1.0 Title Page

Clinical Study Protocol M16-067

A Multicenter, Randomized, Double-Blind, Placebo Controlled Induction Study to Evaluate the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Ulcerative Colitis

Incorporating Amendments 1, 2, 2.01 (Canada Only), 2.02 (China Only), 2.03 (Germany Only) 3, 3.02 (Ukraine and Surrounding Impacted Countries), and 4 and Administrative Changes 5, 6, 7, 8, and 9

AbbVie Investigational Product:	Risankizumab		
Date:	16 December 2022		
Development Phase:	2b/3		
Study Design:	Randomized, Double-Blind, Placebo-Controlled Parallel Group Seamless design		
EudraCT Number:	2016-004677-40		
Investigator(s):	Multicenter Study (Investigator information is on file at AbbVie)		
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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	28 September 2017
Amendment 1	18 October 2017
Amendment 2	14 February 2018
Amendment 2.01 (Canada Only)	18 April 2018
Amendment 2.02 (China Only)	12 November 2018
Amendment 2.03 (Germany Only)	01 September 2020
Amendment 3	01 October 2020
Administrative Change 5	30 November 2020
Amendment 3.01 (France Only)	18 February 2021
Administrative Change 6	10 March 2021
Administrative Change 7	10 June 2021
Administrative Change 8	01 September 2021
Administrative Change 9	13 April 2022
Amendment 3.02 (Ukraine and Surrounding Impacted Countries Only)	09 May 2022

The purpose of this amendment is to:

- Updated Secondary Endpoints and Additional Endpoints for Sub-Study 2 (Phase 3) in the synopsis and in Section 5.3.3

  Rationale: *To ensure objective measures of endoscopic and histologic UC disease activity are prioritized and adjust the ranking of endpoints which include subjective outcomes and subpopulations as additional endpoints.*
- Clarify in the synopsis and Section 5.1 that enrollment target has been met and enrollment is closed

  Rationale: *For clarity.*
- Clarified randomization stratification factors for Period 2 of Sub-Studies 1 and 2 in Section 5.1, Section 5.3.3, and Section 8.3.

  Rationale: *For clarity.*

- Added All Risankizumab safety analysis population for Sub-Study 2 (SA2_ALL) which includes all subjects who received at least one dose of risankizumab any time during Sub-Study 2, and removed combined Sub-Study 1 and Sub-Study 2 All Risankizumab safety analysis set in Section 8.1.1.

  Rationale: *Clarified the safety analyses based on All Risankizumab are to be performed within Sub-Study2 and integrated safety analyses are defined in the Integrated Safety Analysis Plan (ISS SAP).*

- Replaced NRI-C by NRI-MI to handle missing data in binary endpoints in Section 8.1.2.

  Rationale: *To replace NRI-C by NRI-MI to handle both missing due to Covid and missing due to geo-political conflict for binary endpoints*

- Added RTB-MI approach to handle missing data in continuous endpoints in Section 8.1.2.

  Rationale: *Added per regulatory recommendation*

- Added Tipping Point as sensitivity analysis for primary endpoint in Section 8.1.2.

  Rationale: *To evaluate the robustness of departures from the missing-at-random (MAR) assumption in the primary analysis*

- Updated the language of baseline summary in Section 8.1.4.

  Rationale: *Language updated for clarity.*

- Updated CMH test as the primary method for binary endpoints instead of M-N test in Section 8.1.6.1, Section 8.1.6.2, and synopsis

  Rationale*: The test was changed based on regulatory recommendation.*

- Advanced Therapy-IR status (yes vs no), in replacement of "number of prior failed biologics (0, 1, >1)", will be used as a stratification factor in the CMH test in Section 8.1.6.1.

  Rationale: *Advanced Therapy-IR (yes vs no) is anticipated to have stronger association with the outcome of interest*

- Updated multiple testing procedure language for Sub-Study 2 in Section 8.1.6.

  Rationale: *To incorporate the updates in endpoint ranking.*

- *Added RTB-MI analysis method for* secondary efficacy endpoints in Section 8.1.6.2

  ***Rationale**: Added based on regulatory recommendations*
- Clarified efficacy analysis methods for secondary endpoints in Section 8.1.6.2

  ***Rationale:** Updated for clarity*
- Removed the wording that safety analysis for All Risankizumab treated subjects in a population combining SS1 and SS2 In Section 8.1.7

  ***Rationale:** Integrated safety analyses are defined in the Integrated Safety Analysis Plan (ISS SAP).*

Incorporate changes from Amendment 4.02 Ukraine and surrounding Impacted Countries

- Addition of language in the synopsis Section 1.2, Section 5.1 and Section 5.3.1.1, and Study Activities Table (Appendix C) to specify that clinical response at Week 12 and Week 24 can be calculated using the Partial Adapted Mayo Score.

  ***Rationale:** To allow subjects who cannot have endoscopy performed due to the geo-political conflict in Ukraine and surrounding impacted regions to be assessed for clinical response and continue in the maintenance study*
- Addition of study procedure language in Section 5.3.1.1 and Section 9.2

  ***Rationale:** To modify study visits/protocol-specified procedures impacted by the geo-political conflict in Ukraine and surrounding impacted regions, as necessary to ensure the safety of subjects, including use of a local lab, visit frequency, delays and interruptions of dosing, alternative methods of assessments, locations for data collection permitted by IRB/IEC*
- Addition of language in Section 5.4.1

  ***Rationale:** To ensure investigators explore acceptable mitigation strategies before discontinuing a subject due to the geo-political conflict in Ukraine and surrounding impacted regions*
- Addition of protocol deviation language in Section 7.0

  ***Rationale:** To clarify that deviations include deviations occurring due to the geo-political conflict in Ukraine and surrounding impacted regions.*

- Addition of language to address handling of missing data due to the geo-political conflict in Ukraine and surrounding impacted regions in the statistical analysis plan in Section 8.1

  Rationale: *To clarify handling of missing data due to the geo-political conflict in Ukraine and surrounding impacted regions and that modifications to the analysis for missing data due to the geo-political conflict in Ukraine and surrounding impacted regions will be incorporated into the statistical analysis plan*

- Addition of protocol modification language in Section 9.2

  Rationale: *To clarify that AbbVie will modify the study protocol as necessary due to the geo-political conflict in Ukraine and surrounding impacted regions pandemic*

- Addition of Study Subject Information and Informed Consent language in Section 9.3

  Rationale: *To allow obtaining additional temporary verbal consent prior to obtaining signed and dated consent, in accordance with local regulations, in case of further adaptions or substantial changes in study conduct*

- Addition of protocol modification language in Section 10.1

  Rationale: *To clarify that due to the geo-political conflict in Ukraine and surrounding impacted regions, remote source data verification will be allowed if necessary*

Incorporate changes from Administrative Changes 5, 6, 7, 8 and 9

- Update the physician contact in Section 6.1.5 of the protocol
- Remove the sentence "These samples are not applicable for China" from Section 5.3.1.1 Study Procedures- Clinical Laboratory Tests - Table 1 footnote "e," because it does not belong to this footnote
- Move the words "ADA, and nAb assays" to the correct part of the sentence at Section 5.3.1.1 Study Procedures- Clinical Laboratory Tests- Anaphylaxis Testing, to make the sentence more understandable

- Remove the "X" for PGA at screening in Appendix C of the protocol, as collection of PGA assessment starts at baseline and is consistent with Full Mayo Score assessment at baseline.
- Update the sponsor emergency contact on the title page
- Adapt the protocol to the recent civil law amendment in Japan, that has modified the legal age of adulthood from 20 to 18 years old

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M16-067
Name of Study Drug: Risankizumab	**Phase of Development:** 2b/3
Name of Active Ingredient: Risankizumab	**Date of Protocol Synopsis:** 16 December 2022
Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study to Evaluate the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Ulcerative Colitis	
Objective: Study M16-067 comprises two sub-studies: The objective of Sub-Study 1 (Phase 2b induction) is to characterize the efficacy, safety, and pharmacokinetics of risankizumab as induction treatment in subjects with moderately to severely active ulcerative colitis (UC) and to identify the appropriate induction dose of risankizumab for further evaluation in Sub-Study 2 (Phase 3 induction). At the time of this amendment, enrollment have been completed and all subjects in the double-blind, placebo-controlled portion of the study have completed induction. The objective of Sub-Study 2 (Phase 3 induction) is to evaluate the efficacy and safety of risankizumab compared to placebo in inducing clinical remission in subjects with moderately to severely active UC.	
Investigators: Multicenter	
Study Sites: Approximately 400 sites worldwide	
Study Population: Males and females ≥ 18 and ≤ 80 years of age, or minimum age of adult consent according to local regulations, or aged 16 to < 18 year of age who meet the definition of Tanner stage 5 development where locally permitted with a diagnosis of moderately to severely active UC, defined as Adapted Mayo score of 5 – 9 points (using the Mayo scoring system, excluding Physician's Global Assessment) with an endoscopic subscore of 2 or 3 on screening endoscopy, confirmed by central review. Sub-Study 1 enrolled subjects who have had an inadequate response or intolerance (IR) to prior biologic therapy (bio-IR). Sub-Study 2 will enroll subjects who have had an inadequate response or intolerance to prior biologic therapy (bio-IR) and subjects who have not had an inadequate response or intolerance to prior biologic therapy (non-bio-IR). The bio-IR enrollment will be approximately 541 subjects and the non-bio-IR enrollment will be approximately 425 subjects. The **bio-IR** population is defined as subjects with documented intolerance or inadequate response to one or more of the approved biologics for UC (infliximab, adalimumab, golimumab, and/or vedolizumab) or tofacitinib. 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 or tofacitinib in the past but stopped therapy based on reasons other than inadequate response or intolerance (e.g., change in reimbursement coverage, well-controlled disease).	

Number of Subjects to be Enrolled:

Approximately 1547 subjects in total:

- 240 subjects in Sub-Study 1, Phase 2b double-blind, placebo-controlled induction,
- 340 subjects in Sub-Study 1 enrolled during open-label (OL) dose selection period, and
- approximately 966 subjects in Sub-Study 2 Phase 3 induction.

Methodology:

This Phase 2b/3 study has an operationally seamless design and comprises two sub-studies. The purpose of this design is to seamlessly transition from the Phase 2b induction study to the Phase 3 induction study without enrollment pause. Sub-Study 1 was designed as a Phase 2b dose finding study to evaluate the efficacy, safety, and PK of risankizumab as induction treatment to identify the appropriate induction dose of risankizumab for further evaluation in Sub-Study 2. Sub-Study 2 is a Phase 3 induction study to evaluate the efficacy and safety of risankizumab versus placebo.

Sub-Study 1 (Phase 2b Induction):

Induction Period 1:

Subjects (n = 240) who met all of the inclusion criteria and none of the exclusion criteria were randomized into the study in a 1:1:1:1 ratio to one of the following treatment groups:

- Group 1: Risankizumab 1800 mg IV Weeks 0, 4, 8 (n = 60)
- Group 2: Risankizumab 1200 mg IV Weeks, 0, 4, 8 (n = 60)
- Group 3: Risankizumab 600 mg IV Weeks 0, 4, 8 (n = 60)
- Group 4: Placebo IV Weeks 0, 4, 8 (n = 60)

The randomization at baseline was stratified by baseline steroid use (yes vs no) and baseline Adapted Mayo score (≤ 7 vs > 7). Endoscopy and evaluation of clinical response and remission will occur at Week 12.

Subjects in Sub-Study 1 who achieved clinical response per Adapted Mayo score (locally read Mayo endoscopic subscore) after completion of the 12-week Induction Period 1 were eligible to be enrolled into maintenance Study M16-066. Clinical response is defined as a decrease from baseline in the Adapted Mayo score ≥ 2 points and ≥ 30% from baseline, PLUS a decrease in rectal bleeding subscore (RBS) ≥ 1 or an absolute RBS ≤ 1. Subjects who did not achieve clinical response at Week 12 were eligible to receive blinded risankizumab treatment in Induction Period 2 as specified below. Subjects were not eligible to enter Induction Period 2 until the Week 12 endoscopy has been completed.

Methodology (Continued):

Sub-Study 1 (Phase 2b Induction) (Continued):

Induction Period 2:

At Week 12, subjects who did not achieve clinical response were be randomized by Interactive Response Technologies (IRT) to Induction Period 2, a double-blind, double-dummy 12-week treatment period to evaluate reinduction with risankizumab versus starting maintenance dosing on clinical response status.

Subjects who received IV risankizumab induction were randomized 1:1:1 to:

- Group 1: 1800 mg IV risankizumab Weeks 12, 16, 20
- Group 2: 360 mg SC risankizumab Weeks 12, 20
- Group 3: 180 mg SC risankizumab Weeks 12, 20

The randomization in Period 2 was stratified by baseline steroid use (yes vs no) and baseline Adapted Mayo score (≤ 7 vs > 7).

Subjects who received IV placebo induction treatment received:

- Group 4: 1800 mg IV risankizumab Weeks 12, 16, 20

Subjects randomized in Groups 1 and 4 received placebo SC and subjects randomized in Groups 2 and 3 received placebo IV, in order to keep the blind. The IV risankizumab dose or matching IV placebo were given at Weeks 12, 16, and 20. The SC risankizumab dose or matching SC placebo were given at Weeks 12, and 20. At Week 24, subjects who received blinded risankizumab treatment during Induction Period 2 were reassessed and underwent a third endoscopy for evaluation of mucosal inflammation. Subjects who achieved clinical response per Adapted Mayo score (locally read Mayo endoscopic subscore) at Week 24 were eligible to enter into the maintenance Study M16-066. Subjects without clinical response at Week 24, as well as all subjects who terminated the study early (including subjects who were eligible for but did not receive blinded risankizumab therapy during Induction Period 2), were 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.

Dose Selection Analysis:

After 240 subjects were randomized and completed the 12-week Induction Period 1, dose response and exposure response analysis for the key efficacy and safety variables were performed. Based on this analysis, one induction dose of risankizumab has been identified (risankizumab selected dose) for evaluation in Sub-Study 2 (Phase 3 Induction). The results of this analysis were reviewed and discussed with regulatory authorities, as applicable, prior to initiation of enrollment of subjects in Sub-Study 2.

During the analysis period, additional subjects continued to be enrolled in the 1800 mg dosing group, on an open-label basis, to avoid interrupting the study activities during the analysis period and to generate a sufficient number of subjects with clinical response to be enrolled into the maintenance Study M16-066. The data collected from these additional subjects will not be included in the primary analysis but reported in the clinical study report.

Methodology (Continued):

Sub-Study 2 (Phase 3 Induction):

Induction Period 1:

Approximately 966 subjects who meet all of the inclusion criteria and none of the exclusion criteria will be randomized into the double-blind 12-week study in a 2:1 ratio to one of the following treatment groups:

- Group 1: Risankizumab 1200 mg IV Weeks 0, 4, 8 (n = 644)
- Group 2: Placebo IV Weeks 0, 4, 8 (n = 322)

The randomization at baseline will be stratified by number of prior failed biologic treatments (0, 1 vs > 1), baseline steroid use (yes vs no), and baseline Adapted Mayo score (≤ 7 vs > 7). Endoscopy and the primary analyses will occur at Week 12. Subjects in Sub-Study 2 who achieve clinical response after completion of the 12-week Induction Period 1 will be enrolled into maintenance Study M16-066. Subjects who do not achieve clinical response per Adapted Mayo score (locally read Mayo endoscopic subscore) 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.

Induction Period 2:

At Week 12, subjects who do not achieve clinical response will be randomized by IRT to Induction Period 2, a double-blind, double-dummy 12-week treatment period to evaluate reinduction with risankizumab versus starting maintenance dosing on clinical response status.

Subjects who received IV risankizumab will be randomized 1:1:1 to:

- Group 1: 1200 mg IV risankizumab Weeks 12, 16, and 20
- Group 2: 360 mg SC risankizumab Weeks 12, and 20
- Group 3: 180 mg SC risankizumab Weeks 12, and 20

The randomization in Period 2 will be stratified by number of prior failed biologic treatments (0, 1 vs > 1), baseline steroid use (yes vs no), and baseline Adapted Mayo score (≤ 7 vs > 7).

Subjects who received placebo induction treatment will receive:

- Group 4: 1200 mg IV risankizumab Weeks 12, 16, and 20

Subjects randomized in Groups 1 and 4 will receive placebo SC and subjects randomized in Groups 2 and 3 will received placebo IV, in order to keep the blind. 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 receive blinded risankizumab during the Induction Period 2 will be reassessed and undergo a third endoscopy for evaluation of mucosal inflammation. Subjects who achieve clinical response per Adapted Mayo score (locally read Mayo endoscopic subscore) at Week 24 may be eligible to enter into the maintenance Study M16-066. 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 receive blinded risankizumab therapy during 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.

If endoscopy cannot be performed at Week 12 or 24 due to COVID-19 pandemic restrictions or geo-political conflict in Ukraine and surrounding impacted regions, clinical response will be calculated using the Partial Adapted Mayo score and is defined as a decrease from Baseline in the Partial Adapted Mayo

score ≥ 1 points and ≥ 30% from Baseline, PLUS a decrease in rectal bleeding subscore (RBS) ≥ 1 or an absolute RBS ≤ 1.

Study Visits:

Study visits for clinical and safety assessments will be performed at Baseline, Weeks 4, 8, and 12/Premature Discontinuation (PD). For subjects entering Induction Period 2, additional study visits will occur at Weeks 16, 20, and 24/PD. All subjects will be provided with a subject diary where they will record UC related symptoms, use of anti-diarrheals, and use of medications for endoscopy preparation. 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.

Subjects will undergo endoscopies during screening and Week 12. Subjects who enter Induction Period 2 will undergo an additional endoscopy at Week 24. Endoscopies will be evaluated using the Mayo endoscopic subscore and the presence or absence of friability will be documented. All endoscopies will be video recorded. Videos from subjects with eligible Mayo endoscopic sub-scores during Screening and all videos from subjects at Week 12 and Week 24 will be sent to a central review vendor and scored as described in the central review charter. In addition, the central reader will assess the endoscopy findings using the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) for additional exploratory analyses. Biopsy samples for histologic assessment will be collected at each endoscopy visit. Additional biopsies to confirm diagnosis (during Screening) or to rule out dysplasia/malignancy may be performed during the same time points as the endoscopy. For subjects who consent, optional exploratory research samples may be taken during the study.

Subjects will be discontinued from the study if they withdraw consent or if they are deemed unsuitable to continue for any reason by the Investigator.

Concomitant Aminosalicylates, Immunomodulators (Azathioprine [AZA], Mercaptopurine [6-MP], Methotrexate [MTX]), and/or UC-Related Antibiotics:

Subjects taking oral aminosalicylates, immunomodulators, and/or UC-related antibiotics at Baseline must continue these treatments for the duration of the study. Initiating and/or increasing doses of oral aminosalicylates, immunomodulators, and/or UC-related antibiotics after Baseline is prohibited. Decreasing doses of oral aminosalicylates, immunomodulators, and/or UC-related antibiotics is prohibited during the study, except in the event of moderate-to-severe treatment related toxicities (e.g., leukopenia or elevated liver enzymes) in the opinion of the investigator. However, UC-related antibiotics may be discontinued during Induction Period 2 at the discretion of the Investigator.

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

Concomitant Corticosteroids:

Subjects taking oral corticosteroids at Baseline must continue their concomitant treatment at the Baseline dose for the duration of Induction Period 1. Initiation and/or increasing doses of systemic and/or UC-related corticosteroids after Baseline is prohibited. Decreasing doses of oral corticosteroids is prohibited during Induction Period 1, except in the event of moderate-to-severe treatment related toxicities in the opinion of the investigator.

Methodology (Continued):

Subjects who enter Induction Period 2 will be allowed to taper their oral corticosteroids at the discretion of the Investigator. While stopping the taper is permitted, increasing doses above the Baseline dose is prohibited.

Dose Selection:

Sub-Study 2 (Phase 3 induction study) will evaluate IV risankizumab 1200 mg during induction. The selection of doses was informed by the analysis of safety and efficacy data, as well as the dose-response and exposure-response relationships of efficacy from Sub-Study 1 (Phase 2b dose finding study).

Induction Period 2 will evaluate IV (1800 mg [Sub-Study 1] or 1200 mg [Sub-Study 2] 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 versus starting maintenance regimen 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 based on safety and efficacy data, as well as the exposure-response relationship, of the maintenance period during the Phase 2 study in subjects with CD that evaluated 180 mg SC risankizumab for maintenance. A higher dose of 360 mg Q8W is proposed to provide exposures reasonably separated with 180 mg Q8w dose to characterize the exposure-response relationship during maintenance phase with a potential of 360 mg Q8w dose to maintain higher response compared to 180 mg Q8w dose.

Data Monitoring Committee (DMC):

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 time of this amendment, the DMC has provided recommendation that the study may continue without modification and has endorsed the commencement of enrollment for 16 and 17 year old subjects.

For China only: The first 12 subjects enrolled in China will be monitored at an individual subject level. Also, the initial 12 subjects enrolled in China will be monitored on site for 2 hours after completion of the infusion. Once the DMC assesses the safety results of the initial 12 subjects with no safety concerns identified, all sites in China will be notified that subjects should be monitored as necessary after completion of the infusion. In addition, 16 to < 18 year olds will not be enrolled in China until the DMC has reviewed the first 12 adult subjects enrolled in China and provided endorsement.

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:

The following Inclusion/Exclusion Criteria are for subjects enrolled in either Sub-Study 1 or 2, except where specified.

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. In addition, for Sub-Study 2 only: Where locally permissible, subjects 16 to < 18 years of age who meet the definition of Tanner Stage 5 for development (refer to the Appendix G) at the Baseline Visit.
2. Confirmed diagnosis of UC for at least 3 months prior to Baseline. Appropriate documentation of biopsy results consistent with the diagnosis of UC or in the assessment of the Investigator, must be available.
3. Active UC with an Adapted Mayo score of 5 to 9 points and endoscopic subscore of 2 to 3 (confirmed by central review).
4. 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 or tofacitinib.
    - Demonstration of intolerance requires no minimum dose or duration of use.
    - 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 (2 g/day if controlled release), 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, 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, 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
    - Tacrolimus: (for Japan, Taiwan and other countries in Asia with local treatment guidelines that include tacrolimus) documented trough level 5 - 10 ng/mL
  - Biologic Therapies and tofacitinib for UC: Signs and symptoms of persistently active disease despite a history of one or more of the following:
    - At least one 6-week induction regimen of infliximab (≥ 5 mg/kg intravenous [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 golimumab (200 mg SC at Week 0 and 100 mg SC at Week 2),
    - At least one 6-week induction regimen of vedolizumab (300 mg IV at Weeks 0, 2, and 6),
    - At least one 8-week induction regimen of tofacitinib (10 mg PO twice daily)
  - Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit of the above biologics
  - Note: Subjects who discontinued biologics or tofacitinib 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

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

Main Inclusion (Continued):

5. 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.
6. 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 under the legal age of adulthood, a subject's parent or legal guardian must be willing to give written informed consent.

Main Exclusion:

1. Subject with a current diagnosis of Crohn's disease (CD), IBD-unclassified (IBD-U) or a history of radiation colitis or ischemic colitis.

Concomitant Medications and Treatments

2. Subject on oral UC-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 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 anti-infectives (non-UC-related) within 14 days prior to the Baseline visit. This does not apply to TB prophylaxis.
7. Subject who received any parenteral nutrition within 35 days prior to Baseline.
8. Subject who received any live bacterial or viral vaccination within 35 days (8 weeks for Japan) prior to Baseline.
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.

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

Main Exclusion (Continued):

Prior Medications and Treatments

11. Subject who received any:
    - approved biologic agent (e.g., infliximab, adalimumab, golimumab, vedolizumab) within 8 weeks prior to Baseline or tofacitinib within 35 days prior to Baseline
12. Subject with prior exposure to p40 inhibitors (e.g., ustekinumab [Stelara]) or p19 inhibitors (e.g., risankizumab).
13. Subject has been taking combination of two or more of the following oral budesonide, 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 (i.e., rectal aminosalicylates/corticosteroids), other than required for endoscopy, within 14 days prior to 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.

UC Related

18. Extent of inflammatory disease limited to the rectum as assessed by screening endoscopy
19. Subject with currently known complications of UC such as:
    - fulminant colitis,
    - toxic megacolon,
    - previous colectomy (total or subtotal),
    - or any other manifestation that might require surgery while enrolled in the study.
20. Subject with ostomy or ileoanal pouch.

Safety

21. 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).
22. 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 as identified during Screening,
    - Known infection with an intestinal pathogen
    - Are infected with human immunodeficiency virus (HIV),

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

Main Exclusion (Continued):

- 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 with anti-HCV antibody (HCV Ab)

23. 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.
24. 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.
25. Subject with or 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.
26. Subject who has severe, progressive, or uncontrolled renal, hepatic, hematological, endocrine, disorder or symptoms thereof.
27. 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.
28. 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.
29. 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

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

Main Exclusion (Continued):

- Positive serum pregnancy test at the Screening visit or positive urine pregnancy test at the Baseline visit.

30. No known active COVID-19 infection. If a subject has signs/symptoms suggestive of COVID-19, they should undergo molecular (i.e., PCR) testing to rule out SARS-CoV-2 infection.
    - Subjects who do not meet COVID-19 eligibility criteria must be screen failed and may only rescreen after they meet the following criteria:
    - Symptomatic subjects: At least 14 days have passed since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms
    - Asymptomatic subjects: At least 14 days have passed since the first positive molecular (i.e., PCR) test result.

    Laboratory values can be re-tested once during the screening period. 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.

Investigational Product:	Risankizumab
Doses:	Risankizumab 1800 mg IV Q4W Risankizumab 1200 mg IV Q4W Risankizumab 360 mg SC Q8W Risankizumab 180 mg SC Q8W
Mode of Administration:	Risankizumab solution for infusion (IV) Risankizumab solution for injection (SC)
Reference Therapy:	Placebo for Risankizumab
Dose:	Placebo: N/A
Mode of Administration:	Placebo solution for infusion (IV) Placebo solution for injection (SC)

Duration of Treatment: 12 to 24 weeks

The study will include a Screening period of approximately 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 blinded risankizumab treatment 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 enroll into Study M16-066 or discontinue from the study prematurely.

Criteria for Evaluation:

- **Clinical Remission per Adapted Mayo:** stool frequency subscore (SFS) ≤ 1 and not greater than baseline, rectal bleeding subscore (RBS) = 0, and endoscopic subscore ≤ 1 without the evidence of friability
- **Clinical Response per Adapted Mayo:** decrease from Baseline ≥ 2 points and $\geq 30\%$, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1

Criteria for Evaluation (Continued):

- **Clinical Response per Partial Adapted Mayo (without endoscopy):** decrease from Baseline ≥ 1 points and ≥ 30%, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1
- **Clinical Remission per Full Mayo:** Full Mayo score ≤ 2 with no subscore > 1
- **Endoscopic Improvement:** endoscopy subscore of 0 or 1 without the evidence of friability
- **Endoscopic Remission:** endoscopic subscore = 0
- **Histologic Remission:** Geboes score of < 2.0
- **Histologic Endoscopic Mucosal Remission (HEMR**): Endoscopy subscore of 0 and Geboes score < 2.0
- **Histologic Endoscopic Mucosal Improvement (HEMI)**: endoscopic subscore of 0 or 1 without the evidence of friability and Geboes score ≤ 3.1

Note: Evidence of friability during endoscopy in subjects with otherwise "mild" endoscopic activity will confer an endoscopic subscore of 2.

Efficacy (Risankizumab Versus Placebo): The primary endpoint is the same for Sub-Studies 1 and 2.

Primary Endpoint:

The achievement of clinical remission per Adapted Mayo score at Week 12.

Sub-Study 1 Secondary Endpoints:

1. The achievement of endoscopic improvement at Week 12
2. The achievement of clinical remission per Full Mayo score (defined as a Full Mayo score ≤ 2 with no subscore > 1) at Week 12 in subjects with a Full Mayo score of 6 to 12 at Baseline
3. The achievement of clinical response per Adapted Mayo score at Week 12
4. The achievement of clinical response per Partial Adapted Mayo score at Week 4
5. The achievement of endoscopic remission at Week 12
6. Occurrence of subjects with hospitalizations through Week 12
7. The achievement of HEMR at Week 12
8. Change from Baseline to Week 12 in UC-Symptom Questionnaire (UC-SQ)
9. Change from Baseline to Week 12 in Inflammatory Bowel Disease Questionnaire (IBDQ)
10. Change from Baseline to Week 12 in Short Form-36
11. Change from Baseline to Week 12 in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)
12. UC-related surgeries through Week 12

Sub-Study 2 Secondary Endpoints:

1. The achievement of clinical response per Adapted Mayo score at Week 12
2. The achievement of endoscopic improvement at Week 12
3. The achievement of histologic endoscopic mucosal improvement (HEMI: Endoscopic subscore of 0 or 1 without evidence of friability and Geboes score ≤ 3.1) at Week 12
4. The achievement of endoscopic remission at Week 12
5. The achievement of clinical response per Partial Adapted Mayo score at Week 4
6. The achievement of no bowel urgency at Week 12

Criteria for Evaluation (Continued):

Sub-Study 2 Secondary Endpoints (Continued):

7. The achievement of no abdominal pain at Week 12
8. The achievement of histologic endoscopic mucosal remission (HEMR: Endoscopy subscore of 0 and Geboes score < 2.0) at Week 12
9. Change from Baseline to Week 12 in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)
10. Change from Baseline to Week 12 in Inflammatory Bowel Disease Questionnaire (IBDQ) total score
11. Occurrence of UC-related hospitalizations through Week 12
12. The achievement of no nocturnal bowel movements at Week 12
13. The achievement of no tenesmus at Week 12
14. Change from Baseline to Week 12 in number of fecal incontinence episodes per week
15. Change from Baseline to Week 12 in number of days per week with sleep interrupted due to UC symptoms.

Pharmacokinetics (PK):

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 undergo blinded risankizumab treatment during Induction Period 2.

Additionally, intensive pharmacokinetic assessment was performed in 24 subjects in Sub-Study 1 after the 3rd induction dose (Weeks 8 to 12). For Subjects who consented to the intensive pharmacokinetic assessment, in addition to the time points above, blood samples were 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. At the time of finalizing this amendment, intensive PK sub-study has been completed.

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 undergo blinded risankizumab treatment during Induction Period 2.

Safety:

Incidence of adverse events (AEs), changes in vital signs, physical examination results, and clinical laboratory data will be assessed throughout the study.

Exploratory Research (Optional):

Prognostic, surrogate, predictive and pharmacodynamics biomarkers signatures may be investigated. Samples for different applications, potentially including but not limited to pharmacogenetic, epigenetic, transcriptomic, proteomic, metabolomic, metagenomic, phenotypic, functional and targeted investigations will be collected at various time points. Assessments may include but may not be limited to nucleic acids, proteins, metabolites, lipids, or peripheral blood mononuclear cells (PBMC).

Statistical Methods:

Sample Size Determination:

Sub-Study 1:

For Sub-Study 1 (Phase 2b portion of the study), a total of 240 subjects were equally randomized with 1:1:1:1 ratio to three risankizumab treatment groups (600 mg, 1200 mg and 1800 mg IV Q4W) and the placebo group. Assuming clinical remission rate of 7% in the placebo arm and maximum of 25% in at least one of the risankizumab treatment groups at Week 12, a sample size of 60 subjects per treatment group is sufficient to test for the presence of a dose response signal with an average power of approximately 87% at 5% level of significance (one-sided), via modeling using Multiple comparison procedure and modeling (MCP-Mod) approach.

Sub-Study 2:

For Sub-Study 2, a total of 966 subjects will be allocated to risankizumab 1200 mg IV dose or placebo in a randomization ratio of 2:1. The sample size has been re-assessed after analyzing the combined PK, safety and efficacy results from Sub-Study 1. It is determined to provide adequate powers for the primary endpoint and selected ranked secondary endpoints and adequate responders to meet the sample size requirement for Study M16-066. Assuming clinical remission rate of 6% in the placebo arm and 16% of the risankizumab treatment arm at Week 12, a sample size of 644:322 subjects per arm will provide at least 90% power to detect the 10% treatment difference in the primary endpoint using two sided Miettinen and Nurminen test at a 0.05 significant level.

Analysis Sets:

For both Sub-Studies 1 and 2, efficacy analysis will be based on Intent-to-Treat (ITT) population and Safety analysis will be based on safety population. The ITT and safety populations for each sub-study are defined in the protocol Section 8.1.1. Subjects who received treatment in Induction Period 2 after Week 12 in both Sub-Study 1 and Sub-Study 2 will be analyzed separately for exploratory purpose.

Sub-Study 1:

The dose response modeling between risankizumab treatment groups and placebo on the primary efficacy endpoint clinical remission rate at Week 12 was performed using MCP-Mod approach in the ITT1A population.

The pairwise comparison between each risankizumab treatment group and placebo was performed using the 2-sided Cochran-Mantel-Haenszel (CMH) test and stratified by baseline corticosteroid use (yes vs no) and baseline Adapted Mayo score (≤ 7 vs > 7).

Non-responder imputation method (NRI) was used for the primary endpoint as the primary imputation method.

Continuous secondary efficacy endpoints were analyzed using a Mixed-Effect Model Repeated Measures (MMRM) method as the primary analysis.

Categorical secondary efficacy endpoints were analyzed using CMH controlling for stratification variables. NRI was used as the primary imputation method except for occurrence of hospitalization and UC-related surgeries, of which as observed data were used.

Sub-Study 2:

All efficacy comparisons between risankizumab and placebo will be based on corresponding ITT Population.

Statistical Methods (Continued):

Analysis Sets (Continued):

The comparisons between [each] risankizumab treatment group and placebo for the primary efficacy endpoint clinical remission rate at Week 12 will be performed using 2-sided Cochran-Mantel-Haenszel (CMH) test and will be stratified by Advanced Therapy-IR status (yes vs no), baseline corticosteroid use (yes vs no), and baseline Adapted Mayo score (≤ 7 vs > 7). Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19 or geo-political conflict in Ukraine and surrounding impacted regions (NRI-MI) will be used for the primary efficacy endpoint as the primary imputation method.

Continuous secondary efficacy variables will be analyzed using RTB-MI as defined in Section 8.1.2 with MMRM (for endpoints with more than one post-baseline visits) or with ANCOVA (for endpoints with one post-baseline visit) models.

Categorical secondary efficacy endpoints will be analyzed using CMH test controlling for stratification variables. NRI-MI will be used except for occurrence of UC-related hospitalization, of which AO data will be used.

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

Safety:

Treatment Emergent Adverse events (TEAEs), laboratory data and vital signs are the primary safety parameters in this study. All safety comparisons will be performed between treatment groups based on the corresponding safety population. TEAEs for each induction period are defined in protocol Section 8.1.7.

An overview of TEAEs, including TEAEs of special interest such as serious infection, malignancies, major adverse cardiovascular events, systemic hypersensitivity reactions/infusion reactions, TEAEs leading to death and TEAEs leading to premature discontinuation (see details in the SAP), TEAEs by Medical Dictionary for Drug Regulatory Activities (MedDRA version 18.1 or later) preferred term and system organ class, TEAEs by maximum relationship to study drug, and TEAEs by maximum severity will be summarized by number and percentage. Treatment group differences in the overall incidence of TEAEs will be assessed with Fisher's exact test for each preferred term.

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.

* Pinheiro J, Bornkamp B, Bretz F. Design and analysis of dose-finding studies combining multiple comparisons and modeling procedures. J Biopharm Stat. 2006;16(5):639-56.

Bretz F, Pinheiro JC, Branson M. Combining multiple comparisons and modeling techniques in dose-response studies. Biometrics. 2005;61(3):738-48.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

6-MP	Mercaptopurine
AAC	Anaphylaxis Adjudication Committee
ADA	Anti-Drug Antibody
AE	Adverse Event
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AST	Aspartate Transaminase
ANC	Absolute Neutrophil Count
AUC	Area under the plasma concentration-time curve
BID	Twice daily
BMI	Body Mass Index
BP	Blood pressure
BUN	Blood Urea Nitrogen
CAC	Cardiac Adjudication Committee
CD	Crohn's Disease
CDC	Centers for Disease Control and Prevention
CD4, CD8	Cluster of Differentiation
CGC	Common Gamma-Chain
CHF	Congestive Heart Failure
CI	Confidence Interval
C_{max}	Maximum Observed Plasma Concentration
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease - 2019
CPK	Creatine Phosphokinase
CR	Clinical Remission
CRF	Case Report Form
CRP	C-Reactive Protein
C_{min}	Minimum Plasma Concentration During a Dosing Interval
CXR	Chest X-Ray
CYP3A	Cytochrome P450 3A

DMARD	Disease-Modifying Anti-Rheumatic Drug
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EIM	Extra-Intestinal Manifestations
Epro	Electronic Patient Reported Outcomes
EQ-5D	EuroQoL-5D
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
gp130	Glycoprotein 130
HBc Ab	Hepatitis B Core Antibody
HBs Ab	Hepatitis B Surface Antibody
HBs Ag	Hepatitis B Surface Antigen
HBV	Hepatitis B virus
HCV Ab	Hepatitis C Virus Antibody
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HRUQ	Health Resource Utilization Questionnaire
hsCRP	High-Sensitivity C-Reactive Protein
IBDQ	Inflammatory Bowel Disease Questionnaire
IC	Indeterminate Colitis
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGRA	Interferon-Gamma Release Assay
IL	Interleukin
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
JAK	Janus Activated Kinase
LDL	Low Density Lipoprotein

LFT	Enter LFT definition
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Effect Repeated Measure
MTX	Methotrexate
NK	Natural Killer Cells
NOAEL	No Observable Adverse Effect Level
NRI	Non-Responder Imputation
NRI-MI	Non-Responder Imputation while incorporating multiple imputation to handle missing data due to COVID-19 or geo-political conflict in Ukraine and surrounding impacted regions
NSAID	Non-Steroidal Anti-Inflammatory Drug
NYHA	New York Heart Association
OC	Observed Cases
PD	Premature Discontinuation
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PE	Physical Examination
PG	Pharmacogenetic
PK	Pharmacokinetic
PPD	Purified Protein Derivative
QTc	QT Interval Corrected for Heart Rate
QTcF	QT Interval Corrected for Heart Rate by Fridericia's Formula
RA	Rheumatoid Arthritis
RAVE®	EDC System from Medidata
RBC	Red Blood Cell Count
RNA	Ribonucleic Acid
RBS	Rectal Bleeding Subscore
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDP	Study designated physician
SFS	Stool Frequency Subscore
STAT	Signal Transduction Activators of Transcription
TB	Tuberculosis
TEAE	Treatment-Emergent Adverse Event
T_{max}	Time to Maximum Observed Plasma Concentration

TNF	Tumor Necrosis Factor
TPN	Total Parenteral Nutrition
Tyk2	Tyrosine Kinase 2
UC	Ulcerative Colitis
UCEIS	Ulcerative Colitis Endoscopic Index of Severity
ULN	Upper Limit of Normal
WBC	White Blood cell Count
WPAI	Work Productivity and Impairment Questionnaire

2.0 Table of Contents

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3.0 Introduction

Ulcerative colitis (UC) is one of the two primary forms of idiopathic inflammatory bowel disease (IBD). UC is a chronic, relapsing inflammatory disease of the large intestine characterized by inflammation and ulceration of mainly the mucosal and occasionally submucosal intestinal layers. It is postulated to be caused by an unregulated and exaggerated local immune response to environmental triggers in genetically susceptible individuals.[1] The highest annual incidence of UC is 24.3 per 100,000 person-years in Europe, 6.3 per 100,000 person-years in Asia and the Middle East, and 19.2 per 100,000 person-years in North America, with a prevalence of 505 cases per 100,000 persons in Europe and 249 cases per 100,000 persons in North America.[2] The burden of UC on the healthcare system is profound, accounting for nearly 500,000 physician visits and more than 46,000 hospitalizations per year in the United States (US) alone.[3]

The hallmark clinical symptoms include bloody diarrhea associated with rectal urgency and tenesmus. The clinical course is marked by exacerbation and remission. The diagnosis of UC is suspected on clinical grounds and supported by diagnostic testing, and elimination of infectious causes.[4]

The most severe intestinal manifestations of UC include toxic megacolon, fulminent colitis and perforation. Extraintestinal complications include arthritis (peripheral or axial involvement), dermatological conditions (erythema nodosum, aphthous stomatitis, and pyoderma gangrenosum), inflammation of the eye (uveitis), and liver dysfunction (primary sclerosing cholangitis). Patients with UC are at an increased risk for colon cancer, and the risk increases with the duration of disease as well as extent of colon affected by the disease.[5]

The aim of medical treatment in UC is to control inflammation and reduce symptoms. Available pharmaceutical therapies are limited, do not always completely abate the inflammatory process, and may have significant adverse effects. Therapies for mild to moderate active UC include 5-aminosalicylic acid derivatives and immunosuppressants.

Corticosteroids are used in patients with more severe symptoms but are not useful for longer term therapy.[6] The frequency and severity of corticosteroid toxicities are significant, including infections, emotional and psychiatric disturbances, skin injury, and metabolic bone disease. Corticosteroids are not effective for the maintenance of remission and the UC practice guidelines from the American College of Gastroenterology and the European Crohn's and Colitis Organization recommend against chronic steroid treatment.[7] Patients with moderate to severe symptoms may derive some benefits from immunomodulatory agents (azathioprine [AZA], mercaptopurine [6-MP], or methotrexate [MTX]), however, up to 17% of patients on these agents experience adverse events severe enough to necessitate drug withdrawal.[8] Adverse events (AEs) include idiosyncratic flu like reactions, bone marrow suppression, hepatotoxicity, pancreatitis, infections and malignancies.[9,10] Despite these therapies, approximately 15% of ulcerative colitis patients experience a severe clinical course, and 30% of these patients require removal of the colon/rectum, to eliminate the source of the inflammatory process. This procedure is accompanied by significant morbidity.[12] Biological agents targeting specific immunological pathways have been evaluated for their therapeutic effect in treating patients with UC. Anti-tumor necrosis factor (TNF) agents were the first biologics to be used for IBD. Infliximab, adalimumab, and golimumab are successfully being used for the treatment of UC. Vedolizumab, an anti-adhesion therapy, has also been approved for the treatment of UC. Recently, tofacitinib, an oral Janus kinase (JAK) inhibitor, has been approved for the treatment of UC.

Anti-TNF therapies are an effective treatment for patients who are steroid refractory or steroid dependent, who had inadequate response to a thiopurine, or who are intolerant to these medications. Potential risks with anti-TNF therapies include infusion or injection site reactions, serious infections, lymphoma, heart failure, lupus-like syndromes, and demyelinating conditions.[13] Despite the beneficial results achieved with the available biologic agents, only 17% to 45% of patients who receive them are able to achieve clinical remission.[14-17] Thus, there remains a clear medical need for additional therapeutic options in UC for patients with inadequate response to or intolerance to conventional therapies and biologic therapies.

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

The primary difference of this Phase 2b/3 study from other risankizumab studies is that it is the first to evaluate the efficacy, pharmacokinetics and safety of risankizumab in subjects with moderately to severely active UC. Additionally, the Phase 2b portion of this study will test a higher dosing of 1800 mg. Also, the endpoints in this study are different to reflect the changing regulatory requirements for pivotal registrational studies for new agents for the treatment of UC.

3.2 Benefits and Risks

Despite the availability of various UC therapies, including biologic therapies such as anti-TNFs, many patients still do not respond adequately to these treatments, or gradually lose response over time. Thus, there remains a clear medical need for additional therapeutic options in UC for patients with inadequate response to or intolerance to conventional therapies and biologic therapies.

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

At the time of this amendment, study results from Sub-Study 1 (Phase 2b) became available. The primary endpoint was clinical remission per Adapted Mayo Score at Week 12. In pairwise comparisons, all risankizumab doses (600 mg IV, 1200 mg IV, 1800 mg IV) achieved higher clinical remission rates compared to placebo, with both the 1200 mg and 1800 mg groups achieving nominal p-values < 0.1. All risankizumab arms achieved higher response rates on selected clinical and endoscopic secondary endpoints compared to placebo. No new safety-risks were identified and the overall safety profile was consistent with the known safety profile of risankizumab.

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

Blood sampling, intravenous (IV) infusions and subcutaneous (SC) injections can cause local bruising, inflammation, and pain. Endoscopy and biopsy, although generally well tolerated, can be associated with diarrhea, abdominal pain, and in more severe cases, perforation, bleeding, effects from anesthetic 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. An independent anaphylaxis adjudication committee (AAC) will be adjudicating observed systemic hypersensitivity and anaphylactic events. The committee will remain blinded to treatment allocation.

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. As of the time of this amendment, the DMC has provided recommendation that the study may continue without modification and has endorsed the commencement of enrollment of 16 – 17 year old subjects. 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.

As discussed above, at the time of this amendment, data from Sub-Study 1 and Phase 2b dose ranging part of this study has demonstrated efficacy of risankizumab with an acceptable safety profile compared to placebo in subjects with moderately to severely active UC. The benefit-risk profile of risankizumab in Sub-Study 1 supports further evaluation of risankizumab in Sub-Study 2 for subjects with UC.

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

Study M16-067 comprises two sub-studies.

- The objective of Sub-Study 1 (Phase 2b induction) was to characterize the efficacy, safety, and pharmacokinetics of risankizumab as induction treatment in subjects with moderately to severely active UC and to identify the appropriate induction dose of risankizumab for further evaluation in Substudy 2 (Phase 3 induction). At the time of this amendment, the double-blind, placebo-controlled portion of Sub-Study 1 has been completed.
- The objective of Sub-Study 2 (Phase 3 induction) is to evaluate the efficacy and safety of risankizumab compared to placebo in inducing clinical remission in subjects with moderately to severely active UC.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 2b/3, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of risankizumab as induction therapy in adult subjects with moderately to severely active UC, defined as Adapted Mayo score of 5 – 9 points (using the Mayo scoring system, excluding Physician's Global Assessment) with an endoscopic subscore of 2 or 3 on screening endoscopy, confirmed by central review.

This study comprises 2 sub-studies: a Phase 2b dose-ranging induction sub-study (Sub-Study 1) and a Phase 3 induction sub-study (Sub-Study 2). Sub-Study 1 enrolled subjects who have had an inadequate response or intolerance (IR) to prior biologic therapy (bio-IR). Sub-Study 2 will enroll subjects who have had an inadequate response or intolerance to prior biologic therapy (bio-IR) and subjects who have not had an inadequate response or intolerance to prior biologic therapy (non-bio-IR). The bio-IR enrollment in Sub-Study 2 will be approximately 541 subjects and the non-bio-IR enrollment will be approximately 425 subjects. At the time of this amendment the enrollment target has already been met and enrollment is closed

The **bio-IR** population is defined as subjects with documented intolerance or inadequate response to one or more of the approved biologics for UC (infliximab, adalimumab, golimumab, and/or vedolizumab) or tofacitinib.

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 or tofacitinib in the past but stopped therapy based on reasons other than inadequate response or intolerance (e.g., change in reimbursement coverage, well-controlled disease).

This Phase 2b/3 study has an operationally seamless design and comprises two sub-studies. The purpose of this design is to seamlessly transition from the Phase 2b induction study to the Phase 3 induction study without enrollment pause. Sub-Study 1 was designed as a Phase 2b dose finding study and will evaluate the efficacy, safety, and PK of risankizumab as induction treatment to identify the appropriate induction dose of risankizumab for further evaluation in Sub-Study 2. At the time of this amendment, 240 subjects were randomized and completed Week 12 treatment in Sub-Study 1, and the dose selection analysis was conducted. During analysis of Sub-Study 1, subjects could continue to enroll in the highest dosing arm (risankizumab 1800 mg IV Weeks 0, 4, 8) on an open-label basis.

Once an induction dose has been selected, Sub-Study 2 will begin enrollment. Sub-Study 2 is a Phase 3 induction study to evaluate the efficacy and safety of risankizumab versus placebo. Approximately 966 subjects will be randomized in the double-blind portion of Sub-Study 2.

The study is designed to enroll a total of approximately 1547 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.

The study duration may be up to 45 weeks, including a Screening period of approximately 35 days, a 12-week Induction Period 1, 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 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 UC related symptoms throughout the study, use of anti-diarrheals, and use of medications for endoscopy preparation. 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. Endoscopies will be evaluated using the Mayo endoscopic subscore and the presence or absence of friability will be documented. All endoscopies will be video recorded. Videos from subjects with eligible Mayo endoscopic subscores during Screening and all videos from subjects at Week 12 and 24 will be sent to a central review vendor and scored as described in the central review charter. In addition, the central reader will assess the endoscopy findings using the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) scoring system for additional exploratory analyses. Biopsy to confirm diagnosis (during Screening) or to rule out dysplasia/malignancy may be performed during the same time points as the endoscopy. Two mandatory biopsy samples will be taken during each study endoscopy for histopathological scoring. The same mandatory histopathological biopsy samples collected for the main study may be used for exploratory research if subjects provide additional consent for exploratory research. In addition, two additional biopsies may be taken from subjects who consent to participate in the optional RNA biopsies substudy.

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the Study. As of the time of this amendment, the DMC has provided recommendation that the study may continue without modification and has endorsed the commencement of enrollment of 16 – 17 year old subjects.

Screening Period

Approximately 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.

Laboratory values that are exclusionary can be re-tested once during the screening period. 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 Stool Frequency sub-score, average daily Rectal Bleeding sub-score, and Adapted Mayo Score calculated and meet eligibility criteria before randomization at Baseline.

Sub-Study 1: Phase 2b Induction Study:

At the time of this amendment, Sub-Study 1 has closed and all subjects have completed the 12-week double-blind, placebo-controlled induction period.

Sub-Study 1 Induction Period 1:

Subjects (n = 240) who met eligibility criteria were randomized in a 1:1:1:1 ratio to one of the following double-blinded induction treatment groups (Figure 1):

- Group 1: Risankizumab 1800 mg IV Weeks 0, 4, 8 (n = 60)

- Group 2: Risankizumab 1200 mg IV Weeks, 0, 4, 8 (n = 60)
- Group 3: Risankizumab 600 mg IV Weeks 0, 4, 8 (n = 60)
- Group 4: Placebo IV Weeks 0, 4, 8 (n = 60)

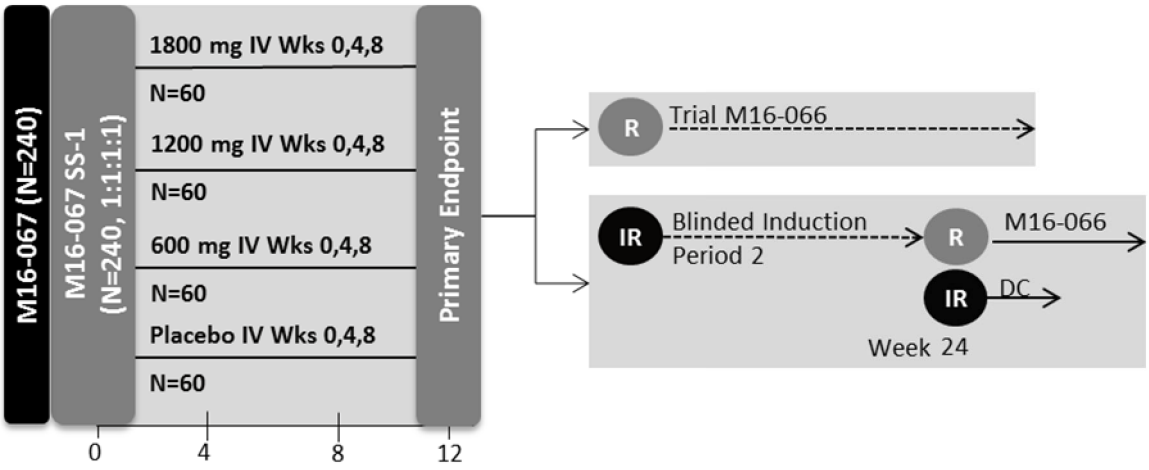
Randomization at Baseline was stratified by baseline steroid use (yes vs no) and baseline Adapted Mayo score (≤ 7 vs > 7). Endoscopy and evaluation of clinical response and remission will occur at Week 12.

After the 240 randomized subjects completed the 12-week Induction Period 1, dose response and exposure response analysis for the key efficacy and safety variables were performed. This analysis is referred to as dose-selection analysis hereafter. Based on this planned analysis, one induction dose of risankizumab will be identified (risankizumab selected dose) for evaluation in Sub-Study 2 (Phase 3 Induction).

Subjects in Sub-Study 1 who achieved clinical response per Adapted Mayo score (locally read Mayo endoscopic subscore) after completion of the 12-week Induction Period 1 were enrolled into maintenance Study M16-066. Clinical response is defined as a decrease from baseline in the Adapted Mayo score ≥ 2 points and ≥ 30% from baseline, PLUS a decrease in rectal bleeding subscore (RBS) ≥ 1 or an absolute RBS ≤ 1.

Subjects who did not achieve clinical response at Week 12, were eligible to receive blinded risankizumab treatment in Induction Period 2 as specified below. Subjects were not eligible to enter Induction Period 2 until the Week 12 endoscopy had been completed.

Figure 1. Induction Period 1 of Study M16-067 Sub-Study 1* (Phase 2b)



DC = discontinue; IR = subjects with inadequate clinical response; IV = intravenous; R = subjects with clinical response; SS-1 = Sub-Study 1

* DBL for Study M16-067 Sub-Study 1 occurs after first randomized 240 subjects complete 12 weeks assessment. After 240 subjects have been enrolled and before the dose has been selected for Sub-Study 2, additional subjects will continue to be enrolled into Sub-Study 1, where they will be assigned to the risankizumab 1800 mg IV Wks 0, 4 and 8 dosing group.

Sub-Study 1 Induction Period 2:

At Week 12, subjects who did not achieve clinical response were randomized by Interactive Response Technologies (IRT) to Induction Period 2, a double-blind, double-dummy 12-week treatment period to evaluate reinduction with risankizumab versus starting maintenance dosing on clinical response status (Figure 2).

Subjects who received IV risankizumab induction were randomized 1:1:1 to:

- Group 1: Risankizumab 1800 mg IV Weeks 12, 16, 20
- Group 2: Risankizumab 360 mg SC Weeks 12, 20
- Group 3: Risankizumab 180 mg SC Weeks 12, 20

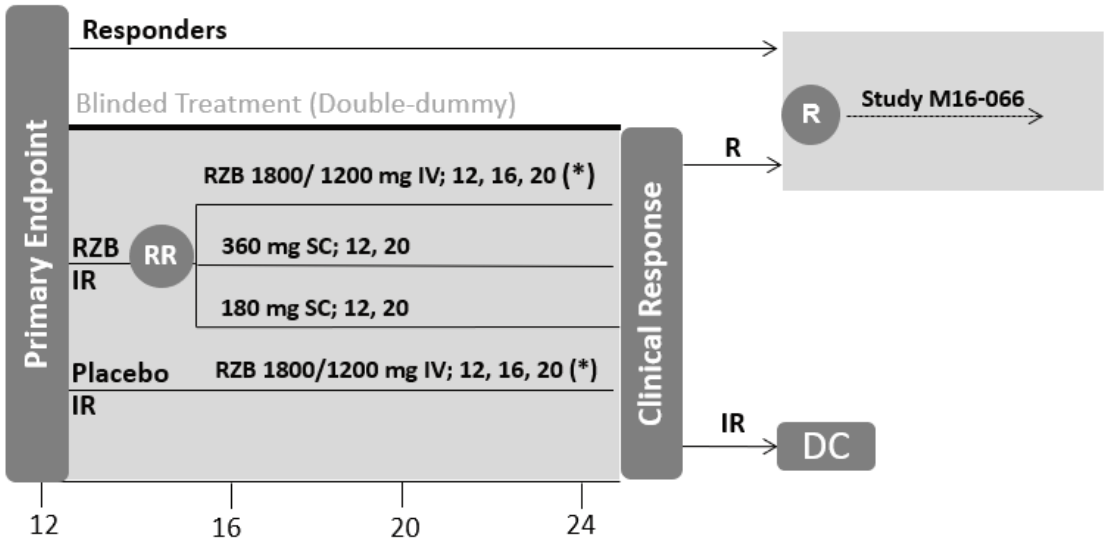
The randomization in Period 2 was stratified by baseline steroid use (yes vs no) and baseline Adapted Mayo score (≤ 7 vs > 7).

Subjects who received IV placebo induction treatment received:

- Group 4: risankizumab 1800 mg IV Weeks 12, 16, 20

Subjects randomized in Groups 1 and 4 received placebo SC and subjects randomized in Groups 2 and 3 received placebo IV, in order to keep the blind. The IV risankizumab dose or matching IV placebo were given at Weeks 12, 16, and 20. The SC risankizumab dose or matching SC placebo were given at Weeks 12, and 20. At Week 24, subjects who received blinded risankizumab treatment during Induction Period 2 were reassessed and underwent a third endoscopy for evaluation of mucosal inflammation. Subjects who achieved clinical response per Adapted Mayo score (locally read Mayo endoscopic subscore) at Week 24 were eligible to enter into the maintenance Study M16-066. Subjects without clinical response at Week 24, as well as all subjects who terminated the study early (including subjects who were eligible for but do not receive blinded risankizumab therapy during Induction Period 2), were discontinued and had a follow-up call 140 days from the last dose of study drug to obtain information on any new or ongoing AEs.

Figure 2. Induction Period 2 of Study M16-067 (Sub-Study 1 and Sub-Study 2)



DC = discontinue; RZB = risankizumab; IR = subjects with inadequate response; IV = intravenous; Plb = placebo; R = subjects with clinical response; RR = re-randomize; SC = subcutaneous

* Subjects who enter from Study M16-067 Sub-Study 1 will receive risankizumab 1800 mg IV. Subjects who enter from Study M16-067 Sub-Study 2 will receive 1200 mg risankizumab IV.

Dose Selection Analysis:

After all 240 randomized subjects completed the 12-week Induction Period 1, dose response and exposure response analysis for the key efficacy and safety variables were performed. Based on this planned analysis, one dose of risankizumab will be identified for further evaluation in Sub-Study 2. During this analysis, Sub-Study 1 enrolled additional subjects in the risankizumab 1800 mg IV Weeks 0, 4 and 8 dosing group, on an open-label basis. The objectives of enrolling these additional subjects are to avoid interrupting the study activities during the analysis period and to support a sufficient number of subjects with clinical response to be enrolled into the maintenance Study M16-066. The data collected from these additional subjects were not included in

the primary analysis of the 240 subjects and will be reported separately as exploratory analysis in the clinical study report.

At the time of this amendment, dose selection enrollment has been closed, 340 subjects were enrolled and received risankizumab 1800 mg IV and all subjects have completed the 12-week double-blind, placebo-controlled induction period.

Subjects follow the same study design described for Sub-Study 1 above (i.e., study visits and subject flow through Induction Period 1 and Induction Period 2). In addition, for subjects where endoscopy cannot be performed at Week 12 or Week 24 due to COVID-19 pandemic restrictions or geo-political conflict in Ukraine and surrounding impacted regions, clinical response will be calculated using Partial Adapted Mayo score (decrease from baseline in the Partial Adapted Mayo score ≥ 1 points and ≥ 30% from baseline, PLUS a decrease in rectal bleeding subscore (RBS) ≥ 1 or an absolute RBS ≤ 1). Subjects who have missing endoscopy due to COVID-19 or geo-political conflict in Ukraine and surrounding impacted regions and achieve clinical response per Partial Adapted Mayo score will be eligible for Study M16-066 Sub-Study 3.

Sub-Study 2: Phase 3 Induction

Sub-Study 2 Induction Period 1:

Once the dose selection analysis in Sub-Study 1 is completed, subjects (n = 966) who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the double-blind 12-week study and randomized in a 2:1 ratio to one of the following treatment groups (Figure 3):

- Group 1: Risankizumab 1200 mg Weeks 0, 4, 8 (n = 644)
- Group 2: Placebo IV Weeks 0, 4, 8 (n = 322)

Sub-Study 2 will enroll approximately 541 bio-IR subjects.

The randomization at Baseline will be stratified by number of prior failed biologics (0, 1 vs > 1), baseline steroid use (yes vs no), and baseline Adapted Mayo score (≤ 7 vs > 7). Endoscopy and efficacy evaluation will occur at Week 12.

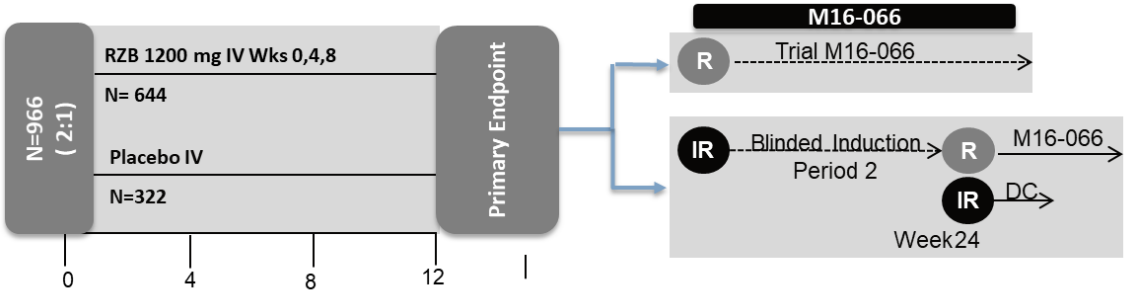
Subjects in Sub-Study 2 who achieve clinical response per Adapted Mayo score (locally read Mayo endoscopic subscore) after completion of the 12-week Induction Period 1 will be enrolled into maintenance Study M16-066. Subjects who do not achieve clinical response at Week 12, may be eligible to enter a 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, except in case of COVID-19 pandemic restrictions or geo-political conflict in Ukraine and surrounding impacted regions.

If endoscopy cannot be performed at Week 12 due to COVID-19 pandemic restrictions or geo-political conflict in Ukraine and surrounding impacted regions, clinical response will be calculated using the Partial Adapted Mayo score.

Subjects with missing endoscopy due to COVID-19 pandemic restrictions or geo-political conflict in Ukraine and surrounding impacted regions and achieve clinical response per Partial Adapted Mayo score at Week 12 may be eligible to enroll in Study M16-066 Sub-Study 3. Subjects who do not achieve clinical response at Week 12, may be eligible to enter a blinded risankizumab treatment in Induction Period 2 as specified below.

Figure 3. Induction Period 1 of Study M16-067 Sub-Study 2 (Phase 3)



DC = discontinue; IR = subjects with inadequate clinical response; R = subjects with clinical response; SS-2 = Sub-Study 2

Sub-Study 2 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 to evaluate reinduction with risankizumab versus starting maintenance dosing on clinical response status (Figure 2).

Subjects who received IV risankizumab will be randomized 1:1:1 to:

- Group 1: Risankizumab 1200 mg IV Weeks 12, 16, and 20
- Group 2: Risankizumab 360 mg SC Weeks 12, and 20
- Group 3: Risankizumab 180 mg SC Weeks 12, and 20

The randomization in Period 2 will be stratified by number of prior failed biologics (0, 1 vs > 1), baseline steroid use (yes vs no), and baseline Adapted Mayo score (≤ 7 vs > 7).

Subjects who received placebo induction treatment will receive:

- Group 4: Risankizumab 1200 mg IV Weeks 12, 16, and 20

Subjects randomized in Groups 1 and 4 will receive placebo SC and subjects randomized in Groups 2 and 3 will received placebo IV, in order to keep the blind. 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 receive blinded risankizumab during the Induction Period 2 will be reassessed and undergo a third endoscopy for evaluation of mucosal inflammation. Subjects who achieve clinical response per Adapted Mayo score (locally read Mayo endoscopic subscore) at Week 24 may be eligible to enter into the maintenance Study M16-066.

If endoscopy cannot be performed at Week 24 due to COVID-19 pandemic restrictions or geo-political conflict in Ukraine and surrounding impacted regions, clinical response will be calculated using the Partial Adapted Mayo score. Subjects with missing endoscopy due to COVID-19 pandemic restrictions or geo-political conflict in Ukraine and surrounding impacted regions who achieve clinical response per Partial Adapted Mayo score at Week 24 may be eligible to enroll into maintenance Study M16-066 Sub-Study 3.

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 receive blinded risankizumab therapy during 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, Corticosteroids, Immunomodulators (Azathioprine [AZA], Mercaptopurine [6-MP], Methotrexate [MTX]), and/or UC-Related Antibiotics

Subjects in Sub-Studies 1 & 2 taking aminosalicylates, immunomodulators, and/or UC-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 UC-related antibiotics after Baseline is prohibited. Decreasing doses of aminosalicylates, immunomodulators, and/or UC-related antibiotics is prohibited during

the study, except in the event of moderate-to-severe treatment related toxicities (e.g., leukopenia or elevated liver enzymes) in the opinion of the investigator. UC-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 (Sub-Studies 1 & 2)

Subjects in Sub-studies 1 & 2 taking oral corticosteroids at Baseline must continue their concomitant treatment at the Baseline dose for the duration of Induction Period 1. Initiation and/or increasing doses of systemic and/or UC related corticosteroids prohibited. Decreasing doses of corticosteroids is prohibited during Induction Period 1, except in the event of moderate-to-severe treatment related toxicities in the opinion of the investigator.

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 and/or increasing the dose back to baseline level is permitted, increasing doses above the Baseline dose is prohibited.

Follow-Up Period/Premature Discontinuation (PD)

Subjects in Sub-Studies 1 & 2 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 M16-066 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 in Sub-Studies 1 & 2 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, unless a subject has a positive COVID-19 molecular (i.e., PCR) test per Exclusion Criterion 30.

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.

If a subject is being rescreened within 14 days (≤ 14 days have passed) from the collection date of the previous screening laboratory testing, repeat laboratory testing for chemistry/hematology, urinalysis, serum pregnancy, and C. *difficile* are not required unless, in the opinion of the Investigator, the subject's health status has changed.

If a subject is being rescreened more than 14 days (> 14 days have passed) from the collection date of the previous screening laboratory testing then chemistry/hematology, urinalysis, serum pregnancy, and C. *difficile* should be repeated during rescreening.

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. All other screening procedures will be repeated unless otherwise stated above. Sites may contact the AbbVie TA MD if there are questions on if subjects should or should not be re-screened.

All subjects need to have their average daily Stool Frequency sub-score, average daily Rectal Bleeding sub-score, and Adapted Mayo score calculated in order to verify eligibility criteria before randomization at Baseline.

5.2 Selection of Study Population

It is anticipated that approximately 1547 subjects with active moderate to severe UC will be enrolled at approximately 400 sites worldwide.

Both bio-IR and non-bio-IR subjects will be included. The bio-IR population will be approximately 1122 subjects and the non-bio-IR population will be approximately 425 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. Males or females ≥ 18 and ≤ 80 years of age, or minimum age of adult consent according to local regulations at the Baseline Visit. Sub-Study 2 only: Where locally permissible, subjects 16 to < 18 years of age who meet the definition of Tanner Stage 5 for development (refer to Appendix G) at the Baseline Visit.
2. Confirmed diagnosis of UC for at least 3 months prior to Baseline. Appropriate documentation of biopsy results consistent with the diagnosis of UC or in the assessment of the Investigator, must be available.
3. Active UC with an Adapted Mayo score of 5 to 9 points and endoscopic subscore of 2 to 3 (confirmed by central review).
4. 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.
    - 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 (2 g/day if controlled release), 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, 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, 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
- Tacrolimus: (for Japan, Taiwan and other countries in Asia with local treatment guidelines that include tacrolimus) documented trough level 5 - 10 ng/mL

- Biologic therapies and tofacitinib for UC:
- Signs and symptoms of persistently active disease despite a history of one or more of the following:
  - At least one 6-week induction regimen of infliximab (≥ 5 mg/kg intravenous [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 golimumab (200 mg SC at Week 0 and 100 mg SC at Week 2),
  - At least one 6-week induction regimen of vedolizumab (300 mg IV at Weeks 0, 2, and 6),
  - At least one 8-week induction regimen of tofacitinib (10 mg PO twice daily)
  - *OR*
- Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit of the above biologics
  - Note: Subjects who discontinued biologics or tofacitinib 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

5. 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.

6. 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 under the legal age of adulthood, a subject's parent or legal guardian must be willing to give written informed consent.

Rationale for Inclusion Criteria

1 – 4	To select the adequate subject population with a disease status representative of the target population for evaluation
5	The impact of risankizumab on pregnancy and reproduction is unknown
6	In accordance with harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

1. Subject with a current diagnosis of Crohn's disease (CD) or IBD-unclassified (IBD-U) or a history of radiation colitis or ischemic colitis.

Concomitant Medications and Treatments

2. Subject on oral UC-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 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 anti-infectives (non-UC-related) within 14 days prior to the Baseline visit. This does not apply to TB prophylaxis.
7. Subject who received any parenteral nutrition within 35 days prior to Baseline.
8. Subject who received any live bacterial or viral vaccination within 35 days (8 weeks for Japan) prior to Baseline.
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 (e.g., infliximab, adalimumab, golimumab, vedolizumab) within 8 weeks prior to Baseline.
    - tofacitinib within 35 days prior to Baseline

- any investigational agent or procedure within 35 days or 5 half-lives prior to the Baseline, whichever is longer or
- subject who is currently enrolled in another interventional clinical study

12. Subject with prior exposure to p40 inhibitors (e.g., ustekinumab [Stelara]) or p19 inhibitors (e.g., risankizumab).
13. Subject has been taking combination of two or more of the following oral budesonide, 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 (i.e., rectal aminosalicylates/corticosteroids), other than required for endoscopy, within 14 days prior to 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.

<u>UC Related</u>

18. Extent of inflammatory disease limited to the rectum as assessed by screening endoscopy.
19. Subject with currently known complications of UC such as:
    - fulminant colitis,
    - toxic megacolon,
    - previous colectomy (total or subtotal),

- or any other manifestation that might require surgery while enrolled in the study.

20. Subject with ostomy or ileoanal pouch.

Safety

21. 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).

22. 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 as identified during Screening,
- Known infection with an intestinal pathogen
- 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 with anti-HCV antibody (HCV Ab)

23. 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.

24. 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.

25. Subject with 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.

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

27. 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.

28. 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.

29. 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's 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. 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.

30. No known active COVID-19 infection. If a subject has signs/symptoms suggestive of COVID-19, they should undergo molecular (i.e., PCR) testing to rule out SARS-CoV-2 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 criteria:

- Symptomatic subjects: At least 14 days have passed since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms
- Asymptomatic subjects: At least 14 days have passed since the first positive molecular (i.e., PCR) test result

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 – 20	To avoid complications of UC that may compromise the evaluations of efficacy and safety
21 – 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 receives 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.

Ulcerative colitis disease specific medications (including but not limited to corticosteroids, aminosalicylates, immunosuppressant agents, and UC-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 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 oral aminosalicylates, immunomodulators, and/or UC-related antibiotics at Baseline must continue their concomitant treatment for the duration of the study.

Initiating and/or increasing doses of oral aminosalicylates, immunomodulators, and/or UC-related antibiotics after Baseline is prohibited. Decreasing doses of oral aminosalicylates, immunomodulators, and/or UC-related antibiotics is prohibited during the study, except in the event of moderate-to-severe treatment related toxicities in the opinion of the investigator. UC-related antibiotics may be discontinued in the blinded Induction Period 2 at the discretion of the Investigator. Rectal aminosalicylates are prohibited from 14 days prior to the screening period and for the entire duration of the study.

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

Concomitant Corticosteroids

Subjects taking oral corticosteroids at Baseline must continue their concomitant treatment at the Baseline dose for the duration of Induction Period 1. Initiation and/or increasing doses of systemic and/or UC related corticosteroids after Baseline is prohibited. Decreasing doses of oral corticosteroids is prohibited during Induction Period 1, 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.

Rectal corticosteroids are prohibited from 14 days prior to the screening period and for the entire duration of the study.

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, pre-medication with diphenhydramine hydrochloride and acetaminophen (or equivalents) is permitted. 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®);
  - Tofacitinib (Xeljanz®);
- Investigational agents (e.g., 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
- Oral or systemic cyclosporine, tacrolimus, or mycophenolate mofetil
- Concomitant cannabis use either recreational or for medical reasons.
- Rectal therapy with any therapeutic enemas or suppositories (i.e., rectal aminosalicylates/corticosteroids), with the exception of those required for endoscopy, is prohibited during the study.
- Apheresis (e.g., Adacolumn apheresis)
- Any parenteral nutrition.
- Any fecal microbial transplant

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 and Pregnancy Testing

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 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, on Baseline (or earlier) 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, initiated at least 1 month prior to Baseline.
  - Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 1 month prior to Baseline.
  - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
  - Vasectomized partner(s), (the vasectomized partner should have received medical assessment of the surgical success and is the sole sexual partner of the 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 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 (discussed in Section 5.3.2.1 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 or geo-political conflict in Ukraine and surrounding impacted regions. 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. Details regarding how informed consent will be obtained and documented are provided in Section 9.3.

Due to the COVID-19 pandemic or the geo-political conflict in Ukraine and surrounding impacted regions, 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 UC-onset date, history of UC 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 therapy for UC 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 a 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.

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 and must include an assessment of EIMs. Symptom-based physical examinations will be performed at all other visits.

The physical examination at the Baseline Visit will serve as the Baseline physical examination for the entire study. Abnormalities noted after the Baseline Visit and first dose of study drug will be evaluated and documented by the Investigator as to whether or not these are adverse events. All findings whether related to an adverse event or part of each subject's medical history will be captured on the appropriate eCRF page.

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

Height will be measured at the Screening visit only (with shoes off). Body weight will be measured at all scheduled visits, as specified in Appendix C. All measurements will be recorded in metric units where applicable.

Blood pressure, pulse rate, respiratory rate and weight should be measured before blood draws are performed.

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 Mycobacterial 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. IRGA 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. 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 pursued according to clinical judgment of Investigator and 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."

- 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 (IBDQ, etc.) are obtained during a visit. Blood draws should be performed before study drug administration.

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, 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 or the geo-political conflict in Ukraine and surrounding impacted regions 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	<u>General:</u> Sodium Potassium Chloride Bicarbonate (CO_2) Urea (BUN) Creatinine Glucose <u>Additional Chemistry Tests:</u> Calcium Phosphate Total Protein Albumin Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline Phosphatase Gamma-Glutamyl Transferase (GGT/γ-GT) Bilirubin Total and Direct <u>Lipid Panel:</u> Cholesterol (total, LDL, and HDL) Triglycerides <u>Additional Calculations:</u> eGFR by simplified 4-MDRD (estimated by CKD-EPI formula; for Japan)[c]	HBsAg anti-HBs Ab anti-HBc Ab HBV DNA PCR reflex only anti-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,f] Histamine[e,f]
Stool Samples:		**Biopsy**
C. difficile toxin Fecal calprotectin (FCP)		Histopathology scoring
PK/Immunogenicity:		**Biomarkers:**
Serum risankizumab Serum anti-drug antibodies (ADA)[e] Serum neutralizing antibodies (nAb)		High-Sensitivity C-Reactive Protein (hs-CRP)
	Coagulation	**Optional Biomarkers:**
	INR[d]	Blood, tissue and stool will be collected for optional exploratory research in countries/sites that allow it

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 listed show leukocytes, nitrite, protein, ketones, or blood greater than negative or glucose greater than normal.

Table 1. Clinical Laboratory Tests (Continued)

c. Calculated by the central laboratory.
d. INR test only drawn if ALT or AST > 3 × ULN (upper limit of normal) and Total Bilirubin ≤ 2 × ULN. Please refer to Section 5.4.1 for further information.
e. To be done with the occurrence of a suspected anaphylactic reaction. Refer to anaphylaxis testing Section 5.3.1.1 below. For ADA these samples are collected in addition to those specified in Appendix C.
f. Tryptase and histamine will not be taken in China.

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 and China 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. In cases where the recurrence of HBV-DNA is observed, the subject should be discontinued from the study drug. Retesting at Week 12 and Week 24 is not necessary for subjects that 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 an 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, in all countries except in China 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:

If the investigator has a reasonable suspicion of a gastrointestinal infection they should ensure this has been excluded prior to screening the subject.

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. If the fecal calprotectin sample is collected during the Screening period it may be used as the Baseline All stool samples should be collected before any bowel preparation for endoscopy is started and returned to the site within 3 days of collection.

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 (IBDQ, etc.), and vital sign determinations are obtained and before study drug administration during a visit. Local laboratory or site testing for hs-CRP is not allowed.

Full Mayo Score, Adapted Mayo Score, Adapted Partial Mayo Score

Data from the subject diaries will be collected in order to calculate Full Mayo Score, Adapted Mayo Score, and Adapted Partial Mayo Score at the time points indicated in Appendix C.

Detailed information about Full Mayo Score, Adapted Mayo Score, and Adapted Partial Mayo Score can be found in Appendix E.

Whenever possible, the same physician (Investigator or Sub-Investigator) should determine the Physician's Global Assessment (PGA) subscore for an individual subject through the duration for the study. The directions for capturing the stool frequency

subscore, rectal bleeding subscore, and PGA subscores of the Full Mayo Score, Adapted Mayo Score, and Adapted Partial Mayo Score are described in Appendix F.

Endoscopy

An endoscopy will be performed on the following visits:

- During Screening*
- Week 12/PD
- Week 24 (subjects in Induction Period 2 only)

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 Week 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:

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

A full colonoscopy will be performed at Screening unless the subject underwent a full colonoscopy within 12 months prior to Screening. There must be appropriate documentation available to confirm the diagnosis, extent of disease, and to exclude dysplasia and colon cancer. If this is available, the screening endoscopy may be either a full colonoscopy or a flexible sigmoidoscopy. All other endoscopies may be flexible sigmoidoscopies or colonoscopies at the discretion of the investigator.

All endoscopies will be performed and recorded at the site in a video format. Videos from subjects with eligible Mayo endoscopic sub-scores during Screening and all videos from subjects at Week 12 and Week 24 will be sent to a central review vendor and scored as described in the central review charter. Endoscopies will be evaluated using the Mayo endoscopic subscore. The Mayo endoscopic subscore, including the presence or absence of friability will be documented by the endoscopist at the site and maintained in the subject's source documents. If, in the assessment of the site endoscopist, the Screening endoscopy does not indicate an endoscopy subscore of 2 or 3 or the extent of inflammation is limited to the rectum, per eligibility requirements, the subject should be screen-failed and the video should not be sent for central reading. In addition to the Mayo endoscopy subscore, the central reader will assess the endoscopy findings using the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) scoring system for additional exploratory analyses.

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 to evaluate clinical response for enrollment in maintenance Study M16-066, as well as for stratification based on clinical remission for maintenance Study M16-066.

There will be a window of ± 7 days to conduct the endoscopy.

If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic or the geo-political conflict in Ukraine and surrounding impacted regions prevent the subject from performing endoscopy at the study site at Week 12 or Week 24, if possible, arrange for subjects to have endoscopy done at an alternate facility. The endoscopist at the alternate facility should be trained using the study training materials. Endoscopy score should be read by an endoscopist already trained on the protocol requirements at the study site.

Every effort should be made to conduct endoscopy at Week 12 or Week 24, however, if endoscopy cannot be performed due to the COVID-19 pandemic restrictions or the

geo-political conflict in Ukraine and surrounding impacted regions, clinical response will be calculated using the Partial Adapted Mayo score.

Biopsy During Endoscopy

The following biopsies should be obtained during the study:

Biopsy for histopathology Scoring: All subjects will have two biopsies taken from an area of the rectosigmoid segment of the colon that represents the general degree of mucosal inflammation for histopathological scoring at each visit with endoscopy. The same histopathological biopsy samples collected for the main study may be used for exploratory research (Section 5.3.1.2) only if subjects provide additional consent.

Optional biopsy for RNA analysis: subjects who consent to participate in the optional RNA biopsies sub-study, will have two additional biopsies taken from an area of the rectosigmoid colon that represents the general inflammation in the segment at each visit with endoscopic procedures.

Histopathology scoring and RNA analysis biopsies, will be sent to the central laboratory for further analysis, except in China. The central laboratory chosen for this study will provide instructions regarding the collection, processing and shipping of these samples.

Additionally, appropriate documentation of biopsy results consistent with the diagnosis of UC, 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 observed 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.

The signed pathology report will be monitored by the responsible Clinical Research Associate (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 M16-066.

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.

- IBDQ – Inflammatory Bowel disease Questionnaire

- WPAI-UC – Work Productivity and Activity Impairment Questionnaire Ulcerative Colitis
- FACIT-F – Functional Assessment of Chronic Illness Therapy-Fatigue
- EQ-5D-5L – European Quality of Life 5 Dimensions
- SF-36 – Short Form 36
- PGIC – Patient Global Impression of Change
- PGIS – Patient Global Impression of Severity
- UC-SQ – UC-Symptom Questionnaire

Due to the COVID-19 pandemic and any local restrictions or the geo-political conflict in Ukraine and surrounding impacted regions, 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. 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. The patient should be assessed for the presence of discontinuation criteria in Section 5.4.1.

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

Interruption/Discontinuation of Study Drug Due to COVID-19 or Geo-Political Conflict in Ukraine and Surrounding Impacted Regions

Continuation of study drug dosing due to a subject with COVID-19 must be discussed with the AbbVie medical contact, along with the possibility of premature discontinuation from the study drug dosing period. Follow subsequent protocol Section 5.4.1 for subjects who discontinued study drug.

Delays in study drug dosing due to the geo-political conflict in Ukraine and surrounding impacted regions must be discussed with the sponsor medical contact, along with the possibility of premature discontinuation from study drug. The investigator should contact the sponsor medical contact before discontinuing a subject from the study for a reason other than described in the protocol to ensure all acceptable mitigation steps have been explored.

5.3.1.2 Collection and Handling of Optional Exploratory Research Samples

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

AbbVie (or people or companies working with AbbVie) will store the optional 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 UC and related conditions continues, but for no longer than 20 years after study completion.

The following samples will be collected according to Appendix D from each subject who consents to provide samples:

- 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 and immunohistochemical analyses.

Samples will be shipped to AbbVie or a designated laboratory for 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 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 central lab requisition form.

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

Endpoints definition (Substudy 1 & 2):

- **Clinical Remission per Adapted Mayo:** stool frequency subscore (SFS) ≤ 1, and not greater than baseline, rectal bleeding subscore (RBS) = 0, and endoscopic subscore ≤ 1 without the evidence of friability
- **Clinical Response per Adapted Mayo:** decrease from Baseline ≥ 2 points and ≥ 30%, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1
- **Clinical Response per Partial Adapted Mayo (without endoscopy):** decrease from Baseline ≥ 1 points and ≥ 30%, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1
- **Clinical Remission per Full Mayo:** Full Mayo score ≤ 2 with no subscore > 1
- **Endoscopic Improvement:** endoscopy subscore of 0 or 1 without the evidence of friability
- **Endoscopic Remission:** endoscopic subscore = 0
- **Histologic Remission:** Geboes score of < 2.0
- **Histologic Endoscopic Mucosal Remission (HEMR):** Endoscopy subscore of 0 and Geboes score < 2.0
- **Histologic Endoscopic Mucosal Improvement (HEMI):** endoscopic subscore of 0 or 1 without the evidence of friability and Geboes score ≤ 3.1

Note: Evidence of friability during endoscopy in subjects with otherwise "mild" endoscopic activity will confer an endoscopic subscore of 2.

5.3.3.1 Primary Variable

The achievement of clinical remission per Adapted Mayo score at Week 12.

5.3.3.2 Secondary Variable

Secondary Endpoints for Sub-Study 1 (Phase 2b):

1. The achievement of endoscopic improvement at Week 12
2. The achievement ofclinical remission per Full Mayo score at Week 12 in subjects with a Full Mayo score of 6 to 12 at Baseline
3. The achievement of clinical response per Adapted Mayo score at Week 12
4. The achievement of clinical response per Partial Adapted Mayo score at Week 4
5. The achievement of endoscopic remission at Week 12
6. Occurrence of hospitalizations through Week 12
7. The achievement of HEMR at Week 12
8. Change from Baseline to Week 12 in UC-Symptom Questionnaire (UC-SQ)
9. Change from Baseline to Week 12 in Inflammatory Bowel Disease Questionnaire (IBDQ)
10. Change from Baseline to Week 12 in Short Form-36
11. Change from Baseline to Week 12 in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)
12. UC-related surgeries through Week 12

Secondary Endpoints for Sub-Study 2 (Phase 3)

1. The achievement of clinical response per Adapted Mayo score at Week 12
2. The achievement of endoscopic improvement at Week 12
3. The achievement of histologic endoscopic mucosal improvement (HEMI) at Week 12
4. The achievement of endoscopic remission at Week 12
5. The achievement of clinical response per Partial Adapted Mayo score at Week 4
6. The achievement of no bowel urgency at Week 12
7. The achievement of no abdominal pain at Week 12
8. The achievement of histologic endoscopic mucosal remission (HEMR) at Week 12
9. Change from Baseline to Week 12 in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)
10. Change from Baseline to Week 12 in Inflammatory Bowel Disease Questionnaire (IBDQ) total score
11. Occurrence of UC-related hospitalizations through Week 12
12. The achievement of no nocturnal bowel movements at Week 12
13. The achievement of no tenesmus at Week 12
14. Change from Baseline to Week 12 in number of fecal incontinence episodes per week
15. Change from Baseline to Week 12 in number of days per week with sleep interrupted due to UC symptoms.

Additional Endpoints for Sub-study 2:

Induction Period 1

- The achievement of SFS = 0, RBS = 0, and endoscopic subscore = 0 at Week 12
- The achievement of SFS ≤ 1 at Week 4, Week 8, Week 12 respectively
- The achievement of RBS = 0 at Week 4, Week 8, Week 12 respectively
- The achievement of clinical response per Partial Adapted Mayo score at Week 8, Week 12 respectively
- Change from Baseline to Week 12 in Full Mayo score
- Change from Baseline in SFS at Week 4, Week 8, Week 12 respectively
- Change from Baseline in RBS at Week 4, Week 8, Week 12 respectively
- Change from Baseline in hs-CRP at Week 4, Week 8, Week 12 respectively
- Change from Baseline in FCP at Week 4, Week 12 respectively
- Change from Baseline to Week 12 in UCEIS
- The achievement of histologic remission at Week 12
- Change from Baseline to Week 12 in European Quality of Life 5 Dimensions (EQ-5D-5L)
- Change from Baseline to Week 12 in Work Productivity and Impairment Questionnaire – UC (WPAI-UC)
- Change from Baseline to Week 12 in UC-SQ
- The achievement of IBDQ remission (IBDQ total score ≥ 170) at Week 12
- The achievement of IBDQ response (increase of IBDQ ≥ 16 from Baseline) at Week 12
- Time to clinical response per Partial Adapted Mayo
- Change from baseline in PGIS at Week 4, Week 8, Week 12 respectively
- PGIC at Week 4, Week 8, Week 12 respectively
- UC-related surgeries through Week 12
- The achievement of clinical response per Adapted Mayo score at Week 12 in subjects with pancolitis at Baseline

- Change from Baseline to Week 12 in Short Form-36 (SF-36)
- The achievement of clinical remission per Full Mayo score at Week 12 in subjects with a Full Mayo score of 6 to 12 at Baseline

Induction Period 2

- The achievement of clinical remission per Adapted Mayo at Week 24
- The achievement of clinical remission per Full Mayo score at Week 24 in subjects with a Full Mayo score of 6 to 12 at Baseline
- The achievement of clinical response per Adapted Mayo score at Week 24
- The achievement of no abdominal pain at Week 24
- The achievement of no bowel urgency at Week 24
- The achievement of endoscopic remission at Week 24
- The achievement of endoscopic improvement at Week 24
- Change from Baseline to Week 24 in Inflammatory Bowel Disease Questionnaire (IBDQ) total score
- Change from Baseline to Week 24 in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)
- The achievement of histologic endoscopic mucosal improvement at Week 24
- The achievement of no nocturnal bowel movements at Week 24
- The achievement of no tenesmus at Week 24
- Change from Baseline to Week 24 in number of fecal incontinence episodes per week
- Change from Baseline to Week 24 in number of days per week with sleep interrupted due to UC symptoms
- The achievement of clinical response per Adapted Mayo score at Week 24 in subjects with pancolitis at Baseline
- Occurrence of UC-related hospitalizations through Week 24
- Change from Baseline to Week 24 in Short Form-36 (SF-36)
- The achievement of SFS ≤ 1 at Week 16, Week 20, Week 24 respectively
- The achievement of RBS = 0 at Week 16, Week 20, Week 24 respectively

- Change from Baseline in Partial Adapted Mayo score at Week 16, Week 20, Week 24 respectively
- Change from Baseline in SFS at Week 16, Week 20, Week 24 respectively
- Change from Baseline in RBS at Week 16, Week 20, Week 24 respectively
- Change from Baseline in hs-CRP at Week 24
- Change from Baseline in FCP at Week 24
- Time to clinical response per Partial Adapted Mayo
- Change from baseline in PGIS at Week 16, Week 20, Week 24 respectively
- PGIC at Week 16, Week 20, Week 24 respectively

5.3.4 Safety Variables

Incidence of adverse events, changes in vital signs, electrocardiogram, 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 as outlined in Appendix C. Serum risankizumab concentrations will be summarized at each time point for each dosing regimen using descriptive statistics. As appropriate, population pharmacokinetic analysis 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 and/or any additional analyses may be performed.

5.3.6 Optional Exploratory Research 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 UC 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. 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 adverse event, 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 adverse event(s), as determined by the Investigator.
- 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 not in the best interest of the subject to enter Induction Period 2.*
- The subject requests withdrawal from the study.
- The subject experiences a severe systemic hypersensitivity infusion/injection reaction or anaphylaxis.
- 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 Therapeutic Area Medical Director.
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk as determined by the AbbVie Therapeutic Area Medical Director.
- 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 trial, as determined by the Investigator, in consultation with the AbbVie Therapeutic Area Medical Director.
- 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 Premature Discontinuation 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 medication 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 M16-066.

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 that 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.

During the COVID-19 pandemic or the geo-political conflict in Ukraine and surrounding impacted regions, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and 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.

The investigator should contact the sponsor medical contact before discontinuing a subject from the study for a reason other than "planned per protocol," to ensure all acceptable mitigation steps have been explored.

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

Sub-Study 1

Each dose of blinded study drug (1800 mg risankizumab, 1200 mg risankizumab, 600 mg risankizumab, or placebo) was administered intravenously to subjects during Induction Period 1. Blinded risankizumab or placebo were administered intravenously at the Baseline visit, Week 4, and Week 8. Subjects who did not achieve clinical response at Week 12 were eligible for Induction Period 2 with blinded risankizumab.

During Induction Period 2, each dose of blinded study drug (1800 mg risankizumab, 360 mg risankizumab or 180 mg risankizumab) was administered both intravenously and subcutaneously. Blinded risankizumab was administered either intravenously at Weeks 12, 16 and 20 or subcutaneously at Weeks 12 and 20.

Subjects who were enrolled during the dose selection period were assigned to the 1800 mg risankizumab arm.

Sub-Study 2

Each dose of blinded study drug (risankizumab 1200 mg or placebo) will be administered intravenously for approximately 2 hours to the subject during Induction Period 1 at the Baseline, Week 4 and Week 8 visits.

Subjects who do not achieve clinical response at Week 12 will be eligible for Induction Period 2 with blinded risankizumab. Each dose of blinded study drug (risankizumab 1200 mg, 360 mg risankizumab or 180 mg risankizumab) will be administered either intravenously at Weeks 12, 16 and 20 (risankizumab 1200 mg) or subcutaneously at Weeks 12 and 20 (risankizumab 360 mg or 180 mg). In order to keep the blind, subjects allocated to intravenous risankizumab will receive matching placebo subcutaneously at Week 12 and 20, and subjects allocated to subcutaneous risankizumab will receive matching placebo intravenously at Weeks 12, 16 and 20.

If the 1200 mg dose is discontinued due to any reason, subjects will continue to enroll into the study and be randomized to 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.

5.5.2 Identity of Investigational Product(s)

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)	NA	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)	NA	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

Blinded 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 their 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 temperature excursions must be reported to the Sponsor immediately. Sites are responsible to report site 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

In Sub-Study 1 (Phase 2b induction), 240 subjects who met all the inclusion and none of the exclusion criteria defined in Section 5.2.1 and Section 5.2.2 were centrally randomized in a 1:1:1:1 ratio to receive one of four treatment groups at Baseline in a double-blind manner during the Induction Period 1 of the study.

After 240 randomized subjects completed the 12-week induction period, a dose-selection analysis was performed. During the analysis period additional subjects were enrolled into Group 1 – risankizumab 1800 mg IV Wks 0, 4 and 8 of Sub-Study 1 in an open-label fashion.

Randomization at Baseline for Sub-Study 1 was stratified by baseline steroid use (yes vs no), and baseline Adapted Mayo score (≤ 7 vs > 7).

In Sub-Study 2 (Phase 3 induction), approximately 966 adult subjects who meet all of the inclusion criteria and none of the exclusion criteria as defined in Section 5.2.1 and Section 5.2.2 will be centrally randomized in a 2:1 ratio to receive one of two treatment groups at Baseline in a double-blind manner during Induction Period 1 of the study.

Randomization at Baseline for Sub-Study 2 will be stratified by number of prior failed biologics (0, 1 vs > 1), baseline steroid use (yes vs no), and baseline Adapted Mayo score (≤ 7 vs > 7).

At Week 12, subjects who do not achieve clinical response (in both Sub-Studies 1 and 2) 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.

Randomization in Period 2 of Sub-Study 1 and 2 will be stratified by the same factors as in Period 1 of Sub-Study 1 and 2 respectively.

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 medication should not be re-dispensed to any subject.

All subjects will keep the same unique subject identification number throughout the study.

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) as well as the Investigator, 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 (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 launch.

A separate DMC charter will be approved by AbbVie and the DMC members before the first subject is enrolled 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 time of this amendment, the DMC has provided recommendation that the study may continue without modification and has endorsed the commencement of enrollment of 16 – 17 year old subjects. 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.

For China only: The first 12 subjects enrolled in China will be monitored at an individual subject level. Also, the initial 12 subjects enrolled in China will be monitored on site for 2 hours after completion of the infusion. Once the DMC assess the safety results of the initial 12 subjects with no safety concerns identified, all sites in China will be notified that subjects should be monitored as necessary after completion of the infusion. In addition, 16 to < 18 year olds will not be enrolled in China until the DMC has reviewed the first 12 adult subjects enrolled in China and provided endorsement.

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 DMC reviews the data in an unblinded manner, including adjudicated cardio-cerebrovascular events and anaphylactic reactions.

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 will verify that study drug supplies are received intact, at the appropriate temperature, and in the correct amounts from the depot. This will be documented by signing and dating the Proof of Receipt (POR) or similar document and by registering the arrival of drug through the IRT. The original POR and the IRT confirmation sheet 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 but not limited to date received, the lot number, kit number(s), date dispensed, subject number, and the identification of the person dispensing the drug. All empty/used study drug packaging will be inventoried by the site. Site staff will complete study drug accountability via IRT by using source documents, and by visually inspecting the packaging whenever possible.

After drug accountability and monitor reconciliation has been completed, used packaging and unused study drug will be destroyed on site according to local procedures or

regulations or returned to the destruction depot (for those sites that do not meet AbbVie's documentation requirements for on-site destruction).

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.

Site monitors will reconcile the site's processes, source documents, IRT or site accountability records, and destruction records to assure site compliance.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

Risankizumab is a selective anti IL-23 inhibitor that may provide an improved clinical benefit to risk profile in UC patients. The proposed study is a Phase 2b/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 UC who have had inadequate response or intolerance to immunosuppressants, corticosteroids and/or biologic therapies and tofacitinib.

The study comprises 2 sub-studies with a 12 week induction period. Sub-Study 1 is a Phase 2b dose-ranging study designed to evaluate the efficacy, pharmacokinetics, and safety of three different risankizumab doses (IV, 600 mg, 1200 mg, or 1800 mg, Q4W) versus placebo. Sub-Study 2 is a Phase 3 study designed to evaluate the efficacy and safety of risankizumab (IV, 1200 mg Q4W) versus placebo. For subjects not in clinical response at Week 12 in either Sub-Study 1 or Sub-Study 2, an optional blinded Induction Period 2 (IV, 1800 mg [Sub-Study 1] or 1200 mg [Sub-Study 2], 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 Period 1 or Induction Period 2 can enter maintenance Study M16-066 for an additional 52 weeks of treatment, with additional OL treatment with risankizumab being offered through approval.

At this time, a placebo-controlled study is necessary for registrational purposes. A comparative study utilizing a placebo control design provides an unbiased assessment of the efficacy and safety profile of risankizumab.

For clinical operational efficiency, AbbVie proposes to conduct this operationally seamless Phase 2b/3 study. Data from Phase 2b and Phase 3 portions of the study will be analyzed separately (i.e., operational seamless) for the efficacy endpoints and will not be combined for statistical inference.

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 Ulcerative colitis. 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 UC.

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 UC 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 biologic therapies.

5.6.4 Selection of Doses in the Study

Sub-Study 1:

Sub-Study 1 is a Phase 2b dose finding study. Doses (600 mg, 1200 mg, and 1800 mg) of IV risankizumab given every 4 weeks (Q4W) were 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 Crohn's disease (CD).

Results from the placebo controlled Study 1311.6 in subjects with CD 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 at 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. In subjects with UC, given the higher inflammatory burden, protein loss through ulcers, and increased proteolytic activity compared to subjects with CD, an 1800 mg dose will also be tested.

The evaluation of higher doses (1200 mg and 1800 mg IV Q4w) will facilitate a more robust characterization of the dose-response and exposure-response relationship for UC related efficacy endpoints. Inclusion of doses up to 1800 mg IV 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 UC. Furthermore, truncated preliminary results from an ongoing heathy volunteer study (Study 1311.16) in six Japanese subjects suggest that a single IV dose of 1200 mg Risankizumab was safe and well tolerated up to 4 weeks post-dosing. Preliminary safety and tolerability data from another planned heathy volunteer study in Japanese and Caucasian subjects (six subjects each) will also be available following a single dose of 1800 mg IV risankizumab prior to initiating this study. Finally, the projected steady state exposures for the 1800 mg IV risankizumab Q4w regimen in subjects with UC are covered by safety margins of ~1 and ~2.3 for C_{max} and AUC_{0-28} days respectively (relative to NOAEL identified in the 26 week GLP toxicology study).

Sub-Study 2:

Sub-Study 2 (Phase 3 induction study) will evaluate IV risankizumab 1200 mg during induction. The selection of this dose was informed by the analysis of safety and efficacy

data, as well as the exposure-response relationship of efficacy from Sub-Study 1 (Phase 2b dose finding study) where risankizumab doses of 1800 mg IV, 1200 mg IV, and 600 mg IV were evaluated. All three risankizumab doses achieved higher clinical remission rates per Adapted Mayo Score (primary endpoint) at Week 12 compared to placebo; both the 1200 mg and 1800 mg groups achieved nominal *P*-values < 0.1 (two-sided) based on pairwise comparisons. All three risankizumab dose groups also achieved higher response rates compared to placebo for other selected endoscopic, clinical and composite endpoints. Exposure-response analyses predicted greater efficacy for key endpoints (clinical remission, clinical response, and endoscopic remission) with higher risankizumab exposures and both doses of 1200 mg and 1800 mg are expected to provide better efficacy than 600 mg for subjects with UC during the induction period. While incremental efficacy is predicted with doses increasing from 1200 mg to 1800 mg, the magnitude of the difference is modest and 1800 mg is not expected to provide clinically meaningful benefit beyond 1200 mg for induction. No new safety risks were identified and the overall safety findings were consistent with the known safety profile of risankizumab.

Induction Period 2:

Induction Period 2 will evaluate IV (1800 mg [Sub-Study 1] or 1200 mg [Sub-Study 2] 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 versus starting maintenance regimen 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. A higher dose of 360 mg Q8W is proposed to provide exposures reasonably separated with 180 mg Q8w dose to characterize the exposure-

response relationship during maintenance phase with a potential of 360 mg Q8w dose to maintain higher response compared to 180 mg Q8w dose.

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 another 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 (AE) 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 case report form.

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 a hepatic related AE
- A 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 F 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 for 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

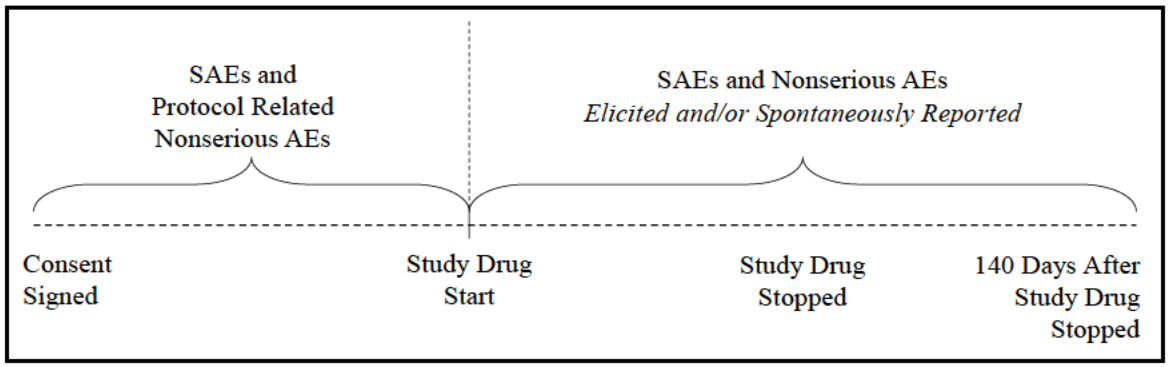
Events that are clearly consistent with progression of the underlying disease (UC) are considered an expected outcome for this study and will not be subject to expedited reporting.

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 4.

Figure 4. 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
[redacted]
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]
Pharmaceutical Development
1 North Waukegan Road
North Chicago, IL 60064, USA
Telephone Contact Information:
Office:
Mobile:
Email:

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director (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 Study Population

Certain events are anticipated to occur in the study population as known consequences of UC (e.g., as symptoms or due to disease progression) independent of drug exposure. These events are listed in Table 3. These AEs 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 UC population hence considered expected for reporting.

Table 3. Common Events Associated with UC

Abscesses
• Anal abscess • Rectal abscess • Perirectal abscess
Others
• Anal fissure • Ulcerative colitis • Ulcerative colitis aggravated • Colitis • Megacolon

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. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly 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 all 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 Adjudication Committee Charter. Dedicated eCRFs will be used for events of MI-unstable angina, stroke-TIA, death and CHF. 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 suspected anaphylactic reactions and will remain blinded to treatment allocation. The events that are adjudicated and the adjudication process will be detailed in the 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 adverse events 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 or geo-political conflict in Ukraine and surrounding impacted regions, after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (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 of Sub-Study 1 (Phase 2b induction) was to characterize the pharmacokinetics, dose-response, efficacy, and safety of risankizumab compared to placebo in subjects with moderately to severely active ulcerative colitis in

order to identify one induction dose of risankizumab for further evaluation in Sub-Study 2 (Phase 3 induction).

The objective of the statistical analyses of Sub-Study 2 (Phase 3 induction) is to evaluate the efficacy and safety of the induction dose of risankizumab 1200 mg IV compared to placebo in subjects with moderately to severely active ulcerative colitis.

Statistical analysis for demographics (where collection is allowed) and baseline characteristics, prior and concomitant medications, and the key efficacy endpoints and safety endpoints are included in this section. More specific details of the statistical analyses for the key efficacy and safety endpoints to address the primary and secondary objectives will be further described and fully documented in the Statistical Analysis Plan (SAP) of each sub-study.

The impact of missing data due to COVID-19 or geo-political conflict in Ukraine and surrounding impacted regions will be monitored and detailed approaches for handling missing data due to COVID-19 infection or logistical restriction or geo-political conflict in Ukraine and surrounding impacted regions will be described in the SAP.

8.1.1 Datasets for Analysis

8.1.1.1 Intent-to-Treat Population

Sub-Study 1 – Induction Period 1: The Intent-to-Treat (ITT) Population for Induction Period 1 in Sub-Study 1 includes all randomized subjects who received at least one dose of study drug during Induction Period 1 in Sub-Study 1 (denoted as ITT1A) at the time of dose-selection analysis. The set of all the additional subjects who enrolled into risankizumab 1800 mg IV treatment group after 240 subjects were randomized during the dose-selection period is denoted as ITT1B. The ITT for Induction Period 1 in Sub-Study 1 will be denoted as ITT1 and will be the combination of ITT1A and ITT1B.

Sub-Study 2 – Induction Period 1: The ITT for Induction Period 1 in Sub-Study 2 includes all randomized subjects who received at least one dose of study drug from Induction Period 1 in Sub-Study 2 (denoted as ITT2).

For the ITT in Induction Period 1 in each sub-study, subjects will be analyzed in a treatment group based on the randomization or re-randomization schedule, regardless of the treatment actually received. The demographic (where collection is allowed)/baseline and efficacy analyses for Induction Period 1 in each sub-study will be based on the corresponding ITT.

Sub-Study 1 and Sub-Study 2 Induction Period 2:

Subjects who received at least one dose of risankizumab during Induction Period 2 in both Sub-Study 1 (denoted as ITT1_P2) and Sub-Study 2 (denoted as ITT2_P2) will be analyzed separately for exploratory purpose. More details will be specified in the SAP of each sub-study.

8.1.1.2 Safety Population

For the safety population in each sub-study, subjects will be analyzed in a treatment group based on the treatment actually received. The safety analysis in each sub-study will be based on the corresponding safety population.

Sub-Study 1 – Induction Period 1

The Safety Population for Induction Period 1 in Sub-Study 1 includes all subjects who receive at least one dose of study drug during Induction Period 1 in Sub-Study 1 (denoted as SAS1A) at the time of dose-selection analysis. The set of all the additional subjects who enrolled into risankizumab 1800 mg IV treatment group after 240 subjects were randomized during the dose-selection period is denoted as SAS1B. The Safety Population for Induction Period 1 in Sub-Study 1 will be denoted SAS1 and will be the combination of SAS1A and SAS1B.

Sub-Study 2 – Induction Period 1

The Safety Population for Induction Period 1 in Sub-Study 2 includes all subjects who received at least one dose of study drug during Induction Period 1 in Sub-Study 2 (denoted as SA2).

Sub-Study 1 and Sub-Study 2 Induction Period 2:

Subjects who received at least one dose of risankizumab during the Induction Period 2 after Week 12 in both Sub-Study 1 (denoted as SA1_P2) and Sub-Study 2 (denoted as SA2_P2) will be analyzed separately for exploratory purpose.

Sub-Study 2 – All Risankizumab:

SA2_ALL includes all subjects who received at least one dose of risankizumab any time during the Sub-Study 2.

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): Subjects who prematurely discontinue the study prior to efficacy assessment or with missing values at Week 12 or Week 24 in Induction Period 2 will be considered non-responders for the categorical efficacy endpoints.

Non-Responder Imputation while incorporating Multiple Imputation (MI) to handle missing data due to COVID-19 or geo-political conflict in Ukraine and surrounding impacted regions (NRI-MI): Subjects who do not have an evaluation at a scheduled assessment visit (either due to missing assessment or due to early withdrawal from the study) will be considered as non-responders for the visit. The only exception is that missing data due to COVID-19 infection or logistical restrictions related to the COVID-19 pandemic or due to geo-political conflict in Ukraine and surrounding impacted regions will be handled by MI.

Observed Cases (OC): No impute values for missing evaluations, and thus a subject who did not have an evaluation on a scheduled visit will be excluded from the OC analysis for that visit.

Multiple Imputation Incorporating Return-to-Baseline (RTB-MI) to handle missing data in the analysis of continuous endpoints: to handle the potential departures from the missing-at-random (MAR) assumption for visits after intercurrent events, the Return-to-Baseline (RTB) approach, which assumes subjects with intercurrent events will have a washout "return to baseline" of any potential treatment effect, will be performed.

As Observed (AO): The AO 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 AO analysis for that visit. AO will include all values collected in the study regardless of intercurrent events.

Tipping Point analysis will be performed as sensitivity analysis for the primary endpoint in Sub-Study 2 to handle the potential departures from the missing-at-random (MAR) assumption.

More details about missing data imputation will be specified in SAP of each sub-study.

8.1.3 Subject Disposition

The number and percentage of subjects who are enrolled, randomized, who received at least one dose of study drug, who completed the study treatment, and who prematurely discontinued, will be summarized overall and for each investigational site by treatment group, as well as for all subjects combined, for each Induction Period in each sub-study.

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 based on corresponding ITT for each Induction Period in each sub-study. 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 will be summarized using descriptive statistics by treatment group for the corresponding ITT for each Induction Period in each sub-study.

Baseline information of each treatment group in each sub-study will be summarized with respect to demographic and baseline variables such as age, gender, race, ethnicity, height, weight, BMI, duration of disease, vital signs (blood pressure, heart rate, and temperature), and planned efficacy assessments such as Adapted Mayo Score, Full Mayo Score, Partial Adapted Mayo Score, hs-CRP, etc.

Summary statistics for continuous variables will include the number of observations, mean, standard deviation, median, and range for each treatment group, in each sub-study. 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 tabulated by treatment group for corresponding ITT for each Induction Period in each sub-study. No statistical test will be performed.

Concomitant drugs will be summarized with frequencies and percentages by treatment group for corresponding ITT in each sub-study using the World Health Organization (WHO) Drug Dictionary.

A subject who reports two or more uses of the same concomitant medication will be counted only once within each generic name. A subject with concomitant medications with more than one generic name will be counted only once in the overall total.

8.1.6 Efficacy Analysis

All analyses for the primary and secondary efficacy endpoints will be based on corresponding ITT in each sub-study as defined in Section 8.1.1.1.

In order to control the family-wise type I error rate at a significance alpha level of 0.05 (2-sided) in Sub-Study 2, a graphical multiple testing procedure will be used to test the primary and secondary endpoints in the order as specified in Section 5.3.3. The primary endpoint will be tested at the pre-specified significant alpha level of 0.05 (2-sided). The secondary efficacy endpoints are divided into two groups. The first group includes the first ten secondary endpoints. The second group includes all the remaining secondary endpoints which will be tested using the Holm procedure. If the primary endpoint achieves statistical significance, continued testing will follow a pre-specified weight of α allocation.

The details of the testing procedure will be specified and documented in SAP.

The separate efficacy analysis for subjects who were randomized and received at least one dose of risankizumab during the Induction Period 2 in both Sub-Study 1 and Sub-Study 2 will be performed for exploratory purpose.

8.1.6.1 Primary Efficacy Variables

The primary endpoint for both Phase 2b induction (Sub-Study 1) and Phase 3 induction (Sub-Study 2) is the achievement of clinical remission per Adapted Mayo score (defined as stool frequency subscore ≤ 1 and not greater than baseline, rectal bleeding subscore of 0, and endoscopic subscore ≤ 1 without the evidence of friability) at Week 12.

8.1.6.1.1 Analysis of Primary Endpoint

For Sub-Study 1 – Induction Period 1

The dose-response relationship among the risankizumab dose groups and the placebo group was characterized for the primary endpoint of clinical remission at Week 12 using

the Multiple Comparison Procedure and dose response Modeling (MCP-Mod)[21,22] method based on the ITT1A Population. Subjects with missing primary endpoint data at Week 12 was classified as "not achieved" (non-responder imputation [NRI] method) for the primary endpoint. Details were specified in the SAP.

The pairwise comparison between each risankizumab treatment group and placebo was also performed using the Cochran-Mantel-Haenszel (CMH) test stratified by baseline corticosteroid use and baseline Adapted Mayo score (≤ 7 and > 7) with one-sided alpha level of 0.05. A two-sided 90% confidence interval for the difference between treatment groups was constructed. There was no multiplicity adjustment for the pairwise comparison. The goal of the CMH test was to provide an estimation of the effect size for each dose to inform the dose selection for Phase 3, not for statistical inference purposes.

The above analyses for Induction Period 1 in Sub-Study 1 were performed based on ITT1A as primary analysis. Additional analysis based on ITT1 with additional subjects enrolled into risankizumab 1800 mg IV treatment group will be conducted separately as exploratory.

For Sub-Study 2 – Induction Period 1

The primary analysis will compare the subjects in risankizumab 1200 mg IV group and placebo group based on the ITT2. The difference between the treatment groups in the primary efficacy endpoint will be assessed using Cochran-Mantel-Haenszel (CMH) test stratified by Advanced Therapy-IR status (yes vs no), baseline steroid use (yes vs no), and baseline Adapted Mayo score (≤ 7 vs > 7) with two-sided alpha of 0.05. A two-sided 95% confidence interval for the difference between treatment groups will be constructed.

The Advanced Therapy-IR is defined as documented intolerance or inadequate response to advanced therapy including one or more of the approved biologics for UC (infliximab, adalimumab, golimumab, ustekinumab, and/or vedolizumab), approved JAK inhibitors for UC (tofacitinib, filgotinib, upadacitinib), and/or ozanimod.

NRI-MI, as defined in Section 8.1.2, will be used for missing data handling in primary analysis.

Sensitivity and subgroup analysis for the primary efficacy endpoint will be specified in SAP.

8.1.6.2 Secondary Efficacy Variables

Sub-Study 1 – Induction Period 1:

For Induction Period 1 in Sub-Study 1, the secondary efficacy variables listed in Section 5.3.3.2 were analyzed by treatment group for ITT1A as the primary analysis at the nominal α level of 0.05 (one-sided).

Categorical secondary efficacy endpoints were analyzed using CMH controlling for stratification variables. NRI imputation were used for primary inference purpose except for occurrence of hospitalization and UC-related surgeries of which as observed data were used. Continuous secondary efficacy endpoints were analyzed using a Mixed-Effect Model Repeated Measures (MMRM) method as the primary analysis.

Additional analysis based on ITT1 with additional subjects enrolled into risankizumab 1800 mg IV will be conducted separately as exploratory purpose.

No multiplicity adjustment will be performed.

Sub-Study 2 – Induction Period 1:

The secondary efficacy endpoints will be compared between the subjects in risankizumab dose group and placebo group based on ITT2.

Categorical secondary efficacy endpoints will be analyzed using the same CMH test as that for primary endpoint as specified in Section 8.1.6.1.1. NRI-MI, as defined in Section 8.1.2, will be the primary approach for missing data handling in the analyses of

categorical secondary efficacy endpoints except for UC-related hospitalization, of which AO data will be used.

Continuous secondary efficacy endpoints will be analyzed using RTB-MI as defined in Section 8.1.2 with MMRM (for endpoints with more than one post-baseline visits) or with ANCOVA (for endpoints with one post-baseline visit) models.

For all endpoints specified in Section 5.3.3.2, descriptive summary will be provided for ITT1_P2 and ITT2_P2 for exploratory purposes.

8.1.7 Safety Analysis

Safety analysis in each sub-study will be carried out using the corresponding safety population as defined in Section 8.1.1.2. The separate safety analysis for SAS1_P2 and SAS2_P2 will be performed for exploratory purpose. Adverse events (AEs), laboratory data and vital signs are the primary safety parameters and will be analyzed in each sub-study.

Sub-Study 1 and Sub-Study 2 – Induction Period 1:

Treatment emergent AEs (TEAEs) for Induction Period 1 in both Sub-Study 1 and Sub-Study 2 are defined as events that begin or worsen either on or after the first dose of the study drug in Induction Period 1 and within 140 days after the last dose administration of the study drug for subjects who do not participate in the maintenance Study M16-066 or until first dose of study drug in the maintenance Study M16-066 if the subject is enrolled into or until first dose of study drug in Induction Period 2 if the subject is enrolled into Induction Period 2.

Sub-Study 1 and Sub-Study 2 – Induction Period 2:

TEAEs for Induction Period 2 in both Sub-Study 1 and Sub-Study 2 are defined as events that begin or worsen either on or after the first dose of the study drug in Induction Period 2 and within 140 days after the last dose administration of the study drug for

subjects who do not participate in the maintenance Study M16-066 or until first dose of study drug in the maintenance Study M16-066 if the subject is enrolled.

An overview of TEAEs, including AEs of special interest such as serious infection, malignancies, major adverse cardiovascular events, systemic hypersensitivity reactions/infusion reactions, TEAEs leading to death and TEAEs leading to premature discontinuation, TEAEs by Medical Dictionary for Drug Regulatory Activities (MedDRA version 18.1 or later) preferred term and system organ class, TEAEs by maximum relationship to study drug, and TEAEs by maximum severity will be summarized by number and percentage. Treatment group differences in the overall incidence of TEAEs will be assessed with Fisher's exact test for each preferred term.

Changes from Baseline in continuous laboratory and vital sign parameters will be summarized by treatment group for corresponding safety population in each sub-study. Treatment group differences in changes from Baseline between risankizumab and the placebo group may be analyzed using a one-way Analysis of Variance (ANOVA). Vital signs and laboratory data will be summarized by descriptive statistics 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.

Missing safety data will not be imputed. More detailed safety analysis for Induction Period 1 and Induction Period 2 will be specified in 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.[23,24]

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. ADA incidence will be summarized by cohort 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 nonlinear 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 or V 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

Sub-Study 1 (Phase 2b):

For Sub-Study 1 (Phase 2b portion of the study), approximately 240 subjects in the Bio-IR population were equally randomized using a 1:1:1:1 ratio to three risankizumab treatment groups (600 mg, 1200 mg and 1800 mg IV Q4W) and the placebo group. The sample size for this study is based on the expected proportion of subjects who achieve

clinical remission per Adapted Mayo Score at Week 12. Assuming clinical remission rate of 7% in the placebo arm and maximum of 25% in at least one of the risankizumab treatment groups at Week 12, a sample size of 60 subjects per treatment group is sufficient to test for the presence of a dose response signal, to select the best dose response model for the observed data out of a pre-specified set of candidate models, and to estimate target doses of interest (e.g., MED) via modeling using MCP-Mod (Multiple comparison procedure and modeling) approach. This approach provides an average power of approximately 87% to detect a dose effect at 5% level of significance (one-sided) with the log linear, E_{max}, exponential, logistic and sigE_{max} models pre-specified as likely candidates to characterize the dose response for risankizumab for the primary endpoint of clinical remission at Week 12 per Adapted Mayo Score.

240 subjects were enrolled into Study M16-067 Sub-Study 1 for dose selection analysis. The additional subjects that enrolled during the dose selection analysis period were not part of the dose selection analysis, but will be evaluated separately as exploratory in the final CSR.

Study M16-067 Sub-Study 2 (Phase 3)

For Sub-Study 2, approximately 966 subjects will be randomized to the risankizumab 1200 mg IV dose or placebo in a randomization ratio of 2:1. The sample size for this study is based on the expected proportion of subjects who achieve clinical remission per Adapted Mayo Score at Week 12. The sample size has been re-assessed after analyzing combined PK, safety and efficacy results from Sub-Study 1. It is determined to provide adequate power for the primary endpoint and selected ranked secondary endpoints and adequate responders to meet the sample size requirement for Study M16-066. Assuming clinical remission rate of 6% in the placebo arm and 16% of the risankizumab treatment arm at Week 12, a sample size of 644:322 subjects in risankizumab 1200 mg IV dose and placebo group will provide at least 90% power to detect the 10% treatment difference in clinical remission rate between the risankizumab dose and placebo using two-sided Miettinen and Nurminen test at a 0.05 significant level. The assumed remission rates were based on Sub-Study 1 for bio-IR population and on ustekinumab data for

Non-Bio-IR population. The same sample size will also provide at least 90% power for ranked secondary endpoints, clinical remission per full mayo score at Week 12, endoscopic response at Week 12, endoscopic remission at Week 12, clinical response per adapted mayo score at Week 12 and clinical response per partial adapted mayo score at Week 4.

8.3 Randomization Methods

A total of approximately 1206 subjects (240 subjects in Sub-Study 1 and 966 subjects in Sub-Study 2) will be randomized into the study.

240 subjects in Sub-Study 1 were randomized into three risankizumab dose groups and the placebo group in a 1:1:1:1 ratio (60 subjects for risankizumab 600 mg, 1200 mg and 1800 mg dose group and placebo group respectively), stratified by Baseline corticosteroid use (yes vs. no) and Baseline Adapted Mayo score (≤ 7 vs. > 7). During the dose analysis period, additional subjects will be enrolled to the risankizumab1800 mg IV Q4W dose group on an open-label basis.

At Week 12, subjects who received IV risankizumab induction and did not achieve clinical response were randomized 1:1:1 to Induction Period 2 (risankizumab 1800 mg IV, risankizumab 360 mg SC, and risankizumab 180 mg SC), stratified by baseline steroid use (yes vs no) and baseline Adapted Mayo score (≤ 7 vs > 7).

Approximately 966 subjects in Sub-Study 2 will be randomized into risankizumab 1200 mg dose group and the placebo group in a 2:1 ratio (644 subjects for risankizumab 1200 mg dose group, 322 subjects for placebo group) stratified by number of prior failed biologics (0, 1 vs > 1), baseline corticosteroid use (yes vs. no), and baseline Adapted Mayo score (≤ 7 vs. > 7).

At Week 12, subjects who received IV risankizumab induction and did not achieve clinical response were randomized 1:1:1 to Induction Period 2 (risankizumab 1200 mg IV, risankizumab 360 mg SC, and risankizumab 180 mg SC), stratified by number of prior

failed biologics (0, 1 vs > 1), baseline steroid use (yes vs no) and baseline Adapted Mayo score (≤ 7 vs > 7).

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.

Any amendments to the protocol will require IEC/IRB approval and approval by Regulatory Authority (ies), if required by local regulations 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 ICH GCP.

Any serious adverse events 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, International Conference on Harmonization (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 or geo-political conflict in Ukraine and surrounding impacted regions 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.

It is possible that additional protocol modifications not outlined in this protocol may become necessary due to the geo-political conflict in Ukraine and surrounding impacted regions. If this situation arises, in addition to the study informed consent, additional temporary verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations. An appropriately signed

and dated informed consent form should be obtained from the subject afterwards, as soon as possible.

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.

Samples for exploratory research will only be collected after the subject has voluntarily signed and dated the separate written consent, approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. If the subject does not consent to provide the optional samples, 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 and optional exploratory research samples 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.

Optional exploratory research samples from adolescent subjects will only be collected if the subject's parent/legal guardian has voluntarily signed and dated a separate written

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 informed consent must be signed before the optional samples are collected. If the subject's parent/legal guardian does not consent to provide optional samples, 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, 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. Data collected during this study must be recorded on the appropriate source documents.

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 or geo-political conflict in Ukraine and surrounding impacted regions, 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

Case report forms (CRF) 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 CRF data for this study are being collected with an electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic case report forms (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 trial 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 Signant 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, Signant 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 Signant 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 printouts from that media.

The ePRO data will be collected by the following methods:

Diary Based

The ePRO data (stool information, bowel urgency, abdominal pain, nocturnal bowel movement, tenesmus, interrupted sleep due to UC symptoms, and general well-being, use of anti-diarrheals and endoscopy prep) will be collected electronically via a handheld device into which the patient 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 Signant 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. Site staff are responsible for regularly checking that each subject is entering data consistently and accurately in the ePRO device via the password protected website. If inconsistencies are noted the site staff are responsible for promptly contacting the subject to re-educate the subject on how to correctly complete the questionnaires at the required timepoints.

Tablet Based

The ePRO data (IBDQ, SF-36, PGIS, PGIC, FACIT-F, WPAI-UC, EQ-5D-5L and UC-SQ) will be collected electronically via a Tablet device into which the patient will directly enter the required pieces of information. The electronic device will be programmed to allow data entry for only the visits specified in the protocol Appendix C and will not allow for patients to complete more than one of the same assessments 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 Signant Health. The Investigator and delegated staff will be able to access all uploaded patient entered data via a password protected website, up until the generation, receipt and confirmation of the study archive.

Investigator will enter the Physician Global Assessment (PGA) in the Trialmax system in every study visit.

11.0 Data Quality Assurance

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 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 from this study may be used in scientific publications or presented at medical conventions. Exploratory research data will be published or presented only in a way that does not identify any individual subject.

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.

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 retain any records related to the study according to local 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 (EMEA) 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 to Evaluate the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Ulcerative Colitis
Protocol Date:	16 December 2022

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 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]	Global Development Lead	Clinical Development, Immunology
	Medical Director	Clinical Development, Immunology
	Director	Statistics
	Director Pharmacokinetics	Clinical Pharmacology and Pharmacometrics
	Senior Scientist	Bioanalysis
	Study Project Manager II	Clinical Operations

Appendix C. Study Activities Sub-Study 1 and Sub-Study 2

Activity	Screening Period (35 Days)[a]	Induction Period 1				Induction Period 2			Unsch[b]	140-Day Follow-Up[c]
	Screening	Baseline	Week 4	Week 8	Week 12/PD[w]	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]	SAEs only	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[k]	X[y]				X[l]			X[l]		
C. difficile toxin	X[x]									
Urinalysis[m,p]	X[x]	X[n]			X			X		
Pregnancy Test[o,p]	X[x]	X[n]	X	X	X	X	X	X		
Chemistry and Hematology[p]	X[x]	X[n]	X	X	X	X	X	X		
COVID-19 Assessment	X[aa]									
hs-CRP[p]		X	X	X	X			X		
Serum Risankizumab[q]			X	X	X			X	X	

Activity	Screening Period (35 Days)[a]	Induction Period 1				Induction Period 2			Unsch[b]	140-Day Follow-Up[c]
	Screening	Baseline	Week 4	Week 8	Week 12/PD[w]	Week 16	Week 20	Week 24		
Serum Anti-Drug Antibody (ADA)[q] and Neutralizing Anti-Drug Antibodies (nAb)[q]		X	X	X	X			X	X	
Fecal calprotectin (FCP)[r,p]		X	X		X			X		
Partial Adapted Mayo[bb]			X	X		X	X		X	
Adapted Mayo/Full Mayo[s]		X			X			X		
Endoscopy[s]	X				X			X		
PGA[z]		X	X	X	X	X	X	X		
Intestinal Biopsies[t]	X				X			X		
Dispense Subject Diary[u]	X									
Subject Diary Review	X	X	X	X	X	X	X	X	X	
Subject Questionnaire: UC-SQ		X	X	X	X	X	X	X	X	
Subject Questionnaire: PGIC PGIS		X (PGIS Only)	X	X	X	X	X	X	X	
Subject Questionnaires: EQ-5D-5L FACIT-F IBDQ SF-36 WPAI-UC		X			X			X		
Study Drug Administration[v]		X	X	X	X[v]	X	X			

a. The Screening period is approximately 35 days. It should be a minimum of 3 days for SFS and RBS calculation. The Baseline Adapted Mayo score 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 subjects who roll-over into Study M16-066 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 blinded treatment during Induction Period 2. Physical examinations at all other visits (including unscheduled visits) are symptom based.

f. Blood pressure, pulse rate, temperature, respiratory rate and weight should be performed before blood draws are performed.

g. Collection of SAEs 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.

   Subjects with a negative QuantiFERON-TB Gold (and/or PPD) test at Screening of the preceding Study M16-067 will be tested annually for TB by either the QuantiFERON-TB Gold Test (or equivalent) or a TB Skin Test Purified Protein Derivative (PPD). If PPD and/or the QuantiFERON-TB Gold test (or Interferon gamma release assay [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, patients may continue their participation in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis.

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. 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.

l. Japan and China 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 for subjects that have a history of HBV vaccine and are HBs Ab (+).

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. 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.

o. 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.

p. 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.

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 lab requisition form.

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 timelines specified in the lab manual. If a sample cannot be obtained during the site visit, the site will give instructions and a stool sample supply kit.

s. A full colonoscopy will be performed at Screening unless the subject underwent a full colonoscopy within 12 months prior to Screening. There must be appropriate documentation available to confirm the diagnosis, extent of disease, and to exclude dysplasia and colon cancer. If this is available, the screening endoscopy may be either a full colonoscopy or a flexible sigmoidoscopy. All other endoscopies may be flexible sigmoidoscopies or colonoscopies at the discretion of the investigator. Endoscopy at/during the screening period or within 45 days of the Baseline visit will be used to calculate the Mayo endoscopy subscore at Baseline. Endoscopic evaluations using Mayo endoscopic subscore confirmed by central review will be done at Screening. Endoscopies completed at Week 12 (or Week 24, for subjects who received blinded treatment during Induction Period 2), will use the local reader results for stratification for Study M16-066 and to evaluate clinical response for enrollment in Study M16-066.

t. Biopsy for histologic assessment by central review will be conducted at each visit with endoscopy. Biopsies may be done when performing the endoscopy to confirm UC 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.

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

v. Administration of drug will be performed after all assessments and examinations scheduled for that day have been completed. Completion of PROs are permitted during administration of study drug. Study drug will only be administered at Week 12 for subjects who receive blinded treatment during 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 Histamine and tryptase samples are not applicable for China.

w. PD refers to any premature discontinuation visit, occurred before or after W12 visit.

x. For Rescreening, if a subject is being rescreened within 14 days (≤ 14 days have passed)from the collection date of the previous screening laboratory testing, repeat laboratory testing for chemistry/hematology, urinalysis, serum pregnancy, and C. *difficile* are not required unless, in the opinion of the Investigator, the subject's health status has changed.

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 XX are met and no more than 90 days have passed since the collection date of the testing.

z. Physician Global Assessment (PGA) will be entered by the investigator in the Trialmax system and in the medical notes at all study visits.

aa. 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.

bb. If the event endoscopy cannot be performed at Week 12 or 24 due to COVID-19 pandemic restrictions or geo-political conflict in Ukraine and surrounding impacted regions, clinical response will be calculated using the Partial Adapted Mayo score.

Appendix D. Study Activities

Optional Exploratory Research Samples (Sub-Study 1)

Samples Collected[a]	Screening Period (35 Days)	Induction Period 1			Induction Period 2
	Screening	Baseline	Week 4	Week 12/PD[e]	Week 24
Pharmacogenetic[b]		X			
Epigenetic		X	X	X	X
Transcriptomic[b]		X	X	X	X
Proteomic and targeted protein investigations (plasma)[b]		X	X	X	X
Proteomic and targeted protein investigations (serum)[b]		X	X	X	X
PBMC (US sites only)[c]		X		X	
Stool[b]		X	X	X	
Intestinal biopsies (RNA)[b,d]	X			X	X

a. Collections to be performed only if subject provides separate written consent to collect the exploratory research 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, proteomics, microbiome analysis and other approaches.

c. Collected at US sites only.

d. Biopsy may be done when performing the endoscopy.

e. PD refers to any premature discontinuation visit, occurred before or after W12 visit.

Optional Exploratory Research Samples (Sub-Study 2)

Samples Collected[a]	Screening Period (35 Days)[a]	Induction Period 1			Induction Period 2
	Screening	Baseline	Week 4	Week 12/PD[d]	Week 24
Pharmacogenetic[b]		X			
Epigenetic[b]		X		X	X
Transcriptomic[b]		X		X	X
Proteomic and targeted protein investigations (plasma)[b]		X		X	X
Intestinal biopsies (RNA)[b,c]	X			X	X

a. Collections to be performed only if subject provides separate written consent to collect the exploratory research 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. Biopsy may be done when performing the endoscopy.

d. PD refers to any premature discontinuation visit, occurred before or after W12 visit.

Appendix E. Script for Collection of Mayo Scores for Use in Study M16-067*

- 3 different Mayo Scores are evaluated in this protocol:
  1. Full Mayo Score
  2. Adapted Mayo Score
  3. Partial Adapted Mayo Score

1. The Full Mayo Score is a composite of the following subscores: Stool Frequency subscore, Rectal Bleeding subscore, Endoscopy subscore, and Physician's Global Assessment subscore.
   - In the protocol Full Mayo Score is calculated at the visits specified in Appendix C to evaluate study endpoints as described in Section 5.3.3.
2. The adapted Mayo Score is a composite of the following subscores: Stool Frequency subscore, Rectal Bleeding subscore and Endoscopy subscore

   In the protocol adapted Mayo Score is calculated:
   - To evaluate subject eligibility at screening as described in Section 5.2.1
   - To be used as stratification factor at baseline
   - To evaluate if subjects achieve clinical response at W12 and W24 as described in Section 5.1
   - To evaluate study endpoints as described in Section 5.3.3 at the visits specified in Appendix C
3. The Partial Adapted Mayo Score is a composite of the following subscores: Stool Frequency subscore and Rectal Bleeding subscore.
   - In the protocol Partial Adapted Mayo Score is calculated at the visits specified in Appendix C to evaluate study endpoints as described in Section 5.3.3

* Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-ASA therapy for mildly to moderately active ulcerative colitis. N Engl J Med. 1987;317(26):1625-9.[25]

Lewis JD, Chuai S, Nessel L, et al. Use of the noninvasive components of the Mayo Score to assess clinical response in ulcerative colitis. Inflamm Bowel Dis. 2008;14(12):1660-6.[26]

Subscores:

Stool frequency Subscore* 0 = Normal number of stools for this subject 1 = 1 – 2 stools more than normal 2 = 3 – 4 stools more than normal 3 = 5 or more stools more than normal * Each patient serves as his or her own control to establish normal stool frequency and the degree of abnormal stool frequency.
Rectal bleeding Subscore** 0 = No blood seen 1 = Streaks of blood with stool less than half the time 2 = Obvious blood with stool most of the time 3 = Blood alone passed ** The daily bleeding score represents the most severe bleeding of the day.
Endoscopy Subscore: Findings of flexible sigmoidoscopy 0 = Normal or inactive disease 1 = Mild disease (erythema, decreased vascular pattern) 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions) 3 = Severe disease (spontaneous bleeding, ulceration)
Physician's Global Assessment Subscore*** 0 = Normal (Subscores are 0) 1 = Mild disease (Subscores are mostly 1's) 2 = Moderate disease (Subscores are 1 to 2) 3 = Severe disease (Subscores are 2 to 3) *** The physician's global assessment acknowledges the three other subscores, the subject's daily record of abdominal discomfort and functional assessment, and other observations such as physical findings, and the subject's performance status.

Source: Schroeder 1987.[25]

Stool Frequency Subscore

- The stool frequency subscore is calculated by comparing the stool frequency to a reference number. The reference number is the number of stools per day (24 hours) that is typical for the subject when having active UC but not experiencing a flare and needs to be designated once prior to enrollment. The reference number should represent a full number of at least 1.

- Subjects will record the daily number of stools throughout the trial. Using these numbers, the Stool Frequency subscore will be assessed for each study day as follows:
  - A number of bowel movements lower than or equal to the reference number of bowel movements should be scored as 0 = Normal.
  - One or 2 bowel movements more than the reference number of bowel movements should be scored as 1.
  - Three or 4 bowel movements more than the reference number of bowel movements should be scored as 2.
  - Five or more bowel movements more than the reference number of bowel movements should be scored as 3.
- The Stool Frequency subscores based on 3 days prior to each study visit will be averaged and used for the Stool Frequency subscore for each study visit.
- The Stool Frequency subscore during days which the subject received anti-diarrheal medication will be scored as a 3.
- Diary entries for stool frequency should not be included in the 3 days prior to the visit that are evaluated for the Stool Frequency subscore for the following days: (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. Earlier diary entries will be used accordingly in order to provide the most recent data for 3 days prior to the respective study visit.

Rectal Bleeding Subscore

- Subjects will be assigned a daily rectal bleeding subscore value as follows:
  - No visible blood with stool during the respective day should be scored as 0.
  - Visible blood with stool less than half the time during the respective day should be scored as 1.
  - Visible blood with stool at least half the time during the respective day should be scored as 2.

- A score of 3 for bleeding requires subjects to have at least 50% of bowel movements accompanied by visible blood and at least one bowel movement with blood alone.

- The score entries into subject's diary based on 3 days prior to each study visit will be averaged and used for the Rectal Bleeding subscore for each study visit.
- Diary entries for rectal bleeding should not be included in the 3 days prior to the visit that are evaluated for the Rectal Bleeding subscore for the following days: (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. Earlier diary entries will be used accordingly in order to provide the most recent data for 3 days prior to the respective study visit.

Physician's Global Assessment Subscore

- The physician's global assessment acknowledges the 2 subject-reported subscores, the endoscopy subscore as applicable, the subject's daily record of abdominal discomfort and general well-being during based on the 3 days prior to the visit, and other observations such as physical findings, and the subject's performance status in order to assess disease activity as follows:
  - 0 = Normal
  - 1 = Mild disease
  - 2 = Moderate disease
  - 3 = Severe disease

Investigator will enter the PGA in the Trialmax study system and record it in the medical notes at each study visit.

Endoscopy Subscore

- The endoscopist should evaluate each observed segment of the colon (rectum, sigmoid, descending colon, transverse colon, ascending colon/cecum) by using the classification as follows:
  - 0 = Normal or inactive disease
  - 1 = Mild disease (erythema, decreased vascular pattern)
  - 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
  - 3 = Severe disease (spontaneous bleeding, ulceration)
- The endoscopic subscore for the subject will be the worst score of the observed segments.
- The local endoscopist should also separately assess presence or absence of friability (yes/no).
- The endoscopy will be recorded (not a still image) and sent to a central review vendor for scoring as described in the central review charter.

* Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-ASA therapy for mildly to moderately active ulcerative colitis. N Engl J Med. 1987;317(26):1625-9.[25]

Lewis JD, Chuai S, Nessel L, et al. Use of the noninvasive components of the Mayo Score to assess clinical response in ulcerative colitis. Inflamm Bowel Dis. 2008;14(12):1660-6.[26]

Appendix F. Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis[27] 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):

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

   f. 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 mmHg from 1 month to 1 year, less than (70 mmHg + [2 × age]) from 1 to 10 years, and less than 90 mgHg 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: ADA, nAb, histamine and tryptase. Separate instructions for the collection, handling, storage and shipping of these labs will be provided outside of the study protocol. Histamine and tryptase samples are not applicable for China.

Appendix G. Tanner Stage 5 for Development*

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

* Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child. 1969;44(235):291-303.[28]

Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child. 1970;45(239):13-23.[29]

Appendix H. Optional Intensive PK Subjects

At the time of this amendment, intense PK sub-study had been already completed during Sub-Study 1.

Samples for pharmacokinetics (PK) analysis will be collected in all subjects as described in Appendix C (Prior to dose at Weeks 4, 8, 12/PD and 24). For the subjects who consent to the optional intensive PK sampling, in addition to the time points above, blood 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.