washout prior to Baseline.
    - any investigational biologic or other agent or procedure within 35 days or 5 half-lives prior to Baseline, whichever is longer.

12. Subject with prior exposure to p19 inhibitors (e.g., risankizumab)

13. Subject has been taking combination of two or more of the following: oral budesonide, or oral beclomethasone and/or oral prednisone (or equivalent) simultaneously, with the exception of inhalers, within 14 days prior to Screening or during the Screening period.

14. Subject who received IV/intramuscular corticosteroids within 14 days prior to Screening or during the Screening period.

15. Subject who received therapeutic enema or suppository, other than required for endoscopy, within 14 days prior to endoscopy used for Screening or during the Screening period.

16. Subject who received apheresis (e.g., Adacolumn apheresis) ≤ 60 days prior to Screening or during the Screening period.

17. Subject who has concomitant cannabis use either recreational or for medical reasons within 14 days of Baseline or any history of clinically significant drug, or alcohol abuse in the last 12 months.

<u>CD Related</u>

18. Subject with currently known complications of CD such as:
    - abscess (abdominal or perianal),
    - symptomatic bowel strictures,
    - > 2 missing segments of the following 5 segments: terminal ileum, right colon, transverse colon, sigmoid and left colon, and rectum
    - fulminant colitis,
    - toxic megacolon,
    - or any other manifestation that might require surgery while enrolled in the study.

19. Subject with ostomy or ileoanal pouch.

20. Subject diagnosed with short gut or short bowel syndrome.

21. Subject with surgical bowel resection within the past 3 months prior to Baseline, or a history of ≥ 3 bowel resections.

Safety

22. Subject who has a known hypersensitivity to risankizumab or the excipients of any of the study drugs or the ingredients of Chinese hamster ovary (CHO).

23. Subjects with the following chronic or active infections:

- Active, chronic, or recurrent infection that based on the Investigator's clinical assessment makes the subject unsuitable candidate for the study,
- Infection with C. difficile toxin or other intestinal pathogen during Screening,
- Are infected with human immunodeficiency virus (HIV),
- QuantiFERON®-TB test or Purified Protein Derivative (PPD) skin test, or both, according to local guidelines, will be performed during Screening. QuantiFERON®-TB test is preferred for subjects who received Bacillus Calmette-Guérin (BCG) vaccination or were exposed to other Mycobacteria species. Subjects with a positive test result (or indeterminate results that have been repeated) may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active tuberculosis. Subjects with a history of active TB who have documented completion of a full course of anti-TB therapy may be allowed to enter the study after consultation with the AbbVie TA MD. If latent TB is established, TB prophylaxis/treatment should be initiated and maintained according to local country guidelines.
- Have active hepatitis B or hepatitis C defined as:
  - HBV: hepatitis B surface antigen (HBs Ag) positive (+), or detected sensitivity on the HBV deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) qualitative test for hepatitis B core antibody (HBc Ab) positive subjects;
  - HCV: HCV ribonucleic acid (RNA) detectable in any subject with positive anti-HCV antibody (HCV Ab)

24. Subject with a previous history of dysplasia of the gastrointestinal tract or found to have dysplasia, other than completely removed low-grade dysplastic lesions, in any biopsy performed during the Screening endoscopy.

25. Subject with a known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly.

26. Subject with current or previous history of malignancy other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix.

27. Subject who has severe, progressive, or uncontrolled renal, hepatic, hematological, endocrine, disorder or symptoms thereof.

28. Female subjects who is pregnant, breastfeeding, or is considering becoming pregnant during the study or for approximately 140 days after the last dose of study drug.

29. Subject who has any condition, including any physical, psychological, or psychiatric condition, which in the opinion of the Investigator, would compromise the safety of the subject or the quality of the data and renders the subject an unsuitable candidate for the study.

30. Screening laboratory and other analyses show any of the following abnormal results:

    - Aspartate transaminase (AST), alanine transaminase (ALT) > 2 × upper limit of the reference range;
    - White blood cell (WBC) count < 3.0×10^9/L;
    - Total bilirubin ≥ 2 mg/dL; except for subjects with isolated elevation of indirect bilirubin relating to Gilbert syndrome;
    - Estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula < 30 ml/min/1.73 m^2.
    - Hemoglobin < 8 g/dL

- Platelets < 100,000/μL
- Positive serum pregnancy test at the Screening visit or positive urine pregnancy test at the Baseline visit.

Laboratory values can be re-tested once during the screening period after discussion and clearance with the TA MD. If the re-tested lab value(s) remain(s) exclusionary, the subject will be considered a screen failure. Redrawing samples if previous samples were unable to be analyzed would not count as a retest since the previous result was never obtained

31. No known active COVID-19 infection. Subject must not have signs/symptoms associated with COVID-19 infection.

Subjects who do not meet COVID-19 eligibility criteria must be screen failed and may only rescreen after they meet the following COVID-19 viral clearance criteria:

- Symptomatic subjects: At least 2 negative viral tests in a row completed locally, ≥ 24 hours apart after at least 10 days have passed since recovery, defined as resolution of fever without use of antipyretics and improvement in respiratory symptoms (e.g., cough, shortness of breath)
- Asymptomatic subjects: At least 2 negative viral tests in a row completed locally, ≥ 24 hours apart after at least 10 days have passed since prior positive result (Note: subjects who develop symptoms will follow guidance above for symptomatic subjects)

Frequency or timing of COVID-19 testing and interval between testing for the above viral clearance criteria may be adjusted to account for epidemiological trends, updated information regarding infectivity and local/institutional guidelines.

Rationale for Exclusion Criteria

1	To avoid medical conditions that may compromise the ability to identify subjects with the correct diagnosis or to interpret medical importance of clinical results
2 – 17	To avoid bias for the evaluation of efficacy and safety by concomitant use of other medications or treatments and to ensure the safety of the subject

18 – 21	To avoid complications of CD that may compromise the evaluations of efficacy and safety
22 – 30	To ensure the safety of the subject and or others

5.2.3 Prior and Concomitant Therapy

5.2.3.1 Prior Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject has received within 35 days prior to Baseline, is receiving at the time of enrollment, or continues during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency in source documents and the (electronic case report forms) eCRFs.

CD specific medications (including but not limited to corticosteroids, aminosalicylates, immunomodulators [AZA, 6-MP, or MTX], and CD-related antibiotics) that the subject has received within 90 days of Baseline should be recorded on the appropriate page of the eCRF and should include the dates of administration and dosages. In addition, if a subject has ever received AZA, 6-MP, or MTX (oral or IM/SC), the duration of therapy, maximum dose, reason for use and reason(s) for termination of treatment will also be recorded in the appropriate eCRF.

For all subjects with a history of biologic use for inflammatory bowel disease, the history of previous use (including the names of biologic therapy used, duration of therapy, the highest known dose taken, reason for use and reason[s] for termination of treatment of the biologic agent will be recorded in the appropriate eCRF.

The AbbVie TA MD identified in Section 6.1.5 should be contacted if there are any questions regarding concomitant or prior therapy(ies).

5.2.3.2 Concomitant Therapy

Subjects taking aminosalicylates, immunomodulators, and/or CD-related antibiotics at Baseline must continue their concomitant treatment for the duration of the study. Initiating and/or increasing doses of aminosalicylates, immunomodulators, and/or CD-related antibiotics during the study is prohibited. Decreasing doses aminosalicylates, immunomodulators, and/or CD-related antibiotics is prohibited during the study, except in the event of moderate-to-severe treatment related toxicities and after discussion with the AbbVie TA MD. CD-related antibiotics may be discontinued in the blinded Induction Period 2 at the discretion of the Investigator.

Note: the duration of the study includes the Induction Period 2.

Concomitant Corticosteroids

Subjects taking corticosteroids at Baseline must continue their concomitant treatment at the Baseline dose for the duration of the 12-week induction period. Initiation and/or increasing doses of systemic and/or CD related corticosteroids during the entire study is prohibited. Decreasing doses of corticosteroids is prohibited during the 12-week induction period, except in the event of moderate-to-severe treatment related toxicities and after discussion with the AbbVie TA MD.

Subjects who receive blinded therapy in Induction Period 2 during Weeks 12 to 24 will be allowed to taper their corticosteroids at the discretion of the Investigator. While stopping the taper is permitted, increasing doses above the Baseline dose is prohibited.

Subjects may not be on both budesonide and prednisone (or equivalent) simultaneously, with exception of inhalers within 14 days prior to Screening.

Setons are authorized as concomitant therapy in subjects with perianal fistulas and should be documented in the eCRF under concomitant medications.

Changes in all concomitant medications will be assessed at each study visit from Baseline through Week 12/PD and during Weeks 12 to 24 visits for subjects who participate in the

blinded Induction Period 2. Any changes will be documented in the source documents and captured on the appropriate eCRF page.

Subjects should not be routinely pre-medicated prior to infusion of study drug. If in the Investigator's judgment the subject requires pre-medication based on prior medical history or symptoms with prior infusions of study drug in the current study, the AbbVie TA MD should be contacted regarding possible permitted pre-medication with diphenhydramine hydrochloride and acetaminophen (or equivalents). Individual dosage, timing, and route of administration would be determined by the Investigator. Any pre-medications administered must be recorded on the appropriate eCRF.

The AbbVie TA MD identified in Section 6.1.5 should be contacted if there are any questions regarding concomitant or prior therapy(ies).

5.2.3.3 Prohibited Therapy

- The following are prohibited medications during the study:
  - All biologic therapy with a potential therapeutic impact on the disease being studied including but not limited to the following:
  - Etanercept (Enbrel®);
  - Abatacept (Orencia®);
  - Anakinra (Kineret®);
  - Rituximab (Rituxan®);
  - Natalizumab (Tysabri®);
  - Tocilizumab (Actemra®);
  - Ustekinumab (Stelara®);
  - Belimumab (Benlysta®);
  - Infliximab (Remicade®);
  - Certolizumab pegol (Cimzia®);
  - Golimumab (Simponi®);
  - Adalimumab (Humira®)
  - Vedolizumab (Entyvio®);

- Investigational agents (e.g., tofacitinib, baracitinib, filgotinib)
- Live or attenuated vaccines are NOT allowed during the study and for 140 days after the last dose of study drug. Examples of such vaccines include but are not limited to the following:
  - live attenuated influenza
  - herpes zoster (e.g., Zostavax®)
  - rotavirus
  - varicella (chicken pox)
  - measles-mumps-rubella (MMR) or measles mumps rubella varicella (MMRV)
  - oral polio vaccine (OPV)
  - smallpox
  - yellow fever
  - Bacille Calmette-Guérin (BCG)
  - oral typhoid
- Cyclosporine, tacrolimus, or mycophenolate mofetil.
- Concomitant cannabis use either recreational or for medical reasons.
- Rectal therapy with any therapeutic enemas or suppositories, with the exception of those required for endoscopy, is prohibited during the study.
- Apheresis (e.g., Adacolumn apheresis).
- Exclusive enteral nutrition or any parenteral nutrition.

The AbbVie TA MD identified in Section 6.1.5 should be contacted if there are any questions regarding prohibited therapy.

5.2.4 Contraception Recommendations

If female, subject must be either postmenopausal defined as:

- Age ≥ 55 years with no menses for 12 or more months without an alternative medical cause.

- Age < 55 years with no menses for 12 or more months without an alternative medical cause AND an Follicle-Stimulating Hormone (FSH) level > 40 IU/L.

OR,

- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

OR, for women of childbearing potential (WOCBP):

- Practicing at least one of the following methods of birth control, prior to Baseline through at least 140 days after the last dose of study drug.
  - Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal, injectable) associated with the inhibition of ovulation, (must start at least 1 month prior to study.
  - Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, (must start at least 1 month prior to study).
  - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
  - Vasectomized sexual partner(s) (the vasectomized partner should have received medical assessment of the surgical success and is the sole sexual partner of trial participant).
  - Intrauterine device (IUD).
  - Intrauterine hormone-releasing system (IUS).
  - True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

5.3 Efficacy, Pharmacokinetic, Pharmacodynamic, Optional Exploratory Research/Validation Studies and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures described are listed in the following section of this protocol and are summarized in tabular format in Appendix C.

5.3.1.1 Study Procedures

The study procedures outlined in Appendix C are discussed in detail in this section, with the exception of the optional exploratory research/validation studies (discussed in Section 5.3.1.2 and Appendix D), pharmacokinetics and pharmacodynamics (discussed in Section 5.3.2), and the collection of AE information (discussed in Section 6.1.4). All study data will be recorded in source documents and on the appropriate eCRFs.

Study visits may be impacted by changes in local regulations due to the COVID-19 pandemic. This may include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study.

Informed Consent

At the Screening visit, the subject will sign and date a study specific, Independent Ethics Committee (IEC)/Independent Review Board (IRB) approved, informed consent form before any study procedures are performed or any medications are withheld from the subject in order to participate in this study. A separate informed consent will be required for each subject in order to participate in the optional exploratory research/validation studies. Details regarding how informed consent will be obtained and documented are provided in Section 9.3.

Due to the COVID-19 pandemic, modifications to the protocol may be necessary. Subjects should be informed of the changes to the conduct of the study relevant to their participation (e.g., cancellation of visits, change in laboratory testing site, etc.). Documentation of this notification or verbal consent should be maintained at the site as required per local regulatory requirements. A signed and dated informed consent form should be obtained from the subject afterwards as soon as possible.

Inclusion/Exclusion Criteria

Subjects will be evaluated to ensure they meet all inclusion criteria and have none of the exclusion criteria at both Screening and Baseline visits.

Medical and Surgical History

A complete medical and surgical history, including CD-onset date, history of CD medication use, and history of alcohol and tobacco use will be obtained from each subject at the Screening visit. An updated medical history will be obtained prior to study drug administration at Baseline, to ensure the subject is still eligible for enrollment, and updated as necessary.

Information on prior biologic, corticosteroid, immunomodulators (i.e., AZA, 6-MP, MTX), CD-related antibiotics, aminosalicylate or any other physician prescribed therapy for CD use will be obtained as outlined in Section 5.2.3.1.

A detailed medical history with respect to TB exposure will be documented. This information will include BCG vaccination, cohabitation with individuals who have had TB, and residence or work in TB endemic locations. Subjects with active TB (during Screening) or documented history of active TB who have documented completion of a full course of anti-TB therapy may be allowed to enter the study after consultation with the AbbVie TA MD. TB history and anti-TB therapy needs to be documented in the source documents and eCRFs.

Physical Examination

A physical examination including evaluation of extra intestinal manifestations (EIMs) will be performed at the designated study visits as specified in Appendix C.

A full physical examination will be performed as outlined in Appendix C. Physical examinations at all other visits (including unscheduled visits) are symptom based and should include the assessment of EIMs as part of calculating the Crohn's disease activity index (CDAI). The number of cutaneous fistulas should be recorded, including the number of fistulas draining upon gentle compression. Fistulas will be classified as abdominal or perianal/anal. Physical exam abnormalities noted by the Investigator at Baseline (including fistulas and fissures) will be recorded in the subject's medical history.

Abnormalities noted after the Baseline visit will be evaluated and documented by the Investigator as to whether they are AEs.

Additionally, physical examination findings that are related to or part of each subject's medical history will be captured on the appropriate medical history eCRFs.

Vital Signs

Vital sign determinations of systolic and diastolic blood pressure in sitting position, pulse rate, respiratory rate, and body temperature will be obtained at each visit. Blood pressure, pulse rate, and respiratory rate should be measured before blood draws are performed.

Height will be measured at the Screening visit only (with shoes off) for subjects ≥ 18 years of age. Height will be re-measured at Week 12 and Week 24 (if applicable) for subjects < 18 years of age at Baseline. Body weight will be measured at all scheduled visits, as specified in Appendix C. All measurements will be recorded in metric units where applicable.

TB Testing

All subjects will be tested for TB by either the QuantiFERON-TB Gold Test (or equivalent) or a TB Skin Test (PPD), or both, according to local guidelines, as specified in Appendix C.

For subjects treated with corticosteroids (equivalent to Prednisone 5 mg or above – with ongoing treatment or treatment within 1 month prior to TB screening), an Interferon-Gamma Release Assay (IGRA; QuantiFERON-TB Gold In-Tube test) must be performed during the Screening Period for all subjects including those with a prior history of Bacille Calmette-Guérin (BCG) administration or who were exposed to other Mycobacteria species.

For subjects NOT treated with corticosteroids (equivalent to Prednisone 5 mg or above – with ongoing treatment or treatment within 1 month prior to TB screening), a PPD skin test (alternatively, also known as tuberculin skin test) must be placed, or alternatively an Interferon-Gamma Release Assay (IGRA; QuantiFERON-TB Gold In-Tube test or T-SPOT TB test) must be performed during the Screening Period for all subjects. IGRA is preferred for subjects with a prior history of Bacille Calmette-Guérin (BCG) administration or who were exposed to other Mycobacteria species.

If PPD and/or the QuantiFERON®-TB Gold test (or IGRA equivalent) is positive, or if there is a repeat indeterminate (note: the first indeterminate results must be repeated) QuantiFERON®-TB Gold test (or IGRA equivalent) upon retesting, subjects may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. Subjects with a history of active TB who have documented completion of a full course of anti-TB therapy may be allowed to enter the study after consultation with the AbbVie TA MD. If active TB is diagnosed, the subject may not enroll in the study. If presence of latent tuberculosis is established, then tuberculosis prophylaxis should be initiated and maintained according to local country guidelines. It is also necessary to report the latent TB or positive TB testing in the source documents and eCRFs.

- QuantiFERON®-TB Gold Test is the preferred method which will be analyzed by the central laboratory (QuantiFERON test is preferred over TB Skin Test). However, if other IGRA equivalent tests are used, these may be performed by a certified local laboratory at the Investigator's discretion.
- If the QuantiFERON®-TB Gold Test is NOT possible (or if both the QuantiFERON®-TB Gold Test and the PPD Skin Test are required per local guidelines) the PPD Skin Test will be performed according to standard clinical practice.
  - The PPD Skin Test should be read by a licensed healthcare professional between 48 and 72 hours after administration. A subject who does not return within 72 hours will need to be rescheduled for another skin test.
  - The reaction will be measured in millimeters (mm) of induration and induration ≥ 5 mm is considered a positive reaction. The absence of induration will be recorded as "0 mm" not "negative."
- If PPD and/or the QuantiFERON®-TB Gold test (or IGRA equivalent) is positive, or if there is a repeat indeterminate QuantiFERON®-TB Gold test (or IGRA equivalent) upon retesting, subjects may continue in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active tuberculosis.
- If presence of latent tuberculosis is established, TB prophylaxis/treatment should be initiated and maintained according to local country guidelines.
- Subjects who have had an ulcerating reaction to the TB Skin Test in the past should not be re-exposed and should not be tested by a PPD skin test.
- In the case of a tuberculosis-related AE, a supplemental eCRF that provides additional information should be completed by the Investigator or designee.

If a CXR or other diagnostic tests are required to be performed to assess TB per local guidelines, this information will also be captured on the appropriate eCRF.

12-Lead Electrocardiogram (ECG)

A resting 12-lead ECG will be performed during Screening as specified in Appendix C. A qualified physician will interpret the clinical significance of any abnormal finding, sign,

and date each ECG. ECG findings, including any clinically significant findings will be documented in the source documents and later transcribed on to the appropriate eCRF. Each signed original ECG will be monitored by the responsible clinical research associate (CRA) and kept with subject's source documents onsite.

For subjects with a normal ECG taken within 90 days of Screening, a repeat ECG at Screening will not be required, provided source documentation is available. If there are other findings that are clinically significant, the Investigator must bring this to the attention of the AbbVie TA MD before the subject can be enrolled.

Subjects can have a repeat ECG at any time during the study as warranted, based on the opinion of the Investigator.

Clinical Laboratory Tests

Blood samples will be obtained for the laboratory tests listed in Table 1. Blood draws should be performed, as much as possible, after vital signs, efficacy assessments and questionnaires (CDAI, IBDQ, etc.) are obtained and before study drug administration during a visit.

A certified central laboratory will be utilized to process and provide results for the clinical laboratory tests. All abnormal laboratory tests that are considered clinically significant by the Investigator will be followed to a satisfactory resolution.

The central laboratory chosen for this study will provide instructions regarding the collection, processing and shipping of these samples.

For serum chemistry tests and some exploratory biomarker tests, it is preferred that the subject has fasted (8 hours, except for water) prior to sample collection, however it is not required. It must be recorded whether the subject has fasted or not at the time of collection in the laboratory request, source document, and eCRF.

If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from having blood drawn for laboratory testing at the study site, if possible, arrange for subjects to have laboratory work done at a local lab, hospital, or other facility. Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. Local lab results should be reviewed by the investigator as soon as possible.

If laboratory samples cannot be obtained, study drug administration may be continued provided the investigator has reviewed all prior laboratory results and confirms and discusses with the subject that there is no safety concern for the subject to continue use of the study drug in the absence of current labs.

Table 1. Clinical Laboratory Tests

Hematology	**Clinical Chemistry**[a]	**Screening Blood Tests**
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count WBC Differential Platelets Coagulation: INR[c]	General: Sodium Potassium Chloride Bicarbonate (CO_2) Urea (BUN) Creatinine Glucose Additional Chemistry Tests: Calcium Phosphate Total Protein Albumin Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline Phosphatase Gamma-Glutamyl Transferase (GGT/γ-GT) Bilirubin Total and Direct Lipid Panel: Cholesterol (total, LDL, and HDL) Triglycerides Additional Calculations: eGFR by simplified 4-MDRD (estimated by CKD-EPI formula; for Japan)[d]	HBs Ag HBs Ab HBc Ab HBV DNA PCR reflex only HCV Ab HCV RNA reflex only QuantiFERON-TB Gold or PPD Test HIV-1 and HIV-2
Urinalysis[b]		**Other Laboratory Tests:**
Leukocyte esterase Nitrite pH Protein Blood Specific Gravity Ketones Glucose Bilirubin		Serum pregnancy (bHCG) test Urine pregnancy test (Local) Optional: FSH, if needed to confirm postmenopausal status Tryptase[e] Histamine[e]
Stool Samples:		**Biomarkers:**
C. difficile toxin Fecal calprotectin (FCP)		High-Sensitivity C-Reactive Protein (hs-CRP)
PK/Immunogenicity:		**Optional Biomarkers:**
Serum risankizumab[e] Serum anti-drug antibodies (ADA)[e] Serum neutralizing antibodies (nAb)[e]		Blood, tissue and stool will be collected for optional exploratory research/validation studies[a]

a. It is preferred that the subject has fasted (8 hours, except for water) prior to sample collection, however it is not required.

b. A microscopic analysis will be performed by the central laboratory in the event the dipstick results show leukocytes, nitrite, protein, ketones, or blood greater than negative or glucose greater than normal.

c. INR test only drawn if ALT or AST > 3 × ULN (upper limit of normal) and Total Bilirubin ≤ 2 × ULN (Refer to Section 5.4.1, for additional information).

d. Only done at screening and calculated by the central laboratory.

e. To be done with the occurrence of a suspected anaphylactic reaction (an additional sample of tryptase to be collected if possible at least 2 weeks post-reaction or at the next study visit); for ADA these samples are collected in addition to those specified in Appendix C.

Hepatitis B Testing

All subjects will be tested for the presence of the HBV at Screening. A positive result for the Hepatitis B surface antigen (HBs Ag) will be exclusionary. Samples that are negative for HBs Ag will be tested for surface antibodies (HBs Ab) and core antibodies (HBc Ab Total). Subjects with HBs Ag (–), HBs Ab (–), and HBc Ab Total (+) require PCR qualitative testing for HBV DNA. Any HBV DNA PCR result that meets or exceeds detection sensitivity will be exclusionary.

Subjects with a negative HBs Ag test and tests showing the results below do not require HBV DNA PCR qualitative testing:

- HBc Ab Total (–) and HBs Ab (–)
- HBc Ab Total (–) and HBs Ab (+)
- HBc Ab Total (+) and HBs Ab (+)

For Japan only: for subjects with HBs Ab (+) and/or HBc Ab (+) at Screening, the HBV-DNA PCR test should be performed as outlined in Appendix C. In cases where the recurrence of HBV-DNA is observed, the subject should be discontinued from the study drug. Retesting according to Appendix C is not necessary with subjects who have a history of HBV vaccine and are HBs Ab (+).

Hepatitis C Testing

All subjects will be tested for the presence of the hepatitis C Virus (HCV) antibody at Screening. Subjects with positive HCV antibody will have a HCV RNA test. If the HCV RNA is positive then the subject will be excluded.

HIV

Subjects with a known history of HIV infection are excluded from study participation. HIV testing will be conducted as part of the infection screening at the Screening visit. The Investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report these results to their health agency per local

regulations, if necessary. If a subject has a confirmed positive result, the Investigator must discuss with the subject the potential implications to the subject's health and subject should be referred for clinical care promptly. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing. This testing is to be done at the central lab.

Anaphylaxis Testing

In the event of a suspected systemic post-dose hypersensitivity reaction, a serum risankizumab, ADA, and neutralizing antibody (nAb) sample should be collected once within 24 hours of the reaction. In addition to serum risankizumab, ADA, and nAb assays, blood tests to be conducted in the event of a systemic hypersensitivity reaction are:

- Tryptase: Optimally, measurement needs to be obtained from 15 minutes to 3 hours of symptom onset, and no later than 6 hours (as tryptase may remain elevated for 6 or more hours after the onset and therefore may still be informative if obtained after 3 hours); it is also requested to collect a follow-up tryptase level a minimum of 2 weeks after the recorded event or at the next study visit.
- Plasma histamine: optimally, within 5 to 15 minutes of the onset of symptoms, and no later than 1 hour.

Stool Samples Collected:

Fecal Calprotectin (FCP)

Fecal calprotectin will be performed for all subjects as indicated in Appendix C. If subjects are unable to provide a sample at the site visit, subjects will be sent home with a stool sample supply kit and the site will give instructions to assist with collection procedures. All stool samples should be collected before any bowel preparation for endoscopy is started and returned to the site per the instructions provided outside of this protocol.

The FCP results will remain blinded to Investigator, study site personnel and the subject throughout the study.

The central laboratory will be utilized to process and provide results for these laboratory tests. In order to maintain the study blind, local laboratory testing for FCP for routine subject monitoring should not be performed.

***C. Difficile* Stool Testing**

During the Screening period a stool sample will be collected and sent to the central laboratory for testing. The sample will be assessed for the presence of *C. difficile* toxin.

The sample must be shipped to the central laboratory using dry ice. Additional information is available in the laboratory manual provided by the central laboratory.

Subjects who are positive for *C. difficile* toxin may be treated appropriately and re-screened.

Urinalysis

Dipstick urinalysis will be completed by the sites at all required visits as listed in Appendix C. A microscopic urinalysis will only be performed by the central laboratory if the dipstick urinalysis results are abnormal, where abnormal is defined as leukocytes, nitrite, ketone, protein, blood or glucose value of greater than a trace.

Pregnancy Testing

A serum pregnancy test will be performed for all female subjects of childbearing potential during Screening.

The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is positive the subject is considered a screen failure. If the serum pregnancy test is borderline, it should be repeated to determine eligibility ≥ 3 days later. If the repeat serum pregnancy test is:

- Positive, the subject is considered a screen failure;
- Negative, the subject can be enrolled into the study;
- Still borderline ≥ 3 days later, this will be considered documentation of continued lack of a positive result and the subject can be enrolled into the study (unless prohibited locally) in the absence of clinical suspicion of pregnancy and other pathological causes of borderline results.

A urine pregnancy test will be performed for all WOCBP as indicated in Appendix C, prior to study drug administration. More frequent pregnancy tests will be performed throughout the study if required per local/country requirements.

- If the baseline urine pregnancy test performed at the site is negative, then dosing with study drug may begin. If the baseline urine pregnancy test performed at the site is positive, dosing with study drug must be withheld and a serum pregnancy test is required. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is negative, study drug may be started. If the serum pregnancy test is positive, study drug must be withheld and the subject must be discontinued from the study. In the event a pregnancy test result is borderline, a repeat test is required.
- If a urine pregnancy test post-baseline is positive, study drug will be temporarily discontinued and a serum pregnancy test is required. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is negative, study drug may be restarted. If the serum pregnancy test is positive, study drug will be permanently discontinued.

A pregnant or breastfeeding female will not be eligible for participation or continuation in this study or be allowed to continue study drug.

High-Sensitivity C-Reactive Protein (hs-CRP)

Blood samples for hs-CRP will be obtained per Appendix C. The hs-CRP results will remain blinded to Investigator, study site personnel and the subject.

Blood draws should be performed, as much as possible, after all efficacy assessments, questionnaires (CDAI, IBDQ, etc.), and vital sign determinations are obtained and before study drug administration during a visit. In order to maintain the study blind, local laboratory testing for hs-CRP for routine subject monitoring should not be performed.

Crohn's Disease Activity Index (CDAI)

Average daily SF, average daily AP score, and well-being will be calculated from the subject diary. During screening subjects will be instructed on how to calculate the number of very soft and liquid stools, including a visual depiction. Physical exam and appropriate laboratory values will be calculated at all study visits beginning at Baseline. The Screening period will be a minimum of 7 days to calculate the Baseline scores.

The CDAI scores must be calculated using a central laboratory hematocrit (Hct) value from the same visit for all visits, except Baseline, where the most recent Screening Hct value will be used. The final CDAI for all other visits will be calculated once the hematocrit value is received from the central lab. If the Hct is missing due to technical issues (e.g., lost sample, clotted sample, etc.), the Hct value from the preceding visit may be used.

Instructions to calculate CDAI

- To answer **questions one (1) through three (3)**, entries from the 7 days prior to the visit should be used as recorded by the subject from the diary.
- Diary entries should not be included in the 7 days evaluated prior to the visit if: (1) the day the subject received medication for bowel preparation prior to endoscopy, (2) the day the subject underwent an endoscopy, and (3) 2 days following the endoscopy. Diary entries, up to 14 days prior to the visit, will be used accordingly in order to provide the most recent data for 7 days prior to the respective study visit. The 7 days do not need to be consecutive.
- In **question four (4)**, for the section regarding presence of anal fistulas and other fistulas, all fistulas detectable on physical examination (draining and

non-draining) should be captured on the CDAI and calculated into the CDAI score.

- And the evaluation for fever should include all the days that are taken into account for the calculation of the CDAI.
- When completing **question five (5)** ("Taking Lomotil/Imodium/Loperamide/opiates for diarrhea, 0 = no, 1 = yes") on the CDAI, "no" should be answered if a subject is taking an opiate(s) solely for pain. The use of these medications takes into account only the day of the scheduled visit and is only assessing their use as anti-diarrheals.
- For **question seven (7)**, hematocrit results from central laboratory will be used for the CDAI calculation. If the hematocrit value contains more than one decimal point, the rounding will be allowed to the tenths decimal (e.g., Hct value 33.44 will be captured as 33.4, Hct value of 33.45 will be captured as 33.5). The Hct values either prior to completing the calculation or at the subtotal box 7 of the CDAI should not be rounded to a whole number.
- For **question eight (8)**, the height obtained at Screening should be used when selecting the standard weight in Appendix G, and this standard weight should be used for calculating every CDAI throughout subject participation in the study.
- Standard height is calculated by using the height obtained at Screening (without shoes) adding one inch or 2.5 cm. For subjects < 18 years of age at Baseline, height will be re-measured at Week 12 and Week 24 (if applicable) and standard height should be recalculated.
- If the body weight obtained at the time of assessment is not captured in kilograms (kg), then when converting into kg, rounding should occur using the second digit after the decimal (also known as the hundredth place) where if the number is 0 – 4, then keep the first digit after the decimal (also known as the tenth place) unchanged. If the second digit after the decimal is 5 – 9, then round up the first digit after the decimal (e.g., 90.246 would be captured as 90.2 and 97.687 would be captured as 97.7).
- The subtotal of box 8 should not be rounded to a whole number.

The calculation of the CDAI score is in Appendix F.

Endoscopy

An endoscopy will be performed on the following visits:

- During Screening*
- Week 12/PD
- Week 24

The same endoscopist, where possible, should perform all endoscopies. In addition, where possible, the Investigator or sub-Investigator should be the endoscopist for the study. It is expected that all subjects who remain in the study through at least Weeks 8 will have a Week 12/PD endoscopy.

* An endoscopy performed before the Screening visit, independently of the study, may be used as the Screening endoscopy, with the approval of the AbbVie TA MD, if the following conditions are met:

1. Biopsy confirmation of the diagnosis is available according to section "Biopsy During Endoscopy" below, as applicable.
2. The endoscopy took place within 45 days prior to Baseline visit.
3. The endoscopy was recorded in a video format as the endoscopic eligibility will be determined by the central reviewers.

All ileocolonoscopies will be performed and recorded at the site in a video format. Sites should also perform the SES-CD assessment and record the findings on the SES-CD score sheet (Appendix E) and in the appropriate eCRF.

All endoscopies will be reviewed by a central reviewer who is blinded. Endoscopies completed at Week 12 and Week 24, for those subjects who undergo blinded therapy in Induction Period 2, will use the local reader results for stratification for Study M16-000.

There will be a window of ± 7 days to conduct the ileocolonoscopy. This window may be extended as necessary after consultation with the AbbVie TA MD in case of external circumstances.

The endoscopies performed at the time points described above will be used to provide the endoscopy subscores to calculate the SES-CD. All attempts should be made by the endoscopist to explore all segments of the colon and terminal ileum, including intubation of the terminal ileum, at every endoscopy visit. The endoscopy subscores by segment will be noted in the subject's source documents and in the database but the central reviewer's endoscopy subscore will be used for the efficacy analyses.

Biopsy During Endoscopy

Appropriate documentation of biopsy results consistent with the diagnosis of CD, in the assessment of the Investigator, must be available in order to confirm the subject's eligibility for the study. If this documentation is not available a diagnostic biopsy from the most affected area of the colon must be performed during the Screening endoscopy and read by a qualified local pathologist and the results reviewed by the Investigator. Biopsies to rule out dysplasia and colon cancer may be taken per the Investigator's discretion during any endoscopy performed during this study and evaluated by the local pathologist.

If any biopsy sample(s) are obtained, it should also be recorded on the video.

Any biopsy sample(s) will be collected from the respective bowel segment during the withdrawal of the endoscope and after sufficient recording for the central reader to calculate the SES-CD.

The signed pathology report will be monitored by the responsible CRA and kept with the subject's source documents onsite. Subjects should not be enrolled if high grade colonic dysplasia or colon cancer is discovered at Screening endoscopy or endoscopy performed within 45 days prior to Baseline visit. Subjects may be enrolled if low grade colonic dysplasia is discovered during endoscopy and is completely removed.

If a diagnosis of high grade colonic dysplasia or colon cancer is discovered during any subsequent endoscopic evaluation during the course of the study, the findings should be recorded as an AE and the subject should be discontinued from the study. If low grade colonic dysplasia is discovered during any subsequent endoscopic evaluation during the course of the study, the findings should be entered as an AE and the subject can continue in the study if the lesion has been completely removed.

Subject Diary

Subjects will be dispensed an electronic diary at Screening and will be trained on how to complete the diary by site staff during the Screening visit. All subjects should complete their subject diary on a daily basis throughout the entire study. The diary will be reviewed by site personnel with the subject at each visit and collected at the Final/PD visit, unless the subject continues into Study M16-000. Subjects should also be dispensed the patient information card at Screening.

Completion will be reinforced during study visits as necessary.

Outcomes and Questionnaires

Subjects will be asked to complete the following electronic questionnaires/outcomes at the time points indicated in Appendix C.

- Inflammatory Bowel Disease Questionnaire (IBDQ)
- Work Productivity and Impairment Questionnaire – CD (WPAI-CD)
- Crohn's Symptom Severity (CSS)
- Patient Global Impression of Change (PGIC)
- Patient Global Impression of Severity (PGIS)
- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)
- European Quality of Life 5 Dimensions (EQ-5D-5L)
- 36-Item Short Form Health Survey (SF-36)

Due to the COVID-19 pandemic and any local restrictions, sites may administer PRO instruments over the phone as needed. Sites may read the PRO questions and response options to the subject and record the subject's responses. Sites may send the questionnaires (email or hard copy) to the subjects to allow them to read/understand the questions and responses when the subject is providing responses over the phone. The date and time of PRO data collection should be recorded along with who collected the information.

Study Drug Dispensing/Administration

Intravenous and SC study drug will be administered to all subjects on-site. For WOCBP subjects, the urine pregnancy test needs to be negative prior to receiving study drug. The site will be provided administration instructions. Also, the initial 20 subjects enrolled between the Phase 3 induction trials will be monitored on site for 2 hours after completion of each infusion. Subjects should be observed after study drug administration until judged clinically stable by the study personnel. If an anaphylactic reaction or other serious allergic reaction occurs, administration of study drug should be discontinued immediately, appropriate laboratory testing samples drawn and appropriate therapy initiated.

Study drug kits are assigned by the IRT following the subjects randomized treatment schedule. (Refer to Section 5.5 for additional information).

During the Study Drug Dosing Period, a subject with confirmed (viral test positive) or suspected COVID-19 infection can only be dosed with study drug if the following COVID-19 viral clearance criteria are met:

- Symptomatic subjects: At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since recovery, defined as resolution of fever without use of antipyretics and improvement in respiratory symptoms (e.g., cough, shortness of breath)
- Asymptomatic subjects: At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since prior positive result (note:

subjects who develop symptoms will follow guidance above for symptomatic subjects)

5.3.1.2 Collection and Handling of Optional Exploratory Research/Validation Studies Samples

Subjects will have the option to provide samples for exploratory research and validation studies. Subjects may still participate in the study even if they decide not to participate in the optional exploratory research/validation. The procedures for obtaining and documenting informed consent are discussed in Section 9.3.

Exploratory research can help to improve our understanding of how individuals respond to drugs and our ability to predict which patients would benefit from receiving specific therapies. In addition, exploratory research may help to improve our understanding of how to diagnose and assess/monitor CD by assessing associations between disease characteristics, outcomes data and biomarkers of interests.

Validation studies, including those related to the development of potential in vitro diagnostic tests, may be carried out retrospectively in order to assess associations between events of interest (i.e., efficacy and/or safety events) and candidate biomarkers.

AbbVie (or people or companies working with AbbVie) will store the biomarker exploratory research/validation studies samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on risankizumab (or drugs of this class) or this disease and related conditions continues, but for no longer than 20 years after study completion.

It is preferred that the subject has fasted (8 hours, except for water) prior to sample collection, however it is not required. It must be recorded whether the subject has fasted or not at the time of collection in the laboratory request, source document, and eCRF. The following samples will be collected according to Appendix D from each subject who consents to provide samples for exploratory research/validation studies:

- DNA samples for pharmacogenetic or epigenetic analyses
- RNA samples for transcriptomic and/or epigenetic analyses
- Serum and plasma samples for systemic analyses including, but not limited to proteomics and metabolomics
- Stool samples for investigations including, but not limited to, proteomics, metabolomics, transcriptomics and metagenomics
- Intestinal biopsies for pathological and biological investigations, including but not limited to transcriptomic analyses.

Samples will be shipped to AbbVie or a designated laboratory for DNA/RNA extraction, if applicable, and/or analyses or long-term storage. Instructions for the preparation and shipment of the samples will be provided in the laboratory manual.

5.3.2 Drug Concentration and Anti-Drug Antibody Measurements

5.3.2.1 Collection of Samples for Analysis

Serum risankizumab concentrations, ADA, and neutralizing antibodies (nAb) will be determined from blood collected by venipuncture just prior to dosing as indicated in Appendix C. The time that each blood sample is collected will be recorded to the nearest minute in the source document and on the appropriate eCRF.

For approximately 20 subjects who consent to participate in the Optional Intensive PK sampling, refer to Appendix H.

5.3.2.2 Handling/Processing of Samples

Specific instructions for collection of blood/serum samples and subsequent preparation and storage of the samples for the assays will be provided by the central laboratory, AbbVie, or its designee.

Refer to the study specific laboratory manual for detailed instructions on sample collection, processing, and shipment.

5.3.2.3 Disposition of Samples

Frozen samples will be packed in dry ice (pellet form) sufficient to last 3 days during transport. Samples will be shipped pursuant to instructions from the onsite CRA. An inventory of the samples will be included in the package for shipment. Arrangements will be made with the central lab for the transfer of samples.

5.3.2.4 Measurement Methods

Serum concentrations of risankizumab and relative titers of risankizumab ADA will be determined using validated methods under the supervision of the Bioanalysis department at AbbVie. Any additional analytes may be analyzed using non-validated methods.

Serum samples collected for risankizumab and risankizumab ADA and risankizumab nAb analysis may be used for future assay development or validation activities.

The nAb samples upon request may be used for the analysis of neutralizing anti-drug antibodies in a validated assay.

5.3.3 Efficacy Variables

Endpoint definitions:

- **Clinical remission:** average daily SF $\leq$ 2.8 and not worse than Baseline AND average daily AP score $\leq$ 1 and not worse than Baseline
- **Enhanced clinical response:** $\geq$ 60% decrease in average daily SF and/or $\geq$ 35% decrease in average daily AP score and both not worse than Baseline, and/or clinical remission
- **Clinical response:** $\geq$ 30% decrease in average daily SF and/or $\geq$ 30% decrease in average daily AP score and both not worse than Baseline
- **Endoscopic response:** decrease in SES-CD > 50% from Baseline (or for subjects with isolated ileal disease and a Baseline SES-CD of 4, at least a 2 point reduction from Baseline), as scored by central reviewer

- **Ulcer-free endoscopy:** SES-CD ulcerated surface subscore of 0 in subjects with SES-CD ulcerated surface subscore ≥ 1 at Baseline, as scored by a central reviewer
- **Endoscopic remission:** SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable, as scored by a central reviewer
- **CDAI clinical response:** reduction of CDAI ≥ 100 points from baseline
- **CDAI clinical remission:** CDAI < 150

5.3.3.1 Primary Variable

Co-Primary Endpoints:

- Proportion of subjects with clinical remission at Week 12
- Proportion of subjects with endoscopic response at Week 12

5.3.3.2 Secondary Variables

Ranked Secondary Endpoints:

1. Proportion of subjects with CDAI clinical remission at Week 12
2. Proportion of subjects with CDAI clinical response at Week 4
3. Proportion of subjects with clinical remission at Week 4
4. Proportion of subjects with CDAI clinical response at Week 12
5. Mean change from baseline of induction in FACIT fatigue at Week 12
6. Mean change from baseline of induction in IBDQ total score at Week 12
7. Proportion of subjects with enhanced clinical response and endoscopic response at Week 12
8. Proportion of subjects with endoscopic remission at Week 12
9. Proportion of subjects with enhanced clinical response at Week 4

10. Proportion of subjects with ulcer-free endoscopy at Week 12
11. Enhanced clinical response at Week 12
12. Proportion of subjects with resolution of extra-intestinal manifestations (EIMs) at Week 12, in subjects with any EIMs at Baseline
13. Proportion of subjects with CD-related hospitalization through Week 12
14. Proportion of subjects without draining fistulas at Week 12 in subjects with draining fistulas at Baseline

5.3.3.3 Other Endpoints

Non-Ranked endpoints are:

- Change from Baseline in IBDQ over time
- Change from Baseline in individual IBDQ domain scores (bowel, emotional, social, systemic) over time
- Change from Baseline individual IBDQ item under Bowel Symptom domain (for Q1, Q5, Q9, Q13, Q17, Q20, Q22, Q24, Q26, and Q29) over time
- Proportion of subjects with IBDQ remission (IBDQ $\geq$ 170 points) over time
- Proportion of subjects with IBDQ response (increase in IBDQ $\geq$ 16 points from Baseline) over time
- Change from Baseline in WPAI-CD over time
- Change from Baseline in EQ-5D-5L over time
- Change from Baseline in FACIT-Fatigue overtime
- Change from Baseline in Short Form-36 overtime
- Change from Baseline in FCP over time
- Change from Baseline in hs-CRP over time
- Change from Baseline in average daily AP score over time
- Change from Baseline in average daily SF over time
- Proportion of subjects with clinical remission over time

- Proportion of subjects with enhanced clinical response over time
- Proportion of subjects with clinical response over time
- Change from Baseline in SES-CD at Week 12
- Proportion of subjects with a SES-CD ulcerated surface subscore ≤ 1 in each segment at Week 12 in subjects with a SES-CD ulcerated surface subscore ≥ 2 at Baseline
- Change from baseline in PGIS over time
- PGIC over time
- Proportion of subjects with endoscopic remission over time
- Proportion of subjects with endoscopic response over time
- Proportion of subjects with CD-related surgeries through Week 12
- Proportion of subjects with any reduction in SES-CD at Week 12
- Proportion of subjects with CDAI clinical remission over time
- Proportion of subjects with CDAI clinical response over time
- Change from Baseline in CDAI over time
- Change from Baseline in CSS over time

5.3.4 Safety Variables

Safety analyses will be performed on safety set which includes all subjects who receive at least one dose of study drug. Incidence of AEs, changes in vital signs, physical examination results, and clinical laboratory data will be assessed throughout the study.

5.3.5 Pharmacokinetic Variables

Serum risankizumab concentrations will be determined during the treatment period and at the follow-up visit as outlined in Appendix C. Serum risankizumab concentrations will be summarized at each time point for each dosing regimen using descriptive statistics. Population pharmacokinetic analyses combining the data from this study and other studies may be performed. Relationships between risankizumab exposures and efficacy and safety variables of interest may be explored.

5.3.6 Optional Exploratory Research/Validation Variables

Optional samples may be collected to conduct exploratory investigations into known and novel biomarkers. The types of biomarkers to be analyzed may include, but are not limited to, nucleic acids, proteins, lipids or metabolites. Biomarker assessments may be used to assess and generate prognostic, predictive, pharmacodynamic, or surrogate biomarker signatures. These assessments may be explored in the context of CD or related conditions and/or risankizumab or drugs of similar classes.

The samples may also be used to develop new diagnostic tests, therapies, research methods or technologies. In addition, samples from this study may be banked for future use. Samples may then be used to validate putative biomarker signatures obtained from a prospective study, leading to the development of diagnostic tests. The results from these analyses are exploratory in nature and may not be included with the study report.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

A subject may withdraw from the study at any time. The Investigator may discontinue any subject's participation for any reason, including an AE, safety concerns or failure to comply with the protocol.

Subjects will be withdrawn from the study immediately if any one of the following occurs:

- Clinically significant abnormal laboratory result(s) or AEs, which rule out continuation of the study drug, as determined by the Investigator in consultation with the AbbVie TA MD.
- The Investigator believes it is in the best interest of the subject, including subjects with no improvement to study drug at Week 12 for whom the investigator believes it is in the best interest of the subject not to enter Induction Period 2.

- Subjects who experience a severe systemic hypersensitivity infusion/injection reaction or anaphylaxis
- The subject requests withdrawal from the study.
- Inclusion and exclusion criteria violation was noted after the subject started study drug, when continuation of the study would place the subject at risk as determined by the AbbVie TA MD.
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk as determined by the AbbVie TA MD.
- The subject becomes pregnant while on study drug.
- Subject has a malignancy, except for localized non-melanoma skin cancer. Discontinuation for carcinoma in-situ of the cervix is at the discretion of the Investigator.
- Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation in the study, as determined by the Investigator, in consultation with the AbbVie TA MD.
- Occurrence of following hepatic test abnormalities considered by the Investigator to be related to study drug (retesting for ALT, AST, and TBL may be needed to confirm):
    - Confirmed ALT or AST > 8 × Upper Limit of Normal (ULN)
    - Confirmed ALT or AST > 5 × ULN for more than 2 weeks
    - Confirmed ALT or AST > 3 × ULN and (TBL > 2 × ULN or INR > 1.5)
    - Confirmed ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

If, during the course of study drug administration, the subject prematurely discontinues study drug use, the procedures outlined for the PD visit must be completed within 2 weeks of the last dose of study drug, and preferably prior to the initiation of another therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subject's

condition. Following discontinuation of the study drug, the subject will be treated in accordance with the Investigator's best clinical judgment.

A final visit will occur for all subjects, approximately 140 days after the last dose of study drug to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs, except for those who are rolled over to the Study M16-000.

All attempts must be made to determine the date of the last dose of study drug and the primary reason for premature discontinuation. The information will be recorded on the appropriate eCRF page.

For subjects who are considered lost to follow-up, reasonable attempts must be made to obtain information on the final status of the subject. At a minimum, two phone calls must be made and one certified letter must be sent and documented in the subject's source documentation.

Subjects who discontinue the study prematurely will not be replaced.

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The Investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the Investigator by telephone and subsequently provide written instructions for study termination.

5.5 Treatments

5.5.1 Treatments Administered

Each dose of blinded study drug (1200 mg risankizumab, 600 mg risankizumab, or placebo) will be administered intravenously to the subject during 12-Week Induction Period.

Each dose of blinded study drug (1200 mg risankizumab, 360 mg risankizumab, or 180 mg risankizumab) will be administered intravenously or subcutaneously in Induction Period 2.

If the 1200 mg dose is discontinued due to any reason, subjects will continue to enroll into the study and be randomized to either 600 mg risankizumab or placebo at 2:1 ratio. In this case, the randomization ratio and sample size may be further updated in an amendment to the protocol. In addition, for subjects already randomized and for future randomization, 600 mg will be administered during Induction Period 2.

Subjects should not be routinely pre-medicated prior to infusion of study drug. If in the Investigator's judgment the subject requires pre-medication based on prior medical history or symptoms with prior infusions of study drug in the current study, the AbbVie TA MD should be contacted regarding possible permitted pre-medication with diphenhydramine hydrochloride and acetaminophen (or equivalents). Individual dosage, timing, and route of administration would be determined by the Investigator. Any pre-medications administered must be recorded on the appropriate eCRF.

Subjects who do not achieve clinical response at Week 12 will be eligible for Induction Period 2 with blinded risankizumab. Blinded risankizumab will be administered either intravenously at Weeks 12, 16, and 20 or subcutaneously at Weeks 12 and 20.

5.5.2 Identity of Investigational Product

The individual study drug information is presented in Table 2.

Table 2. Identity of Investigational Product

Study Drug	Strength	Route of Administration	Manufacturer
Risankizumab (ABBV-066)	90 mg/mL	IV	Boehringer Ingelheim Pharma GmbH & Co. KG
Placebo for Risankizumab (ABBV-066)	N/A	IV	Boehringer-Ingelheim Pharma GmbH & Co. KG
Risankizumab (ABBV-066)	90 mg/mL	SC	Boehringer-Ingelheim Pharma GmbH & Co. KG
Placebo for Risankizumab (ABBV-066)	N/A	SC	Boehringer-Ingelheim Pharma GmbH & Co. KG

AbbVie will not provide 5% dextrose to be used as a diluent for administration for risankizumab or placebo and it should be sourced locally from approved marketed products from various commercial manufacturers depending on availability.

5.5.2.1 Packaging and Labeling

Risankizumab or placebo will be provided as one (1) vial per carton or one (1) prefilled syringe per carton to accommodate the study design.

Each kit label will contain a unique kit number. This kit number is assigned to a subject via IRT and encodes the appropriate study drug to be dispensed at the subjects corresponding study visit. Each kit will be labeled as required per country requirements. Labels must remain affixed to the kits. All blank spaces on the label will be completed by site staff prior to dispensing to the subjects.

5.5.2.2 Storage and Disposition of Study Drug

Study drug must be kept protected from light in the original packaging, in a refrigerator between 2° to 8°C (36° to 46°F). Study drug must not be frozen at any time.

The investigational products are for investigational use only and are to be used only within context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until

dispensed for subject use or destroyed as appropriate. A temperature log must be maintained for documentation.

The refrigerator temperature must be recorded each business day. Malfunctions or any temperature excursion must be reported to the Sponsor immediately. Sites are responsible to report temperature excursions into the AbbVie Temperature Excursion Management System (ATEMS). Study drug should be quarantined and not dispensed until AbbVie or ATEMS deems the drug as acceptable.

Upon receipt of the study drugs, the site will acknowledge receipt within the IRT system.

5.5.2.3 Preparation/Reconstitution of Dosage Form

Administration Instructions and Dose Preparation Instructions will be provided as separate documents outside of this protocol. Dose preparation will be performed by a licensed unblinded pharmacist or qualified designee, as appropriate.

5.5.3 Method of Assigning Subjects to Treatment Groups

All subjects will be assigned a unique identification number by the IRT at the Screening visit and will keep the same unique subject identification number throughout the study. Subjects who meet the inclusion and none of the exclusion criteria defined in Section 5.2.1 and Section 5.2.2 will be centrally randomized in a 2:2:1 ratio to one of the three treatment groups at Baseline during the 12-Week Induction Period of the study. The randomization will be stratified by number of prior biologics failed (0, 1, > 1), Baseline steroid use (yes, no), and Baseline SES-CD (original, alternative). The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule generated by the Statistics Department at AbbVie.

IRT will provide the appropriate medication kit number(s) to dispense to each subject. Study drug will be administered at the study visits as summarized in Section 5.5. Returned study drug should not be re-dispensed to any subject.

At Week 12, subjects who do not achieve clinical response will be eligible for Induction Period 2 where subjects receiving blinded IV risankizumab will be re-randomized 1:1:1 to receive blinded risankizumab in one of three groups and subjects who are receiving blinded placebo will receive blinded IV risankizumab as summarized in Section 5.5.

5.5.4 Selection and Timing of Dose for Each Subject

Subject will be administered study drug at the clinical site as outlined in Section 5.5.1.

5.5.5 Blinding

All AbbVie personnel with direct oversight of the conduct and management of the study (with the exception of AbbVie's Drug Supply Management Team and unblinded CRA/monitor (as applicable)), as well as the Investigator, the blinded study site personnel (with the exception of the unblinded site staff), and the subject will remain blinded to each subject's treatment throughout the study. The IRT will provide access to blinded subject treatment information in the case of medical emergency.

In the event of a medical emergency in which the Investigator believes that knowledge of study drug treatment is required, reasonable efforts must be made to contact the AbbVie TA MD (see Section 6.1.5) prior to breaking the blind, as long as it does not compromise subject safety. However, if an urgent therapeutic intervention is necessary which warrants breaking the blind prior to contacting AbbVie TA MD, the Investigator can directly access the IRT system to break the blind without AbbVie agreement. In the event that the blind is broken before notification to AbbVie TA MD, it is requested that the AbbVie TA MD be notified within 24 hours of the blind being broken. Also, the date and reason that the blind was broken must be recorded in the source documents and eCRF, as applicable.

5.5.5.1 Blinding of Investigational Product

In order to maintain the blind, it is necessary to have unblinded site staff (unblinded licensed pharmacist or qualified designee) to prepare the IV solutions and blind the doses. Study personnel who administer the infusions to the subjects must remain blinded.

The Administration Instructions and Dose Preparation Instructions are to be checked for the staff requirements for all activities concerning handling of study kits, including IRT transactions.

5.5.5.2 Data Monitoring Committee

An external independent DMC will review unblinded safety data on a cohort level, at a minimum of 6-month intervals throughout the course of the study launch.

A separate DMC charter will be prepared outside of the protocol and approved by AbbVie and the DMC members before a subject is initiated into the study. The DMC charter will describe the composition of the DMC, the roles and responsibilities of the DMC members, frequency and triggers of data reviews, relevant safety data to be assessed, meeting occasions, and communication with AbbVie as well as relevant competent authorities, if necessary. The DMC is responsible for monitoring safety data, alerting AbbVie to possible safety concerns related to the conduct of the study, and recommending appropriate actions for study conduct and management.

At the timing of this amendment, the DMC has provided recommendation that the study may continue without modification and allowed enrollment to begin for 16 - 17 year-olds. A patient information card with information of the symptoms and signs of hypersensitivity reactions, infusion related reactions as well as late stage reactions will be provided to the patients at Screening so that any such events once occurred will be reported immediately by the patients to the investigator.

The DMC will review safety data at a minimum of 6-month intervals throughout the course of the study. The DMC will determine if more frequent DMC meetings are required based on review of the accumulating safety data. In addition, ad-hoc DMC meetings will be scheduled in the event of any significant safety concerns. Based on these reviews, the DMC will make recommendations, as appropriate, regarding the conduct and management of the study.

The CAC and AAC adjudicate blinded data and the DMC reviews the data in an unblinded manner. Unblinded adjudicated cardio-cerebrovascular events and anaphylactic reactions will be presented to the DMC for review on a periodic basis.

Communications from the DMC to the Study Teams will not contain information that could potentially unblind the team to subject treatment assignments.

5.5.6 Treatment Compliance

The Investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

5.5.7 Drug Accountability

The Investigator or designee (blinded or unblinded as applicable) will verify that study drug supplies are received intact, at the appropriate temperature, and in the correct amounts from the depot. This will be accomplished by documenting the condition of the shipment, verifying the kit numbers in the package against the Proof of Receipt (POR) or similar document included with each drug shipment, and documenting this verification by signing and dating the POR or similar document and via direct reporting in IRT. The original POR note or similar document will be kept in the site files as a record of what was received.

In addition, IRT will be used to document investigational product accountability including date received, the lot number, kit number(s), date and number of vials and syringes dispensed and subject number. For this study, unless otherwise prohibited locally, these records will be maintained electronically as part of the IRT system.

An overall accountability of the study drug will be performed by the site and reconciliation will be performed by the CRA/monitor (blinded or unblinded according to the monitoring plan) throughout the study and at the site close-out visit. After verification

of drug accountability, used study drug must be destroyed at the site according to local regulations governing biohazardous waste. Destruction of used study supplies must be completed and documented in such a way that blinding is maintained for all blinded study personnel. All unused supplies must be inventoried, accounted for and destroyed on site according to local procedures or regulation or returned to a destruction facility. A copy of the, Return Consignment Form from IRT, in accordance with instructions provided by the monitor/CRA (blinded or unblinded according to the monitoring plan), will be included in the return shipments.

The use of a third party vendor for drug destruction must be pre-approved by AbbVie. For sites performing on-site drug destruction or using a third party vendor for drug destruction, a copy of the destruction methodology and date of destruction should be maintained at the site's facility.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

Risankizumab is a selective IL-23 inhibitor that may provide improved clinical benefit to risk profile in CD patients. The proposed study is a Phase 3, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of risankizumab compared to placebo in subjects with moderately to severely active CD, who have had inadequate response or intolerance to aminosalicylates, oral locally acting corticosteroids, oral and/or IV systemic corticosteroids, immunomodulators, and/or biologic therapies.

The study consists of a 12 week induction period to evaluate the efficacy and safety of two different IV risankizumab doses (IV, 600 mg or 1200 mg, Q4w) versus placebo. For subjects not in clinical response at Week 12, an optional blinded Induction Period 2 (IV, 1200 mg, Q4w; SC 360 mg, Q8w; SC 180 mg, Q8w) for an additional 12 weeks will be offered. Subjects with clinical response at the end of induction or Induction Period 2 can enter Study M16-000 for an additional 52 weeks of treatment, with additional OL treatment with risankizumab being offered through approval.

At this time, a 12-week placebo controlled study is necessary for registrational purposes. A comparative study utilizing placebo provides an unbiased assessment of the efficacy and safety profile of risankizumab. To ensure all subjects are given the opportunity to receive potentially efficacious therapy, all subjects not responding after 12 weeks can participate in the blinded Induction Period 2 with risankizumab.

5.6.2 Appropriateness of Measurements

Standard statistical, clinical, endoscopy-related and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in subjects with CD. All clinical and laboratory procedures in this study are standard and generally accepted. Central reading of endoscopy will increase study rigor and ensure enrollment of subjects with moderately to severely active CD.

5.6.3 Suitability of Subject Population

Adult male and female subjects, and 16 to 17 years old where locally permitted, with moderately to severely active CD who meet all of the inclusion criteria and none of the exclusion criteria are eligible for enrollment in this study. The specific population chosen was based on the unmet medical need of those subjects with a history of inadequate response or intolerance to immunomodulators (AZA, 6-MP, or MTX), corticosteroids, and/or biologic therapies.

5.6.4 Selection of Doses in the Study

AbbVie plans to evaluate two doses of risankizumab (600 mg and 1200 mg) via IV administration every 4 weeks (Q4w; Weeks 0, 4, 8) through induction (12-Week Induction Period) and an additional three doses of 1200 mg of risankizumab via IV administration (Q4w; Weeks 12, 16, 20) or two doses of 180 or 360 mg SC (Q8w, Weeks 12 and 20; Induction Period 2) for subjects who do not achieve clinical response at Week 12. The selection of the doses in this study is informed by the analysis of the safety and efficacy data, as well as the exposure-response relationship of efficacy, of a Phase 2

study in subjects with CD (Study 1311.6) and the pharmacokinetic data from the completed studies in subjects with psoriasis (Studies 1311.1 and 1311.2).

Results from the placebo controlled Study 1311.6 that evaluated 200 mg and 600 mg IV doses of risankizumab at Weeks 0, 4, 8 for induction suggests increasing trend of clinical response and remission (for both CDAI and PRO-2 based measures) at Week 12 with increasing risankizumab dose and exposure, indicating a potential for further improvement in proportion of subjects with response and remission with evaluation of higher doses. Preliminary model predictions suggest further incremental benefit in CDAI remission in subjects with CD at 1200 mg IV Q4w dose compared to 600 mg IV Q4w dose. The evaluation of higher dose data (1200 mg IV Q4w) will facilitate a more robust characterization of the dose-response and exposure-response relationship for these efficacy endpoints. Inclusion of 1200 mg IV dose in this study is further supported by the safety results from the 12 week blinded induction period in Study 1311.6. The safety profile of the 600 mg risankizumab group compared favorably with the placebo group and no overall safety concerns were identified which would preclude evaluation of IV induction doses higher than 600 mg risankizumab in patients with CD. Furthermore, the projected steady state exposures for the 1200 mg IV risankizumab Q4w regimen in subjects with CD are covered by safety margins of ~1.6 and ~3.6 for C_{max} and $AUC_{0\text{-}28\ days}$ respectively (relative to NOAEL identified in the 26 week GLP toxicology study).

Induction Period 2 will evaluate IV (1200 mg Q4w) or SC (180 mg or 360 mg Q8w) risankizumab. The purpose of Induction Period 2 is to evaluate the efficacy and safety of re-induction of risankizumab versus starting maintenance dosing on clinical response. Data from the Phase 2 study in subjects with CD suggested that re-induction with 600 mg IV increased both clinical response and clinical remission. The selection of the SC doses is informed by the analysis of the safety and efficacy data, as well as the exposure-response relationship of efficacy, of the maintenance period during the Phase 2 study in subjects with CD that evaluated 180 mg SC risankizumab for maintenance. The results from the Phase 2 study suggest a potential for increased benefit with 360 mg SC administration for maintenance regimen.

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

The investigational product in this study contains:

- Biologic compound(s)

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1 through 6.1.7. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The Investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The Investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the Investigator will provide an "Other" cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention and/or if the Investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

Supplemental study case report forms should be completed in the event of COVID-19 related missed/virtual visits, study drug interruptions or discontinuations, or adverse events (including capture of specific signs/symptoms of infection and testing results).

COVID-19 infections should be captured as adverse events. If the event meets the criteria for a serious adverse event (SAE), then follow the SAE reporting directions per the

protocol and above. The following COVID-19 related supplemental eCRFs should be completed:

- COVID-19 Supplemental Signs/Symptoms
- COVID-19 Status Form

If a subject has a confirmed or suspected COVID-19 infection and study drug was interrupted, the investigator should contact the sponsor emergency medical contact listed above before reintroducing study drug.

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) within 24 hours of the site being made aware of the serious adverse event.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the Investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate eCRF.

6.1.1.3 Areas of Safety Interest

Additional information may be collected for the following events.

Hepatic Events

In the case of any of the following AEs, the appropriate supplemental eCRFs should be completed:

- Discontinuation or interruption of study drug due to any hepatic related AE
- Any hepatic related SAE
- A subject experiencing an ALT/AST > 8 × ULN
- A subject experiencing an ALT/AST > 3 × ULN in conjunction with a total bilirubin > 2 × ULN.

Systemic Hypersensitivity/Anaphylactic Reactions

Therapeutic protein products, such as biologics, may elicit a range of acute effects, from symptomatic discomfort to sudden, fatal reactions that have often been grouped as 'infusion reactions' in the past. Although the term implies a certain temporal relationship, infusion reactions are otherwise not well defined and may encompass a wide range of clinical events, including anaphylaxis and other event that may not be directly related to antibody responses, such as cytokine release syndrome.

In the event of a suspected systemic hypersensitivity/anaphylactic reaction, in addition to the standard AE eCRF, a supplemental eCRF should also be completed by the site. The clinical criterion for diagnosing anaphylaxis is provided in Appendix I for reference; symptoms of anaphylactic reaction usually occur within 24 hours after exposure to an allergen. These are guidelines that are used to help diagnose anaphylaxis. The investigator is encouraged to report any suspected reactions.

All intravenous and subcutaneous doses of risankizumab will be administered by study-site personnel under the direction of the Investigator. Subjects will be monitored throughout the study for signs and symptoms suggestive of hypersensitivity reactions, including allergic reactions and anaphylaxis. A medical person qualified in the treatment of acute hypersensitivity reactions must be present during the infusions. All appropriate medical support measures (e.g., diphenhydramine, steroids, epinephrine, oxygen) for the treatment of suspected hypersensitivity reactions should be available for immediate use in the event that a suspected hypersensitivity reaction occurs. Subjects who manifest any new signs or symptoms during the infusion should be monitored for appropriate resolution prior to leaving the site. Subjects are encouraged to report any symptoms related to a possible infusion related reactions or local injection site reaction or late phase reactions to the site any time during the study. A patient information card listing the symptoms of these reactions will be provided to the participants.

Cardiac Events/Procedures

In the case of any of the following reported MACE, the appropriate supplemental eCRFs should be completed:

- Cardiac events;
- Myocardial infarction or unstable angina;
- Cerebral vascular accident and transient ischemic attack;
- Cardiovascular procedures

Tuberculosis (TB)

In the case of any positive TB test or diagnosis of active TB, the appropriate supplemental eCRFs should be completed.

6.1.2 Adverse Event Severity

When criteria are available, events should be graded as described in the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03,[20] which can be accessed at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

If no specific criteria are provided to grade the reported event, the event should be graded as follows:

Mild (Grade 1)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Moderate (Grade 2)	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
Severe (Grade 3)	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Severe (Grade 4)	Life-threatening consequences; urgent intervention indicated.

Severe (Grade 5)	Death related to AE

Use the following guidelines when entering the severity grading criteria into the electronic data capture (EDC) system.

Grade 1 as Mild; Grade 2 as Moderate; and Grade 3 to 5 as Severe.

6.1.3 Relationship to Study Drug

The Investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

Reasonable Possibility	After consideration of factors including timing of the event biologic plausibility, clinical judgment and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event biologic plausibility, clinical judgment and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the Investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

If an Investigator's opinion of no reasonable possibility of being related to study drug is given, an "Other" cause of event must be provided by the Investigator for the serious adverse event.

6.1.3.1 Lack of Efficacy or Worsening of Disease

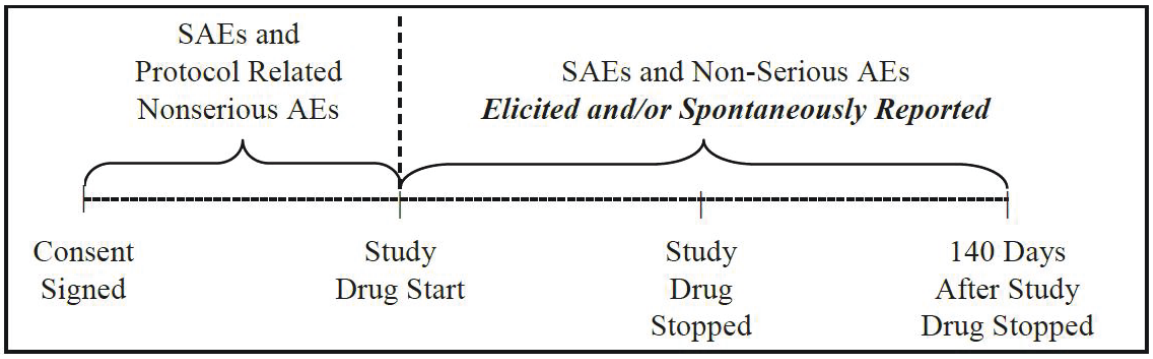
Events that are clearly consistent with progression of the underlying disease (CD) are considered an expected outcome for this study and will not be subject to expedited reporting.

6.1.4 Adverse Event Collection Period

All adverse events reported from the time of study drug administration until 140 days from the last dose of study drug have elapsed will be collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events and protocol-related nonserious adverse events will be collected from the time the subject signed the study-specific informed consent.

Adverse event information will be collected as shown in Figure 2.

Figure 2. Adverse Event Collection



6.1.5 Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the electronic data capture (EDC) system. Serious adverse events that occur prior to the site

having access to the RAVE® system, or if RAVE® is not operable, should be documented on the SAE Non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event.

Email: PPDINDPharmacovigilance@abbvie.com

FAX to: +1 (847) 938-0660

For safety concerns, contact the Immunology Safety Team at:

Immunology Safety Team
Dept. R48S, Bldg. AP31-2
1 North Waukegan Road
North Chicago, IL 60064

Safety Hotline: +1 847-938-8737
Email: GPRD_SafetyManagement_Immunology@abbvie.com

For any subject safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director:

[redacted]
100 Research Drive, Suite 3009
Worcester, MA 01605

Telephone Contact Information:
Office: [redacted]
Mobile:
Email:

In emergency situations involving study subjects when the primary AbbVie TA MD is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie TA MD:

Phone: +1 (973)-784-6402

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the investigational medicinal product (IMP) in accordance with global and local guidelines and Appendix A of the Investigator Brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a DSUR reporting period serves as the RSI during the reporting period. For follow up report, the RSI in place at the time of occurrence of the suspected Serious Adverse Reaction will be used to assess expectedness.

In Japan, the principal Investigator will provide documentation of all serious adverse events to the Director of the investigative site and the Sponsor.

6.1.5.1 Adverse Events Commonly Associated with CD in Study Population

Certain events are anticipated to occur in the study population as known consequences of CD (e.g., as symptoms or due to disease progression) independent of drug exposure. These events are listed in Table 3. These AEs, which should be captured on the appropriate eCRF, are considered expected for reporting purposes for this protocol. Although exempt from expedited reporting to certain Health Authorities and ECs/IRBs as individual cases, if any of these events meets seriousness criteria, it must be reported to AbbVie within 24 hours of the site being made aware of the SAE (as defined in Section 6.1.5).

Events commonly associated with CD population hence considered expected for reporting.

Table 3. Common Events Associated with CD

Fistulae	Abscesses	Stenoses/Obstruction
• Anal fistula • Colovaginal fistula • Colovesical fistula • Enterocolonic fistula • Enterocutaneous fistula • Enterovaginal fistula • Female genital-digestive tract fistula • Ileal fistula • Ileorectal fistula • Ileovaginal fistula • Perineal fistula • Rectal fistula • Rectovaginal fistula	• Anal abscess • Anorectal abscess • Rectal abscess **Others** • Anal fissure • Worsening of Crohn's disease • Intestinal perforation	1. Anal stenosis 2. Ileal stenosis 3. Intestinal obstruction 4. Small intestine obstruction

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 24 hours of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued from study drug (Section 5.4.1).

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected.

Pregnancy in a study subject is not considered an adverse event. The medical outcome for either mother or infant, meeting any serious criteria including an elective or spontaneous abortion, is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.1.7 Cardiac Adjudication Committee

The independent external CAC will be adjudicating observed cardio- and cerebro-vascular events and will remain blinded to treatment allocation. The events that are adjudicated

and the adjudication process will be detailed in the Cardiac Adjudication Committee Charter. Dedicated eCRFs will be used for events of myocardial infarction-unstable angina, stroke-transient ischemic attack, and death. In addition, the site may be contacted for additional source documentation for relevant events.

6.1.8 Anaphylaxis Adjudication Committee

The independent external AAC will be adjudicating observed potential anaphylactic events and will remain blinded to treatment allocation. The events that are adjudicated and the adjudication process will be detailed in the Anaphylaxis Adjudication Committee Charter. A supplemental eCRF will be used to collect information pertinent to the events. In addition, the site may be contacted for additional source documentation for relevant events.

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product.

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, or packaging issues.

Any information available to help in the determination of causality to the events outlined directly above should be captured.

6.2.2 Reporting

Product Complaints concerning the investigational product must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a

satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition. In instances where a return is requested, every effort should be made by the Investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects. The principal Investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic) after a subject has been enrolled, the principal Investigator is responsible for notifying IEC/IRB regulatory authorities (as applicable), and AbbVie.

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

In Japan, the Investigator will record all protocol deviations in the appropriate medical records at site.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

The objective of the statistical analyses is to evaluate the efficacy and safety of risankizumab versus placebo in subjects with moderately to severely active CD who had baseline eligibility SES-CD of ≥ 6 (≥ 4 for isolated ileal disease).

When all patients complete their Week 12/PD visit, the database will be locked and un-blinded for the 12-week induction period. The planned analysis for the 12-week induction period will be performed. This is the only and final analysis for co-primary endpoints of the 12-week induction period. When all the patients who enter the induction Period 2 finish Week 24/PD visit, the database will be locked for the whole study and all the planned analyses for the induction Period 2 will be performed.

Complete, specific details of the statistical analyses will be described and fully documented in the study Statistical Analysis Plan (SAP). The SAP will be finalized prior to the study database lock.

The impact of missing data due to COVID-19 will be monitored and appropriate modifications to the analysis of primary and key secondary endpoints for handling such missing data will be reflected and incorporated in the final SAP.

8.1.1 Datasets for Analysis

8.1.1.1 Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set includes all randomized subjects who received at least one dose of study drug. The primary population for efficacy analysis are the subjects in the intent-to-treat set who had baseline eligibility SES-CD of ≥ 6 (≥ 4 for isolated ileal disease). The ITT subjects will be analyzed as randomized.

8.1.1.2 Safety Analysis Set

The safety analysis set consists of all subjects who received at least one dose of the study drug. The safety set will be analyzed as treated, according to treatment the subject actually received. The safety set will be used for safety analysis.

8.1.2 Definition of Missing Data Imputation

Missing data will be imputed using one or more of the following methods:

Non-Responder Imputation (NRI): In NRI analyses, subjects who prematurely discontinue the study prior to efficacy assessment at Week 12 will be considered non-responders with respect to the efficacy endpoint.

Observed Cases (OC): The OC analysis will not impute values for missing evaluations, and thus a subject who does not have an evaluation on a scheduled visit will be excluded from the OC analysis for that visit.

8.1.3 Subject Disposition

The number and percentage of subjects who are enrolled, randomized and received at least one dose of study drug, and the number of subjects who prematurely discontinued and the reason for premature discontinuation will be summarized by treatment group. Premature discontinuation of study drug will be summarized for each treatment group, as well as for all subjects combined, with frequencies and percentages overall and by reason for discontinuation for all randomized subjects who received at least one dose of study drug. Subjects may have multiple reasons for prematurely discontinuing study drug, but will be counted no more than once for the total ("Any Reason").

8.1.4 Demographics and Baseline Characteristics

Demographics (where collection is allowed) and Baseline characteristics of the study subjects will be summarized using descriptive statistics. Summary statistics for continuous variables will include the number of observations, mean, standard deviation,

median, and range for each treatment group. For other categorical or discrete variables, frequencies and percentages will be computed in each category for each treatment group, as well as for all subjects combined.

8.1.5 Prior and Concomitant Medications

Prior therapy and medications will include all therapies and medications administered prior to the date of the first dose of study drug. Prior therapy and medication will be summarized for all randomized subjects. No statistical test will be performed.

Concomitant medications will be summarized for all randomized subjects. Concomitant medications will be summarized using the World Health Organization Drug Dictionary with frequencies and percentages for each treatment group. No statistical test will be performed.

8.1.6 Efficacy Analysis

8.1.6.1 Primary Efficacy Variables

The co-primary endpoints are the proportion of subjects who achieve clinical remission at Week 12 and proportion of subjects with endoscopic response at Week 12.

The comparisons between each risankizumab dose versus placebo for the primary efficacy variable will be performed using the Cochran-Mantel-Haenszel (CMH) test adjusted by number of prior biologics failed (0, 1, > 1) and steroid use at Baseline (yes, no). A multiple testing procedure will be used to provide strong control of the type 1 error rate at alpha = 0.05 (2-sided) across analyses comparing each risankizumab dose level to placebo with respect to the co-primary endpoints, and ranked secondary endpoints. Specifically, testing will utilize a sequence of hypothesis testing for the co-primary endpoints followed by the ranked secondary endpoints, and will begin with testing each of the co-primary endpoints using α of 0.025 (2-sided) for each dose compared to placebo. If both co-primary endpoints achieve statistical significance within a dose level, continued testing will follow a pre-specified weight of α allocation between the single hypothesis within the family, as well as between the families of hypotheses across the doses. Details will be

provided in the Statistical Analysis Plan. A CMH based two-sided 95% confidence interval for the difference between treatment groups will be calculated. If average daily SF or average daily AP score or endoscopic data at Week 12 are missing, the NRI approach will be applied. Subjects who discontinue prior to Week 12 for any reason will be considered as "not-achieved" for clinical remission and endoscopic response endpoints.

The analysis of co-primary efficacy endpoints will be performed in bio-IR and non-bio-IR population. Additional subgroup analyses will be outlined in the SAP. Sensitivity analyses for missing data handling using MI, PMM and OC will be performed for co-primary endpoints and details will be outlined in the SAP.

8.1.6.2 Secondary Efficacy Variables

The secondary efficacy variables are divided into two groups. The first group includes ranked secondary endpoints, which are ranked by clinical importance. Statistical significance is assessed at the pre-specified alpha level (two-sided) in ranked endpoint order until the significant level exceeds the pre-specified alpha level. No additional statistically significant treatment differences could be declared if the preceding ranked endpoint fails to achieve the pre-specified alpha level. The second group includes all other additional secondary variables. All analyses of secondary endpoints will be performed using the ITT analysis set.

In general, continuous secondary efficacy variables will be analyzed using a Mixed-Effect Model Repeated Measure (MMRM) model including factors for treatment group, visit, visit by treatment interaction, and stratification variables, for the longitudinal continuous endpoints. The MMRM analysis is considered primary for inferential purposes.

Categorical secondary efficacy variables will be analyzed using the CMH test controlling for stratification variables. Non-responder imputation for missing data will be used for categorical secondary endpoints.

Analysis of Pattern Mixture Model (PMM) will be performed as sensitivity analyses for ranked secondary endpoints.

8.1.7 Safety Analysis

Safety analyses will be carried out using the safety analysis sets, which includes all subjects who receive at least one dose of study drug. Incidence of AEs, including those related to study drug, changes in vital signs, physical examination results, and clinical laboratory values will be analyzed.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Treatment-emergent AEs are defined as AEs that began or worsened in severity after initiation of study drug and within 140 days after the last dose of the study drug. An overview of treatment-emergent AEs, including AEs leading to death and AEs leading to premature discontinuation (see details in the SAP), AEs by MedDRA preferred term and system organ class, AEs by maximum relationship to study drug, and AEs by maximum severity will be summarized by number and percentage.

Continuous laboratory and vital sign parameters will be summarized for each treatment group by visit. Treatment group differences between each of the risankizumab dosing groups and the placebo group for changes from Baseline may be analyzed using a one-way Analysis of Variance (ANOVA). Vital signs and laboratory data will be described by statistical characteristics and frequency of abnormal values. In addition, shift tables and listings will be provided for abnormal values, whereby the normal range of the analyzing laboratory will be used. Analysis details will be specified in the SAP.

8.1.8 Analysis of Optional Exploratory Variables

For exploratory biomarkers that are measured, including but not limited to pharmacogenetic, epigenetic, transcriptomic, proteomic, and metabolomic biomarkers, the association of biomarkers to the efficacy and safety endpoints may be explored for each biomarker one at a time, and also for combinations of biomarkers via some multivariate predictive modeling algorithms. Optimal multivariate combinations of biomarkers that associate with efficacy endpoints, subject response/non-response (with respect to appropriate clinical endpoints), and also with safety endpoints may be explored via a variety of statistical predictive modeling algorithms. Cut-points for individual biomarkers

and optimal combinations of biomarkers that differentiate the subject response with respect to efficacy/safety endpoints may be explored using the in-house developed subgroup identification algorithms: Sequential BATTing, PRIM, AIM BATTing, and AIM Rule. The significance of these multivariate combinations of biomarkers may be assessed via at least 20 iterations of 5-fold cross-validation.[21,22]

8.1.9 Analysis of Pharmacokinetic and Pharmacodynamic Variables

Serum risankizumab concentrations will be summarized at each time point for each dosing regimen using descriptive statistics. In addition, ADA incidence will be summarized by cohorts and study visits. ADA titers will be tabulated for each subject at the respective study visits. Data from this study may be combined with data from other studies for the population pharmacokinetic and exposure-response analyses and may not be part of the clinical study report. Population pharmacokinetic and exposure-response analyses of only data from this study may not be conducted. The following general methodology will be used for the population pharmacokinetic analysis.

Population pharmacokinetic analyses of risankizumab will be performed using the actual sampling time relative to dosing. Pharmacokinetic models will be build using a non-linear mixed-effects modeling approach with NONMEM software (Version 7, or a higher version). The structure of the starting pharmacokinetic model will be based on the pharmacokinetic analysis data from previous studies. Systemic Clearance and volume of distribution of risankizumab will be the pharmacokinetic parameters of major interest in the NONMEM analyses. If necessary, other parameters, including the parameters describing absorption characteristics, may be estimated if useful in the analysis.

The evaluation criteria described below will be used to examine the performance of different models:

1. The objective function of the best model is significantly smaller than the alternative model(s).

2. The observed and predicted concentrations from the preferred model are more randomly distributed across the line of unity (a straight line with zero intercept and a slope of one) than the alternative model(s).
3. Visual inspection of model fit, standard errors of model parameters, and change in inter-subject and intra-subject error.

Once an appropriate base pharmacokinetic model (including inter- and intra-subject error structure) is developed, empirical Bayesian estimates of individual model parameters will be calculated by the posterior conditional estimation technique using NONMEM. The relationship between these conditional estimates CL/F or Vss/F values with only potentially physiologically relevant or clinically meaningful covariates (such as ADA classification, subject age, sex, body weight, concomitant medications, possibly baseline inflammatory and disease markers) may be explored using stepwise forward selection method, or another suitable regression/smoothing method at a significance level of 0.01.

After identification of all relevant covariates, a stepwise backward elimination of covariates from the full model will be employed to evaluate the significance (at $P < 0.001$, corresponding to a decrease in objective function > 10.83 for one degree of freedom) of each covariate in the full model.

Linear or non-linear relationships of primary pharmacokinetic parameters with various covariates may also be explored.

Relationships between exposure and clinical observations (primary or secondary efficacy or safety variables of interest) may be explored. Additional analyses will be performed if useful and appropriate.

8.2 Determination of Sample Size

The co-primary endpoints are the proportion of subjects with clinical remission at Week 12 and proportion of subjects with endoscopic response at Week 12.

Sample size calculation is based on the larger sample size needed to detect treatment difference for each of the co-primary endpoints. Since historical data show slightly lower event rate and similar treatment difference versus placebo for the endoscopic response rate than the clinical remission rate at Week 12, clinical remission rates at Week 12 are used for power calculation. A total of approximately 855 subjects will be randomized into two risankizumab treatment groups and the placebo group in a 2:2:1 ratio (342 subjects for risankizumab 600 mg dose group, 342 subjects for risankizumab 1200 mg dose group, and 171 subjects for placebo group). Assuming the Week 12 clinical remission rate will be 27.8% for one of the risankizumab dose groups and 12% for the placebo group, a sample size of 342 subjects for each of the risankizumab dose groups and 171 for the placebo group will have 97% power to detect the treatment difference between the risankizumab dose groups and placebo in clinical remission rates at Week 12 using Fisher's exact test at alpha of 0.025 (two-sided). Assuming the Week 12 endoscopic response rate will be 25.5% for one of the risankizumab dose groups and 8% for the placebo group, this sample size will have 99% power to detect the treatment difference between the risankizumab dose groups and placebo in endoscopic response rates at Week 12 using a Fisher's exact test at alpha of 0.025 (two-sided).

In addition, with sample size of approximately 540 bio-IR subjects, this study will have approximately 80% power for the bio-IR population to detect the treatment difference between one of the risankizumab dose groups and placebo in clinical remission rates at Week 12 using Fisher's exact test at alpha of 0.025 (two-sided) for the bio-IR population, assuming the Week 12 clinical remission rate will be 24.2% for the risankizumab dose groups and 10% for the placebo group. Similarly, with sample size of approximately 315 non-bio-IR subjects, this study will have 72% power to detect the treatment difference between one of the risankizumab dose groups and placebo in clinical remission rates at Week 12 using Fisher's exact test at alpha of 0.025 (two-sided) for the non-bio-IR population, assuming the Week 12 clinical remission rate will be 35% for the risankizumab dose groups and 15% for the placebo group for non-bio-IR subjects.

8.3 Randomization Methods

A total of approximately 855 subjects will be randomized into two risankizumab dose groups and the placebo group in a 2:2:1 ratio (342 subjects for risankizumab 600 mg dose group, 342 subjects for risankizumab 1200 mg dose group, and 171 subjects for placebo group). Randomization will be stratified by number of prior biologics failed (0, 1, > 1), the steroid use at Baseline (yes, no), and Baseline SES-CD (original, alternative), where the stratum of "original" includes the patients with baseline SES-CD of ≥ 6 (or ≥ 4 for subjects with isolated ileal disease), and the stratum of "alternative" includes the patients with baseline SES-CD of ≥ 3 to < 6 for ileocolonic or colonic disease or SES-CD of 3 for isolated ileal disease.

Subjects with clinical non-response to risankizumab at Week 12 will be re-randomized in a 1:1:1 ratio to 1200 mg IV dose group, 360 mg SC dose group, or 180 mg SC dose group. Subjects with clinical non-response to placebo at Week 12 will blindly receive 1200 mg risankizumab IV dose.

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Following local regulation, substantial amendments may also be reviewed and approved by the national competent authority.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The Investigator will be required to submit, maintain and archive study essential documents according to International Conference on Harmonization (ICH) GCP and all other applicable regulatory requirements.

Any SAEs that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the Investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical Investigator are specified in Appendix A.

In the event of a state of emergency due to the COVID-19 pandemic leading to difficulties in performing protocol-specified procedures, AbbVie will engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local lab instead of a central lab). In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

9.3 Subject Information and Consent

For adult subjects the Investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

The optional samples for intensive PK analyses will only be collected if the subject has voluntarily signed and dated the intensive PK section of the main ICF, approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions.

Samples for exploratory research/validation studies will only be collected if the subject has voluntarily signed and dated the separate written consent for exploratory research/validation studies, approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The separate written consent must be signed before the exploratory research/validation studies samples are collected and testing is performed. If the subject does not consent to the exploratory research/validation studies, it will not impact the subject's participation in the study.

For adolescent subjects, the investigator or his/her representative will explain the nature of the study to the subject and the subject's parent/legal guardian, and answer all questions regarding this study. Adolescent subjects will be included in all discussions in order to

obtain verbal or written assent. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject's parent/legal guardian, the person who administered the informed consent, and any other signatories according to local requirements. Additionally, in keeping with each institution's IRB/IEC requirements, an informed assent form may also be obtained by each subject prior to any study-related procedures being performed. If a subject becomes of legal age during the course of the study, that subject will need to be re-consented. A copy of the informed consent form and the assent form will be given to the subject and the subject's parent/legal guardian and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Genetic and non-genetic biomarker analysis will only be performed if the subject's parent/legal guardian has voluntarily signed and dated a separate genetic and non-genetic biomarker informed consent, approved by an IRB/IEC, after the nature of the testing has been explained and the subject and subject's parent/legal guardian has had an opportunity to ask questions. The separate genetic and non-genetic biomarker informed consent must be signed before the genetic and non-genetic biomarker testing is performed. If the subject's parent/legal guardian does not consent to the genetic and non-genetic biomarker testing, it will not impact the subject's participation in the study.

In the event a subject withdraws from the main study, optional exploratory research samples will continue to be stored and analyzed unless the subject specifically withdraws consent for the optional samples. If consent is withdrawn for the optional sampling, the subject must inform their study doctor, and once AbbVie is informed, the optional samples will be destroyed. However, if the subject withdraws his/her consent and the samples have already been tested, those results will still remain as part of the overall research data.

9.3.1 Informed Consent Form and Explanatory Material

In Japan, the principal Investigator will prepare the consent form and explanatory material required to obtain subject's consent to participate in the study with the cooperation of the sponsor and will revise these documents as required. The prepared or revised consent forms and explanatory material will be submitted to the sponsor. Approval of the IRB will be obtained prior to use in the study.

9.3.2 Revision of the Consent Form and Explanatory Material

In Japan, when important new information related to the subject's consent becomes available, the principal Investigator will revise the consent form and explanatory material based on the information without delay and will obtain the approval of the IRB prior to use in the study. The Investigator will provide the information, without delay, to each subject already participating in the study, and will confirm the intention of each subject to continue the study or not. The Investigator shall also provide a further explanation using the revised form and explanatory material and shall obtain written consent from each subject of their own free will to continue participating in the study.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, ECGs, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. IRT may also be the source for drug accountability. Data collected during this study must be recorded on the appropriate source documents. The Investigator Awareness Date (SAE eCRF) may serve as the source for this data point. This AE data point required for eCRF completion can be entered directly in the eCRF.

The Investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

During the COVID-19 pandemic, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10.2 Case Report Forms

Electronic case report forms (eCRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The eCRF data for this study are being collected with an EDC system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific eCRFs will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The Investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

The Investigator or an authorized member of the Investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The principal Investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the study through a password-protected method of internet access. Such access will be removed from Investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the Investigator at that time as a durable record of the site's eCRF data. It will be possible for the Investigator to make paper printouts from that media.

10.3 Electronic Patient Reported Outcomes (ePRO)

Patient reported data must be completed for each subject screened/enrolled in this study. Some of these data are being collected with an ePRO system called Trialmax, provided by the technology vendor CRF Health of Plymouth Meeting, PA, USA. The ePRO system is in compliance with Title 21 CFR Part 11. The documentation related to the system validation of the ePRO system is available through the vendor, CRF Health, while the user acceptance testing of the study specific PRO design will be conducted and maintained at AbbVie.

The subject will be entering the data on an electronic device; these data will be uploaded to a server. The data on the server will be considered source, and maintained and managed by CRF Health.

Internet access to the ePRO data will be provided by CRF Health for the duration of the study. This access will be available for the duration of the study to the site Investigator, as well as delegated personnel. Such access will be removed from Investigator sites following the receipt of the study archive. Data from the ePRO system will be archived on appropriate data media (CD-ROM, etc.) and provided to the Investigator at that time as a durable record of the site's ePRO data. It will be possible for the Investigator to make paper print-outs from that media.

The ePRO data will be collected by the following methods:

Diary Based

The ePRO data (number of liquid or very soft stools, use of medications used for endoscopy preparation, abdominal pain, and general well-being) will be collected electronically via a handheld device into which the subject will record the required pieces of information on a daily basis. The electronic device will be programmed to allow data entry once per day. All data entered on the device will be immediately stored to the device itself and manually/automatically uploaded to a central server administrated by CRF Health. The investigational site staff will be able to access all uploaded subject entered data via a password protected website, up until the generation, receipt and confirmation of the study archive.

Tablet Based

The PROs listed below will be collected electronically via a Tablet device into which the subject will directly enter the required pieces of information while at the site. The electronic device will be programmed to allow data entry for only the visits specified in the protocol and will not allow for subjects to complete more than one of the same assessment at any one visit. All data entered on the device will be immediately stored to the device itself and (manually/automatically) uploaded to a central server administrated by CRF Health. The investigational site staff will be able to access all uploaded subject entered data via a password protected website, up until the generation, receipt and confirmation of the study archive.

- CSS
- PGIC
- PGIS
- EQ-5D-5L
- FACIT-F
- IBDQ
- SF-36
- WPAI-CD

11.0 Data Quality Assurance

To ensure data integrity and subject safety, a study monitor will, throughout the study, verify that all subjects signed agreement of informed consent prior to any study-specific procedures being conducted. The study monitor will confirm that the Investigator is conducting the study in compliance with the protocol, GCP and applicable regulations, and verify that the information reported in the eCRF is complete, accurate, and supported by information in source documents.

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

12.0 Use of Information

All information concerning risankizumab and AbbVie operations, such as AbbVie patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of risankizumab. This information may be disclosed as deemed necessary by AbbVie to other clinical Investigators, other pharmaceutical companies, to the Food and Drug Administration (FDA) and to other governmental agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the Investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to source data/documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection.

This confidential information shall remain the sole property of AbbVie, shall not be disclosed to others without the written consent of AbbVie, and shall not be used except in the performance of this study.

If this protocol or the information gained from the conduct of this study will be made public (disclosed/published), AbbVie will determine the information that is not yet in the public domain and if the disclosure of such information may undermine AbbVie's interests, will remain confidential at the time of disclosure/publication.

The Investigator will maintain a confidential subject identification code list of all subjects enrolled in the study (by name and subject number). This list will be maintained at the site and will not be retrieved by AbbVie.

Any exploratory research/validation studies that may be done using the samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management, hence, neither the Investigator, the subject, nor the subject's physician (if different from the Investigator) will be informed of individual subject results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate data from exploratory research/validation studies from this study may be used in scientific publications or presented at medical conventions. Exploratory research/validation studies data will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

The Investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the Investigator (Director of the Site in Japan) and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the Investigator (Director of the Site in Japan) and AbbVie. The Investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The Investigator (Director of the Site in Japan) must submit, maintain, and archive any records related to the study according to ICH GCP and all other applicable regulatory requirements. If the Investigator (Director of the Site in Japan) is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory Investigator from the Investigators who participate in the study. Selection criteria for this Investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory Investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last visit.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for risankizumab.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study of the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Crohn's Disease
Protocol Date:	28 July 2020

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

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Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the Investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee/competent authority reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	[redacted]	Clinical Development, Immunology
		Clinical Development, Immunology
		Statistics
		Statistics
		Clinical Pharmacology and Pharmacometrics
		Bioanalysis
		Clinical Operations

Appendix C. Study Activities for Efficacy, Safety, and PK/PD

Activity	Screening Period (35 Days)[a]	12-Week Double-Blind Induction				Induction Period 2			Unsch[b]	140-Day Follow-Up[c]
	Screening	Baseline	Week 4	Week 8	Week 12/PD	Week 16	Week 20	Week 24		
Informed consent	X									
Inclusion/Exclusion	X	X[d]								
Medical/Surgery History	X	X[d]								
Previous and Concomitant Medication	X	X[d]	X	X	X	X	X	X	X	
Physical Exam[e]/Vital Signs[f]	X	X	X	X	X	X	X	X	X	
Adverse Event Assessment[g]	X	X	X	X	X	X	X	X	X	X
TB Screening[h]	X[y]									
ECG[i]	X[y]									
Hepatitis B, Hepatitis C Screening[j], and HIV Test[l]	X[y]				X[k]			X[k]		
C. difficile toxin	X[x]									
Urinalysis[m,n]	X[x]	X[o]			X			X		
Pregnancy Test[p]	X[x]	X	X	X	X	X	X	X		
Chemistry and Hematology[n]	X[x]	X[o]	X	X	X	X	X	X		
Optional Blood Sample for Biologic Drug Level	X									
COVID-19 Assessment[z]	X									
hs-CRP[n]		X	X	X	X			X		
Serum Risankizumab[q]			X	X	X			X	X	

Activity	Screening Period (35 Days)[a]	12-Week Double-Blind Induction				Induction Period 2			Unsch[b]	140-Day Follow-Up[c]
	Screening	Baseline	Week 4	Week 8	Week 12/PD	Week 16	Week 20	Week 24		
Serum Anti-Drug Antibody (ADA)[q,w] and Neutralizing Anti-Drug Antibodies (nAb)[q]		X	X	X	X			X	X	
Fecal calprotectin (FCP)[n, r]		X	X		X			X		
Crohn's Disease Activity Index (CDAI)		X[t]	X	X	X	X	X	X	X	
Endoscopy/SES-CD[u]	X				X			X		
Intestinal Biopsies[v]	X				X			X		
Dispense Subject Diary[s]	X									
Subject Diary Review		X	X	X	X	X	X	X	X	
Subject Questionnaire: CSS		X	X	X	X	X	X	X	X	
Subject Questionnaire: PGIC and PGIS		X (PGIS only)	X	X	X	X	X	X	X	
Subject Questionnaires: EQ-5D-5L FACIT-F IBDQ SF-36 WPAI-CD		X	X		X			X		
Study Drug Administration[w]		X	X	X	X[w]	X	X			

a. The Screening period should be a minimum of 4 days, preferably 7 days for CDAI calculation, (refer to Section 5.3.1.1). The Baseline CDAI will be calculated using the data collected during the Screening period. Baseline visit date will serve as the reference for all subsequent visits. A ± 7 day window is permitted around all study visits.

b. Visits to retest a lab will not be considered an Unscheduled visit. Unscheduled visits according to this table are for purposes when the subject is coming in a visit for evaluation and assessment.

c. Subjects will be contacted 140 days following last dose of study drug for an assessment of any new or ongoing AEs, except those subjects who roll-over into Study M16-000 after the end of study participation.

d. Update inclusion/exclusion, prior and concomitant therapy, and medical/surgical history information to assure subject eligibility.

e. Physical examinations are full physical examinations at Screening and Week 12 and Week 24 if the subject receives treatment in Induction Period 2. Physical examinations at all other visits (including unscheduled visits) are symptom based and should include the assessment of EIMs and a count of the number of cutaneous fistulas as part of calculating the CDAI.

f. Blood pressure, pulse rate, temperature, respiratory rate and weight should be performed before blood draws are performed. Height will be measured at Screening only (with shoes off and then adding 1 inch or 2.5 cm) for subjects ≥ 18 years of age. Height will be re-measured at Week 12 and Week 24 (if applicable) for subjects < 18 years of age at Baseline.

g. Collection of SAEs and protocol-related nonserious AEs begins the day the subject signs the informed consent.

h. Subjects with negative QuantiFERON-TB Gold test and/or PPD test within 90 days of Screening will not require a repeat test (documentation must be available). PPD skin test is to be read 48 to 72 hours after placement. In case of positive PPD/positive or repeat indeterminate IGRA testing, subjects may participate in the study if further work up (according to local practice/guidelines) is negative for active TB.

i. For subjects with a normal ECG taken within 90 days of Screening, a repeat ECG at Screening will not be required, provided source documentation is available. Subjects can have a repeat ECG at any time during the study as warranted based on the opinion of the Investigator.

j. Subjects will be tested for the presence of the HBV and HCV at Screening. A positive result for the hepatitis B surface antigen (HBs Ag) or hepatitis C (HCV RNA detectable in any subject with anti-HCV Ab) will be exclusionary. For subjects who are negative for HBs Ag but are positive for core antibodies (HBc Ab), HBV DNA PCR will be performed and any result that meets or exceeds detection sensitivity will be exclusionary.

k. For Japan only: for subjects with HBs Ab (+) and/or HBc Ab (+) at Screening, the HBV-DNA PCR test should be performed again at Week 12 and Week 24. Retesting at Week 12 and Week 24 is not necessary with subjects that have a history of HBV vaccine and are HBs Ab (+).

l. HIV testing will be performed at the central laboratory, which will report the results directly to the sites. AbbVie will not receive results from the testing.

m. Dipstick urinalysis will be completed by the sites at required visits. A microscopic analysis will be performed by the central laboratory, in the event the dipstick results show leukocytes, nitrite, protein, ketones or blood greater than negative or glucose greater than normal.

n. Urinalysis, chemistry and hematology, hs-CRP, and FCP may be collected at other scheduled and unscheduled visits than indicated in the table if they are warranted by the Investigator.

o. Lab assessments will only need to be repeated at Baseline if the time between Screening and Baseline is greater than 14 days, or if the subject's health status has changed to warrant a repeat test.

p. Serum pregnancy test will be performed on all WOCBP at Screening. Urine pregnancy test will be performed locally as indicated in the table for all WOCBP. The urine pregnancy test must be negative to receive study drug. If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory. FSH will be performed in all female subjects < 55 years old with no menses for 12 months.

q. Serum risankizumab concentrations and ADA will be determined from samples collected just prior to dosing at every visit. The date and time of sample collection will be captured on the eCRF. If the subject consented to the optional intensive PK sampling, refer to Appendix H.

r. Stool sample will be collected at each time point indicated in the table. For the visit when endoscopy will be conducted, stool sample should be collected prior to bowel prep and should be returned to the site per the instructions provided outside of this protocol. If a sample cannot be obtained during the site visit, the site will give instructions and a stool sample supply kit.

s. Subjects should also be dispensed the patient information card.

t. Diary information collected during Screening will serve to calculate Baseline CDAI. During screening, subjects will be instructed on how to calculate the number of very soft and liquid stools, including a visual depiction. CDAI should be completed at the Baseline visit, just prior to randomization.

u. Endoscopy at/during the screening period or within 45 days of the Baseline visit will be used to calculate the SES-CD score at Baseline. Endoscopic evaluations using SES CD confirmed by central reader will be done at Screening. Endoscopies completed at Week 12 and Week 24, for those subjects who receive treatment in Induction Period 2, will use the local reader results for stratification for Study M16-000.

v. Biopsies may be done when performing the endoscopy to confirm CD diagnosis (if appropriate documentation for confirmation of the diagnosis does not exist), and/or to rule out dysplasia and colon cancer at the Investigator's discretion. These samples will be processed and assessed locally. Histology report should be available in the subject's source records.

w. Administration of drug will be performed after all assessments and examinations scheduled for that day have been completed, including endoscopy. Completion of PROs are permitted during administration of study drug. At Week 12, study drug will only be administered for subjects who are to receive treatment in Induction Period 2. Subjects will also be dispensed a patient information card. In the event of a suspected systemic post-dose hypersensitivity reaction, serum risankizumab, ADA, and nAb should be collected once within 24 hours of the reaction. In addition, tryptase sample should be obtained between 15 minutes to 3 hours of symptom onset, and no later than 6 hours, and another sample is requested a minimum of 2 weeks after the recorded event or at the next study visit. Also, plasma histamine sample should be obtained within 5 to 15 minutes of the onset of symptoms and no later than 1 hour.

x. For Rescreening, if a subject is being rescreened within 14 days (≤ 14 days have passed) from the collection date of the previous screening testing, it is not required to repeat Screening testing for chemistry/hematology, urinalysis, serum pregnancy, and C. *difficile* provided that the subject's health status has not changed to warrant a repeat test.

y. For Rescreening, if the subject had a complete initial screening evaluation including the TB test, hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and electrocardiogram (ECG), these tests will not be required to be repeated for re-screening provided the conditions noted in Section 5.3.1.1 are met and no more than 90 days have passed since the collection date of the testing.

z. Assessment for signs/symptoms of COVID-19 infection. If the investigator suspects the possibility of COVID-19 based on the signs, symptoms and medical complaint (chief complaint, history of exposure, etc.), local laboratory testing must be completed to confirm negative for infection.

Appendix D. Study Activities – Optional Exploratory Research Samples

Samples Collected[a,b]	Screening Period (35 Days)	12-Week Double-Blind Induction	
	Screening	Baseline	Week 12/PD
Pharmacogenetic		X	
Transcriptomic and epigenetic[c]		X	X
Proteomic and targeted protein investigations (plasma)[c]		X	X
Proteomic and targeted protein investigations (serum)[c]		X	X
Stool		X	X
Intestinal biopsies (RNA)[d]	X		X

a. Collections to be performed only if subject provides separate written consent to collect the exploratory research/validation studies samples; if the separate consent is not signed, no samples can be collected.

b. Based on the value of different technologies, samples may also be used to assess other biomarker signatures, including but not limited to metabolomics, lipidomics, and other approaches.

c. It is preferred that the subject has fasted (8 hours, except for water) prior to sample collection, however it is not required. It must be recorded whether the subject has fasted or not at the time of collection.

d. Biopsy may be done when performing the endoscopy.

Appendix E. Sample SES-CD Scoring

SES-CD Scoring[23]

	Rectum	Sigmoid and Left Colon	Transverse Colon	Right Colon	Ileum	Total
Size of Ulcers Enter: 0 if none 1 if aphthous ulcers (Ø 0.1 to 0.5 cm) 2 if large ulcers (Ø 0.5 to 2 cm) 3 if very large ulcers (Ø > 2 cm)						
Ulcerated Surface Enter: 0 if none 1 if < 10% 2 if 10% – 30% 3 if > 30%						
Affected Surface Enter: 0 if unaffected segments 1 if < 50% 2 if 50% – 75% 3 if > 75%						
Presence of Narrowing Enter: 0 if none 1 if single, can be passed 2 if multiple, can be passed 3 if cannot be passed						
					TOTAL =	

Appendix F. Crohn's Disease Activity Index (CDAI)

			Factor	Subtotal
1. Number of liquid or very soft stools (Record the frequency per day)	__+__+__+__+__+__+__+__=__ Days: 1 2 3 4 5 6 7 Sum	×	2	
2. Abdominal pain rating: 0 = none, 1 = mild, 2 = moderate, 3 = severe	__+__+__+__+__+__+__+__=__ Days: 1 2 3 4 5 6 7 Sum	×	5	
3. General well-being: 0 = generally well, 1 = slightly underpar, 2 = poor, 3 = very poor, 4 = terrible	__+__+__+__+__+__+__+__=__ Days: 1 2 3 4 5 6 7 Sum	×	7	
4. Number of 6 listed categories the subject now has **Check all items that apply:** ☐ Arthritis/arthralgia ☐ Iritis/uveitis ☐ Erythema nodosum/pyoderma gangrenosum/aphthous stomatitis ☐ Fissure, abscess and/or anal fistula (draining/non-draining) ☐ Other cutaneous fistula (draining/non-draining) Fistula ☐ Fever over 100°F (37.8°C) during past week	_____ _____ Record "0" if no categories checked	×	20	
5. Taking Lomotil/Imodium/ Loperamide/opiates for diarrhea 0 = no, 1 = yes	_____	×	30	
6. Abdominal mass 0 = none, 2 = questionable, 5 = defined	_____	×	10	
7. Hematocrit: ___.__	Male: (47 – hematocrit) = Female: (42 – hematocrit) = Subtotal If hematocrit > normal, enter "0"	×	6	
8. Body weight: ___.__(kg) Standard weight: ___.__(kg)	100 × [1 – (Body wt/Standard wt)] = Percent below standard weight: _____ If body wt > std. wt, enter "0"	×	1	
			Total	

NOTE: During Screening subjects will be instructed on how to calculate the number of very soft and liquid stools, including a visual depiction.

Appendix G. Standard Weights

Standard Height and Weight Tables – Use to Calculate CDAI Score		
Standard Height cm (Inches)	**Standard Weight (Men) kg (Pounds)**	**Standard Weight (Women) kg (Pounds)**
121.9 (48.0)		40.8 (89.9)
123.2 (48.5)		41.3 (91.0)
124.5 (49.0)		41.8 (92.1)
125.7 (49.5)		42.3 (93.3)
127.0 (50.0)		42.8 (94.4)
128.3 (50.5)		43.4 (95.6)
129.5 (51.0)		43.9 (96.8)
130.8 (51.5)		44.4 (98.0)
132.1 (52.0)	55.5 (122.4)	45.0 (99.2)
133.4 (52.5)	55.7 (122.7)	45.5 (100.4)
134.6 (53.0)	55.8 (123.1)	46.1 (101.6)
135.9 (53.5)	56.0 (123.5)	46.6 (102.8)
137.2 (54.0)	56.2 (123.9)	47.2 (104.1)
138.4 (54.5)	56.4 (124.4)	47.8 (105.3)
139.7 (55.0)	56.7 (124.9)	48.3 (106.6)
141.0 (55.5)	56.9 (125.5)	48.9 (107.9)
142.2 (56.0)	57.2 (126.1)	49.5 (109.1)
143.5 (56.5)	57.4 (126.7)	50.1 (110.4)
144.8 (57.0)	57.7 (127.3)	50.7 (111.7)
146.1 (57.5)	58.1 (128.0)	51.3 (113.0)
147.3 (58.0)	58.4 (128.7)	52.2 (115.0)
148.6 (58.5)	58.7 (129.5)	52.6 (116.0)
149.9 (59.0)	59.1 (130.3)	53.1 (117.0)
151.1 (59.5)	59.5 (131.1)	53.6 (118.3)
152.4 (60.0)	59.9 (132.0)	54.2 (119.5)
153.7 (60.5)	60.3 (132.9)	54.8 (120.8)
154.9 (61.0)	60.7 (133.8)	55.3 (122.0)
156.2 (61.5)	61.1 (134.8)	56.0 (123.5)
157.5 (62.0)	61.7 (136.0)	56.7 (125.0)

Standard Height and Weight Tables – Use to Calculate CDAI Score		
Standard Height cm (Inches)	**Standard Weight (Men) kg (Pounds)**	**Standard Weight (Women) kg (Pounds)**
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)	71.2 (156.9
185.4 (73.0)	75.7 (167.0)	71.9 (158.5)
186.7 (73.5)	76.6 (169.0)	72.6 (160.2)
188.0 (74.0)	77.5 (171.0)	73.4 (161.8)
189.2 (74.5)	78.4 (172.8)	74.1 (163.4)
190.5 (75.0)	79.1 (174.5)	74.9 (165.1)
191.8 (75.5)	80.2 (176.8)	75.6 (166.8)
193.0 (76.0)	81.2 (179.0)	76.4 (168.4)
194.3 (76.5)	82.0 (180.8)	77.2 (170.1)
195.6 (77.0)	82.9 (182.9)	77.9 (171.8)
196.9 (77.5)	83.9 (185.0)	78.7 (173.5)

Standard Height and Weight Tables – Use to Calculate CDAI Score		
Standard Height cm (Inches)	**Standard Weight (Men) kg (Pounds)**	**Standard Weight (Women) kg (Pounds)**
198.1 (78.0)	84.9 (187.2)	79.5 (175.2)
199.4 (78.5)	85.9 (189.4)	80.3 (177.0)
200.7 (79.0)	86.9 (191.6)	81.0 (178.7)
201.9 (79.5)	87.9 (193.9)	81.8 (180.5)
203.2 (80.0)	89.0 (196.2)	82.6 (182.2)
204.5 (80.5)	90.0 (198.6)	*Standard height is calculated using actual height obtained at screening (without shoes) plus one inch
205.7 (81.0)	91.1 (200.9)	*Indoor clothing weighing 5 pounds for men and 3 pounds for women
207.0 (81.5)	92.2 (203.3)	*Centimeters × 0.3937 = inches
208.3 (82.0)	93.3 (205.8)	*Pounds × 0.4535 = kilograms

Appendix H. Optional Intensive PK Subjects

Samples for pharmacokinetics (PK) analysis will be collected in all subjects as described in Appendix C (Prior to dose at the specified weeks). For the subjects who consent to the optional intensive PK sampling, in addition to the time points in Appendix C, blood samples for PK evaluation will be collected per the schedule shown below. All other study procedures should be conducted as outlined in Section 5.0.

- Week 8: immediately after completion of infusion and 2 hours post completion of infusion
- Weeks 9, 10, 11: a visit window of ± 3 days would be applicable for these visits

PK samples should be processed according to the guidelines in Section 5.3.2.2 and Section 5.3.2.3. Subjects will follow all other protocol-specified procedures (as outlined in Appendix C)

NOTE: The date and time of site-administered dose and blood sample collection will be recorded to the nearest minute in the source documents and will be recorded to the nearest minute on the eCRF.

Appendix I. Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis[24] is highly likely when any one of the following 3 criteria are fulfilled:

1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING

   a) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

   b) Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

   a) Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips tongue-uvula)

   b) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

   c) Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)

   d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3) Reduced BP after exposure to known allergen for that patient (minutes to several hours):

   a) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*

b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline.

PEF: peak expiratory flow; BP: blood pressure

* low systolic BP for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mg Hg from 11 to 17 years.

Serious Systemic Hypersensitivity Reaction: A hypersensitivity reaction is a clinical sign or symptom, or constellation of signs or symptoms, caused by an inappropriate and excessive immunologic reaction to study drug administration. A systemic hypersensitivity reaction is a hypersensitivity reaction that does not occur at the local site of study drug administration (e.g., not an injection site reaction). A serious systemic hypersensitivity reaction is a systemic hypersensitivity reaction that fulfills criteria for a serious adverse event as specified in Section 6.1.1.2.

In the event of an anaphylactic reaction, blood samples will be drawn per Appendix C after the onset of the reaction. This will include: histamine and tryptase. A blood sample for ADA assessment will also be collected along with 1 hour blood samples for above assessments. Separate instructions for the collection, handling, storage and shipping of these labs will be provided outside of the study protocol.

Appendix J. Tanner Stage 5 for Development

Tanner Stage 5 for Development[25,26]

Puberty and the Tanner Stages – developed by Professor James M Tanner

Introduction

Adolescents experience several types of maturation, including cognitive (the development of formal operational thought), psychosocial (the stages of adolescence), and biologic. The complex series of biologic transitions are known as puberty, and these changes may impact psychosocial factors.

The most visible changes during puberty are growth in stature and development of secondary sexual characteristics.

Equally profound are changes in body composition; the achievement of fertility; and changes in most body systems, such as the neuroendocrine axis, bone size, and mineralization; and the cardiovascular system. As an example, normal cardiovascular changes, including greater aerobic power reserve, electrocardiographic changes, and blood pressure changes, occur during puberty.

The normal sequence of pubertal events and perils of puberty are reviewed here. This is within the normal ranges and does not take into account Precocious Puberty or Delayed Puberty.

Tanner Stages

Conceptually, pubertal maturation can be described in terms of sequence, timing, and tempo (Puberty consists of a series of predictable events, and the sequence of changes in secondary sexual characteristics has been categorized by several groups. The staging system utilized most frequently is that published by Marshall and Tanner and the sequence of changes, commonly referred to as "Tanner stages," is described below.

Boys – development of external genitalia

Stage 1: Prepubertal

Stage 2: Enlargement of scrotum and testes; scrotum skin reddens and changes in texture

Stage 3: Enlargement of penis (length at first); further growth of testes

Stage 4: Increased size of penis with growth in breadth and development of glans; testes and scrotum larger, scrotum skin darker

Stage 5: Adult genitalia

Girls – breast development

Stage 1: Prepubertal

Stage 2: Breast bud stage with elevation of breast and papilla; enlargement of areola

Stage 3: Further enlargement of breast and areola; no separation of their contour

Stage 4: Areola and papilla form a secondary mound above level of breast

Stage 5: Mature stage: projection of papilla only, related to recession of areola

Boys and girls – pubic hair

Stage 1: Prepubertal (can see velus hair similar to abdominal wall)

Stage 2: Sparse growth of long, slightly pigmented hair, straight or curled, at base of penis or along labia

Stage 3: Darker, coarser and more curled hair, spreading sparsely over junction of pubes

Stage 4: Hair adult in type, but covering smaller area than in adult; no spread to medial surface of thighs

Stage 5: Adult in type and quantity, with horizontal distribution ("feminine")

Boys Growth

- Stage 1: 5 – 6 cm/year
- Stage 2: 5 – 6 cm/year
- Stage 3: 7 – 8 cm/year
- Stage 4: 10 cm/year
- Stage 5: No further height increase after 17 years

Girls Growth

- Stage 1: 5 – 6 cm/year
- Stage 2: 7 – 8 cm/year
- Stage 3: 8 cm/year
- Stage 4: 7 cm/year
- Stage 5: No further height after 16 years

Appendix K. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes

Section 1.2 Synopsis
Subsection Diagnosis and Main Criteria for Inclusion/Exclusion:
Heading "Main Exclusion:"
Subheading "Safety"
Add: new Criterion 31

31. No known active COVID-19 infection. Subject must not have signs/symptoms associated with COVID-19 infection.

    Subjects who do not meet COVID-19 eligibility criteria must be screen failed and may only rescreen after they meet the following COVID-19 viral clearance criteria:

    - Symptomatic subjects: At least 2 negative viral tests in a row completed locally, ≥ 24 hours apart after at least 10 days have passed since recovery, defined as resolution of fever without use of antipyretics and improvement in respiratory symptoms (e.g., cough, shortness of breath)
    - Asymptomatic subjects: At least 2 negative viral tests in a row completed locally, ≥ 24 hours apart after at least 10 days have passed since prior positive result (Note: subjects who develop symptoms will follow guidance above for symptomatic subjects)

    Frequency or timing of COVID-19 testing and interval between testing for the above viral clearance criteria may be adjusted to account for epidemiological trends, updated information regarding infectivity and local/institutional guidelines.

Section 1.3 List of Abbreviations and Definition of Terms
Subsection Abbreviations
Add:

COVID-19	Coronavirus Disease - 2019

Section 3.2 Benefits and Risks
Add: new last paragraph

Considering the coronavirus (COVID-19) pandemic, the benefit and risk to subjects participating in this study have been re-evaluated. Based on the limited information to date, no additional risk to study participants is anticipated with the use of risankizumab.

Section 5.2.2 Exclusion Criteria
Subsection Safety
Add: new Criterion 31

31. No known active COVID-19 infection. Subject must not have signs/symptoms associated with COVID-19 infection.

    Subjects who do not meet COVID-19 eligibility criteria must be screen failed and may only rescreen after they meet the following COVID-19 viral clearance criteria:

    - Symptomatic subjects: At least 2 negative viral tests in a row completed locally, ≥ 24 hours apart after at least 10 days have passed since recovery, defined as resolution of fever without use of antipyretics and improvement in respiratory symptoms (e.g., cough, shortness of breath)
    - Asymptomatic subjects: At least 2 negative viral tests in a row completed locally, ≥ 24 hours apart after at least 10 days have passed since prior positive result (Note: subjects who develop symptoms will follow guidance above for symptomatic subjects)

    Frequency or timing of COVID-19 testing and interval between testing for the above viral clearance criteria may be adjusted to account for epidemiological trends, updated information regarding infectivity and local/institutional guidelines.

Section 5.3.1.1 Study Procedures
Add: new last paragraph

Study visits may be impacted by changes in local regulations due to the COVID-19 pandemic. This may include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study.

Section 5.3.1.1 Study Procedures
Subsection Informed Consent
Add: new last paragraph

Due to the COVID-19 pandemic, modifications to the protocol may be necessary. Subjects should be informed of the changes to the conduct of the study relevant to their participation (e.g., cancellation of visits, change in laboratory testing site, etc.). Documentation of this notification or verbal consent should be maintained at the site as required per local regulatory requirements. A signed and dated informed consent form should be obtained from the subject afterwards as soon as possible.

Section 5.3.1.1 Study Procedures
Subsection Clinical Laboratory Tests
Add: new fifth and sixth paragraph

If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from having blood drawn for laboratory testing at the study site, if possible, arrange for subjects to have laboratory work done at a local lab, hospital, or other facility. Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. Local lab results should be reviewed by the investigator as soon as possible.

If laboratory samples cannot be obtained, study drug administration may be continued provided the investigator has reviewed all prior laboratory results and confirms and discusses with the subject that there is no safety concern for the subject to continue use of the study drug in the absence of current labs.

Section 5.3.1.1 Study Procedures
Subsection HIV
Seventh sentence previously read:

AbbVie will not receive results from the testing and will not be made aware of any positive result.

Has been changed to read:

AbbVie will not receive results from the testing.

Section 5.3.1.1 Study Procedures
Subsection Outcomes and Questionnaires
Add: new last paragraph

Due to the COVID-19 pandemic and any local restrictions, sites may administer PRO instruments over the phone as needed. Sites may read the PRO questions and response options to the subject and record the subject's responses. Sites may send the questionnaires (email or hard copy) to the subjects to allow them to read/understand the questions and responses when the subject is providing responses over the phone. The date and time of PRO data collection should be recorded along with who collected the information.

Section 5.3.1.1 Study Procedures
Subsection Study Drug Dispensing/Administration
Add: new last paragraph and bullet list

During the Study Drug Dosing Period, a subject with confirmed (viral test positive) or suspected COVID-19 infection can only be dosed with study drug if the following COVID-19 viral clearance criteria are met:

- Symptomatic subjects: At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since recovery, defined as resolution of fever without use of antipyretics and improvement in respiratory symptoms (e.g., cough, shortness of breath)
- Asymptomatic subjects: At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since prior positive result (note: subjects who develop symptoms will follow guidance above for symptomatic subjects)

Section 5.5.2.2 Storage and Disposition of Study Drug
Third paragraph, last sentence previously read:

Study drug should be quarantined and not dispensed until AbbVie or AbbVie Temperature Excursion Management System (ATEMS) deems the drug as acceptable.

Has been changed to read:

Sites are responsible to report temperature excursions into the AbbVie Temperature Excursion Management System (ATEMS). Study drug should be quarantined and not dispensed until AbbVie or ATEMS deems the drug as acceptable.

Section 5.5.7 Drug Accountability
Second paragraph, first sentence previously read:

In addition, an accurate running inventory of study drug will be kept by the site (blinded or unblinded staff, as applicable) on a Site Drug Accountability log including date received, the lot number, kit number(s), date and number of vials and syringes dispensed and subject number.

Has been changed to read:

In addition, IRT will be used to document investigational product accountability including date received, the lot number, kit number(s), date and number of vials and syringes dispensed and subject number.

Section 5.5.7 Drug Accountability
Third paragraph, first sentence previously read:

An overall accountability of the study drug will be performed and verified by the CRA/monitor (blinded or unblinded according to the monitoring plan) throughout the study and at the site close-out visit.

Has been changed to read:

An overall accountability of the study drug will be performed by the site and reconciliation will be performed by the CRA/monitor (blinded or unblinded according to the monitoring plan) throughout the study and at the site close-out visit.

Section 5.5.7 Drug Accountability
Third paragraph, fourth and fifth sentence previously read:

All unused supplies must be inventoried, accounted for and destroyed on site according to local procedures or regulation or returned to a destruction facility by the monitor/CRA (blinded or unblinded according to the monitoring plan). A copy of the Drug Accountability Form, in accordance with instructions provided by the monitor/CRA (blinded or unblinded according to the monitoring plan), will be included in the return shipments.

Has been changed to read:

All unused supplies must be inventoried, accounted for and destroyed on site according to local procedures or regulation or returned to a destruction facility. A copy of the, Return Consignment Form from IRT, in accordance with instructions provided by the monitor/CRA (blinded or unblinded according to the monitoring plan), will be included in the return shipments.

Section 6.1.1.1 Adverse Event
Add: new fourth, fifth, and sixth paragraph

Supplemental study case report forms should be completed in the event of COVID-19 related missed/virtual visits, study drug interruptions or discontinuations, or adverse events (including capture of specific signs/symptoms of infection and testing results).

COVID-19 infections should be captured as adverse events. If the event meets the criteria for a serious adverse event (SAE), then follow the SAE reporting directions per the protocol and above. The following COVID-19 related supplemental eCRFs should be completed:

- COVID-19 Supplemental Signs/Symptoms
- COVID-19 Status Form

If a subject has a confirmed or suspected COVID-19 infection and study drug was interrupted, the investigator should contact the sponsor emergency medical contact listed above before reintroducing study drug.

Section 7.0 Protocol Deviations
First paragraph, last sentence previously read:

If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal Investigator is responsible for notifying IEC/IRB regulatory authorities (as applicable), and AbbVie.

Has been changed to read:

If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic) after a subject has been enrolled, the principal Investigator is responsible for notifying IEC/IRB regulatory authorities (as applicable), and AbbVie.

Section 8.1 Statistical and Analytical Plans
Add: new last paragraph

The impact of missing data due to COVID-19 will be monitored and appropriate modifications to the analysis of primary and key secondary endpoints for handling such missing data will be reflected and incorporated in the final SAP.

Section 9.2 Ethical Conduct of the Study
Add: new last paragraph

In the event of a state of emergency due to the COVID-19 pandemic leading to difficulties in performing protocol-specified procedures, AbbVie will engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or

virtual site visits), alternative locations for data collection (e.g., use of a local lab instead of a central lab). In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

Section 10.1 Source Documents
Add: new last paragraph

During the COVID-19 pandemic, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]		Clinical Development, Immunology
		Clinical Development, Immunology
		Statistics
		Statistics
		Clinical Pharmacology and Pharmacometrics
		Bioanalysis
		Clinical Operations

Has been changed to read:

Name	Title	Functional Area
[redacted]		Clinical Development, Immunology
		Clinical Development, Immunology
		Statistics
		Statistics
		Clinical Pharmacology and Pharmacometrics
		Bioanalysis
		Clinical Operations

Appendix C. Study Activities for Efficacy, Safety, and PK/PD
Add: new Activity "COVID-19 Assessment[z]"

	Screening Period (35 Days)[a]	12-Week Double-Blind Induction				Induction Period 2			Unsch[b]	140-Day Follow-Up[c]
Activity	**Screening**	**Baseline**	**Week 4**	**Week 8**	**Week 12/PD**	**Week 16**	**Week 20**	**Week 24**		
COVID-19 Assessment[z]	X									

Appendix C. Study Activities for Efficacy, Safety, and PK/PD
Table note "l.," last sentence previously read:

AbbVie will not receive results from the testing and not be made aware of any positive result.

Has been changed to read:

AbbVie will not receive results from the testing.

Appendix C. Study Activities for Efficacy, Safety, and PK/PD
Add: new table note "z."

Assessment for signs/symptoms of COVID-19 infection. If the investigator suspects the possibility of COVID-19 based on the signs, symptoms and medical complaint (chief complaint, history of exposure, etc.), local laboratory testing must be completed to confirm negative for infection.