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Protocol for Study M25-540

Ulcerative Colitis: Risankizumab Versus Vedolizumab for Subjects with Ulcerative Colitis Naïve to Targeted Therapies

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FULL TITLE: A Phase 3b, Multicenter, Randomized, Open-Label Study of Risankizumab Compared to Vedolizumab for the Treatment of Adult Subjects With Moderate to Severe Ulcerative Colitis Who are Naïve to Targeted Therapies

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PRINCIPAL INVESTIGATOR(S): Investigator information on file at AbbVie.

SPONSOR/EMERGENCY MEDICAL CONTACT:*

[redacted], MD
[redacted]
AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen, Germany

Office:
Mobile:
Email:
[redacted]

EMERGENCY 24-hour Number: +1 973-784-6402

*For European Union countries: the sponsor is AbbVie Deutschland GmbH & Co. KG. The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

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1 PROTOCOL SUMMARY

1.1 Protocol Synopsis

Protocol Title:

A Phase 3b, Multicenter, Randomized, Open-Label Study of Risankizumab Compared to Vedolizumab for the Treatment of Adult Subjects With Moderate to Severe Ulcerative Colitis Who are Naïve to Targeted Therapies

Background and Rationale:

Ulcerative colitis (UC) is a chronic, relapsing, and incurable inflammatory disease of the large intestine. It is postulated to be caused by an unregulated and exaggerated local immune response to environmental triggers in genetically susceptible individuals. Despite significant advancements in the treatment of patients with moderate to severe UC and benefits of available targeted therapies (TaTs), the efficacy of current treatments is not adequate in meeting the needs of all patients, with some patients not achieving clinical and/or endoscopic remission with initial treatment or losing response or remission over time. Therefore, new therapeutic options are required in order to continue to improve the outcomes of patients with UC. Furthermore, the growing number of treatments for inflammatory bowel disease (IBD) now raises the question of strategic therapeutic sequences to help to prescribe the right drug to the right patient and at the right time.

Risankizumab is a humanized monoclonal antibody (mAb) of the immunoglobulin (Ig)G1 subclass directed towards interleukin (IL) 23p19. The mAb has been engineered to reduce Fcγ receptor and complement binding and potential charge heterogeneity and binds with high affinity to human IL-23. Risankizumab (Skyrizi®) is currently approved in multiple countries for the treatment of adults with moderate to severe UC and Crohn's disease (CD). Vedolizumab (Entyvio®) is a monoclonal antibody directed against the α4β7 heterodimer. It has been approved in multiple countries for both moderately to severely active UC and CD.

This study is being conducted to compare efficacy and safety of risankizumab versus vedolizumab for the treatment of adult subjects with moderate to severe UC who are naïve to TaTs. With a growing number of therapies in UC, head-to-head study in 100% naïve patients to the TaTs will inform the HCPs with empirical data to aid in their treatment strategies to optimize long term outcomes in UC patients. Patients who are 100% naïve to approved TaTs for UC, present a homogenous patient population to compare the efficacy and safety of two established treatment options for UC patients within a head-to-head study design.

Objectives and Endpoints:

The objective of this study is to compare the efficacy and safety of risankizumab versus vedolizumab over 48 weeks for the treatment of adult subjects with moderate to severe UC who are naïve to TaTs.

Primary Endpoint:

The primary endpoint is the achievement of endoscopic improvement at Week 48, defined as a centrally read endoscopy subscore of 0 or 1 (score of 1 modified to exclude friability): superiority of risankizumab vs. vedolizumab.

Secondary Endpoint:

The achievement of clinical remission per modified Mayo Score (mMS) at Week 48, defined as SFS ≤ 1 and not greater than Baseline, RBS = 0, and a centrally read endoscopy subscore of 0 or 1 (score of 1 modified to exclude friability): non-inferiority of risankizumab vs. vedolizumab test first followed by superiority test.

Investigators:

Multicenter

Study Sites:

There will be approximately 285 sites across approximately 30 countries worldwide.

Study Population and Number of Subjects to be Enrolled:

Approximately 530 adult subjects with moderate to severe UC who are naïve to TaTs.

Investigational Plan:

Phase 3b, multicenter, randomized, open label study to compare efficacy and safety of risankizumab versus vedolizumab for the treatment of adult subjects with moderate to severe UC who are naïve to TaTs.

A subset of sites will participate in an abdominal intestinal ultrasound substudy.

Key Eligibility Criteria:

Inclusion:

- Adults 18 to ≤ 80 years old
- Confirmed diagnosis of UC for at least 3 months prior to Baseline. Documentation of biopsy results consistent with the diagnosis of UC as assessed by the Investigator must be available.
- Active UC with an mMS of 5 to 9 points and endoscopic subscore of 2 to 3 (confirmed by central reader).
- 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.
    - 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 ≤ 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 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:
    - Azathioprine: ≥ 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-mercaptopurine: ≥ 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)
    - Methotrexate (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

Exclusion:

- Subject has received any TaTs for UC, including but not limited to: infliximab, etanercept, adalimumab, natalizumab, certolizumab, golimumab, ozanimod, ustekinumab, etrolizumab, vedolizumab, tofacitinib, filgotinib, etrasimod, guselkumab, mirikizumab, upadacitinib, or risankizumab.
- Subject who received IV/intramuscular corticosteroids within 14 days prior to Screening or during the Screening period.
- 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.
- Subjects with any of the following:
  - History of gastrointestinal perforation (other than due to appendicitis or mechanical injury), diverticulitis, or significantly increased risk for gastrointestinal (GI) perforation per investigator judgment including history of volvulus and/or intussusception (telescoping of bowels);
  - Diagnosis of CD or IBD-unclassified, or a history of radiation colitis or ischemic colitis;
  - Currently known complications of UC such as: fulminant colitis and/or toxic megacolon, acute severe UC, previous colectomy (total or subtotal), or any other manifestation that might require surgery while in the study;
  - Current diagnosis of short bowel syndrome;
  - Known or suspected primary immune deficiency;
  - Ostomy or ileoanal pouch;

    - Current or history of dysplasia of the GI tract or the presence of dysplasia, other than completely removed low-grade dysplastic lesions, in any biopsy performed during the Screening endoscopy.
- Subjects with active, chronic or recurrent infections
- Subjects with infection with *Clostridium difficile* or other intestinal pathogens during Screening.
- Current severe, progressive, or uncontrolled renal, hepatic, hematological, endocrine, disorder or symptoms thereof
- Current or history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly

Study Treatment and Duration of Treatment:

Subjects randomized to risankizumab at Baseline:

A 1200 mg induction dose of risankizumab intravenous (IV) will be administered at Baseline and Weeks 4 and 8. At Week 12, depending on the clinical remission status per mMS, the subjects will receive a risankizumab maintenance dose of either 180 mg (clinical remission: Yes) or 360 mg (clinical remission: No) subcutaneous (SC) every 8 weeks with the last dose of risankizumab SC at Week 44.

The 140-day follow-up visit/phone call following the last dose of risankizumab study treatment during the trial will not be required for any subject who initiates commercially available risankizumab following the last dose of study treatment.

Optional primary-trial extension (PTE):

Subjects randomized to risankizumab at Baseline in countries where no commercial risankizumab or local access mechanism is available will be able to participate in an optional PTE for up to 144 weeks after study completion of the Primary Treatment Period (Week 48).

Subjects randomized to vedolizumab at Baseline:

Vedolizumab 300 mg IV will be administered at Baseline, Weeks 2 and 6, and every 8 weeks with the last dose of vedolizumab IV at Week 46.

A 140-day follow-up visit/phone call following the last dose of vedolizumab study treatment during the trial will be required regardless of the use of subsequent treatment by the investigator.

Date of Protocol Synopsis:

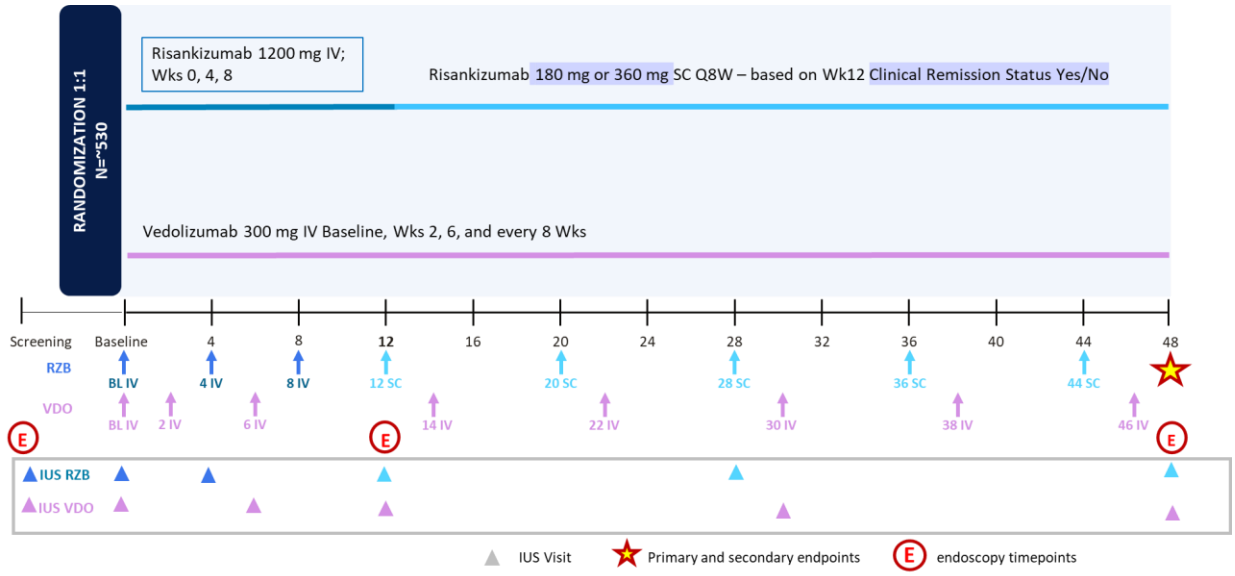
08 July 2025

1.2 Study Schema

The schematic of the study is shown in Figure 1. Further details regarding the overall study design are provided in Section 4 and study procedures are located in Section 8.

See Section 5 for information regarding eligibility criteria.

Figure 1. Study Schematic



1.3 Activity Schedule

The following table shows the required activities. The individual activities are described in detail in Section 8.

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Study Activities Table

Table 1. Study Activities for Subjects Enrolled in the Risankizumab Arm

Activity Visit window ± 7 days	Screening	Baseline	Week 4	Week 8	Week 12	Week 20	Week 28	Week 36	Week 44	Unscheduled	Week 48/PD	140-day Follow-up Visit/Call
INTERVIEWS & QUESTIONNAIRES												
Informed consent	X											
Eligibility criteria	X	X										
Medical/surgical/UC history including history of alcohol and tobacco	X	X										
Adverse event assessment	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]												
mMS (*if needed to confirm inadequate response)		X			X					X*	X	
Partial mMS		X	X	X	X	X	X	X	X	X	X	
[redacted]												
Dispense Subject eDiary	X											
Subject eDiary Review		X	X	X	X	X	X	X	X	X	X	
Latent TB risk assessment form	X											
LOCAL LABS & EXAMS												
Endoscopy (*If needed to confirm inadequate response)	X				X					X*	X	
Mandatory intestinal biopsies	X				X						X	
Abdominal Ultrasound (IUS Substudy only)		X	X		X		X				X	
12 lead ECG	X											

Activity Visit window ± 7 days	Screening	Baseline	Week 4	Week 8	Week 12	Week 20	Week 28	Week 36	Week 44	Unscheduled	Week 48/PD	140-day Follow-up Visit/Call
Height (screening only) and weight	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	
Full physical examination	X	X			X						X	
Targeted physical examination			X	X		X	X	X	X	X		
Urine pregnancy test		X	X	X	X	X	X	X	X		X	
CENTRAL LABS												
Hepatitis B, Hepatitis C Screening and HIV Test	X											
Serum pregnancy test	X											
QuantiFERON TB Gold test (and/or local purified protein derivative TB skin test)	X											
Fecal calprotectin		X			X			X		X	X	
hs CRP		X			X			X		X	X	
Clinical chemistry, Hematology (CBC)	X	X	X	X	X		X	X		X	X	
Urinalysis	X											
C. difficile	X											
Tryptase		**In the event of a suspected systemic post dose hypersensitivity reaction, tryptase samples should be obtained between 15 minutes and 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.**										
Serum risankizumab, serum ADA and nAb		**Only for subjects randomized to the risankizumab treatment group, in the event of a suspected systemic post dose hypersensitivity reaction, samples should be collected once within 24 hours of the reaction.**										
Optional biomarker sample: Whole blood DNA PG		X										
Optional biomarker sample: Serum/Plasma		X	X		X			X			X	
Optional biomarker sample: Whole blood DNA Epi		X	X		X			X			X	

Activity Visit window ± 7 days	Screening	Baseline	Week 4	Week 8	Week 12	Week 20	Week 28	Week 36	Week 44	Unscheduled	Week 48/PD	140-day Follow-up Visit/Call
Optional biomarker sample: Whole blood RNA		X	X		X			X			X	
Optional biomarker sample: Stool		X			X						X	
Optional biomarker sample: Tissue biopsies (RNA)	X				X						X	
Optional biomarker sample: Tissue biopsies (Formalin)	X				X						X	
Optional biomarker sample: PBMCs (at limited sites)		X	X		X						X	
℞ TREATMENT												
Randomization/Drug assignment		X			X							
Administer risankizumab study treatment		X	X	X	X	X	X	X	X			
Perform drug accountability			X	X	X	X	X	X	X			

Table 2. Study Activities for Subjects Enrolled in the Vedolizumab Arm

Activity Visit window ± 7 days	Screening	Baseline	Week 2	Week 6	Week 12	Week 14	Week 22	Week 30	Week 38	Week 46	Unscheduled	Week 48/PD	140-day Follow-up
INTERVIEWS & QUESTIONNAIRES													
Informed consent	X												
Eligibility criteria	X	X											
Medical/surgical/UC history including history of alcohol and tobacco	X	X											
Adverse event assessment	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]													
mMS (*If needed to confirm inadequate response)		X									X*	X	
Partial mMS		X	X	X		X	X	X	X	X	X	X	
[redacted]													
Dispense Subject eDiary	X												
Subject eDiary Review		X	X	X		X	X	X	X	X	X	X	
Latent TB risk assessment form	X												
LOCAL LABS & EXAMS													
Endoscopy (*If needed to confirm inadequate response)	X				X						X*	X	
Intestinal biopsies	X				X							X	
Abdominal ultrasound (IUS Substudy only)		X		X	X			X				X	

Activity Visit window ± 7 days	Screening	Baseline	Week 2	Week 6	Week 12	Week 14	Week 22	Week 30	Week 38	Week 46	Unscheduled	Week 48/PD	140-day Follow-up
12 lead ECG	X												
Height (screening only) and weight	X	X	X	X		X	X	X	X	X	X	X	
Vital signs	X	X	X	X		X	X	X	X	X	X	X	
Full physical examination	X	X										X	
Targeted physical examination			X	X		X	X	X	X	X	X		
Urine pregnancy test		X	X	X		X	X	X	X	X		X	
CENTRAL LABS													
Hepatitis B, Hepatitis C Screening and HIV Test	X												
Serum pregnancy test	X												
QuantiFERON TB Gold test (and/or local purified protein derivative TB skin test)	X												
Fecal calprotectin (**to be collected at home prior to endoscopy preparation)		X			X**						X	X	
hs CRP		X				X					X	X	
Clinical chemistry, Hematology (CBC)	X	X	X	X		X		X	X		X	X	
Urinalysis	X												
C. difficile	X												
Tryptase		**In the event of a suspected systemic post dose hypersensitivity reaction, tryptase samples should be obtained between 15 minutes and 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. Plasma histamine should be obtained, optimally, within 5 to 15 minutes of the onset of symptoms, and no later than 1 hour.**											
Optional biomarker sample: Whole blood DNA PG		X											
Optional biomarker sample: Serum/Plasma		X		X		X						X	
Optional biomarker sample: Whole blood DNA Epi		X		X		X						X	

Activity Visit window ± 7 days	Screening	Baseline	Week 2	Week 6	Week 12	Week 14	Week 22	Week 30	Week 38	Week 46	Unscheduled	Week 48/PD	140-day Follow-up
Optional biomarker sample: Whole blood RNA		X		X		X						X	
Optional biomarker sample: Stool		X			X							X	
Optional biomarker sample: Tissue biopsies (RNA)	X				X							X	
Optional biomarker sample: Tissue biopsies (Formalin)	X				X							X	
Optional biomarker sample: PBMCs (at limited sites)		X		X		X						X	
℞ TREATMENT													
Randomization/Drug assignment		X											
Administer vedolizumab study treatment		X	X	X		X	X	X	X	X			
Perform drug accountability			X	X		X	X	X	X	X			

2 INTRODUCTION

2.1 Background and Rationale

UC is a chronic, relapsing, and incurable inflammatory disease of the large intestine. It is postulated to be caused by an unregulated and exaggerated local immune response to environmental triggers in genetically susceptible individuals.[1] Despite significant advancements in the treatment of patients with moderate to severe UC and benefits of available TaTs, the efficacy of current treatments is not adequate in meeting the needs of all patients, with some patients not achieving clinical and/or endoscopic remission with initial treatment or losing response or remission over time. Therefore, new therapeutic options are required in order to continue to improve the outcomes of patients with UC. Furthermore, the growing number of treatments for IBD now raises the question of therapeutic strategies and sequences based on head-to-head trials to help to prescribe the right drug to the right patient and at the right time.[2,3]

Risankizumab (Skyrizi®) is a humanized mAb of the IgG1 subclass directed towards IL23p19. The mAb has been engineered to reduce Fcγ receptor and complement binding and potential charge heterogeneity and binds with high affinity to human IL-23. Risankizumab (Skyrizi®) is currently approved in multiple countries for the treatment of adults with moderate to severe UC and CD.[4-7]

Vedolizumab (Entyvio®) is a monoclonal antibody integrin receptor antagonist directed against the α4β7 heterodimer. It has been approved in multiple countries for both UC and CD.

Why Is This Study Being Conducted?

This study is being conducted to compare efficacy and safety of risankizumab versus vedolizumab for the treatment of adult subjects with moderate to severe UC who are naïve to TaTs. With a growing number of therapies in UC, head-to-head study in 100% naïve patients to the TaTs will inform the HCPs with empirical data to aid in their treatment strategies to optimize long term outcomes in UC patients. Patient population which is 100% naïve to available TaTs for UC presents a homogenous patient population to compare the efficacy and safety of two established treatment options for UC patients within a head-to-head study design.

Refer to Section 1.2, Study Schema, and Section 1.3, Activity Schedule, for more information on the study design.

2.2 Benefits and Risks to Subjects

This study is designed to evaluate the potential treatment effect of risankizumab in UC compared to another approved treatment, vedolizumab, in UC.

The Phase 2 and Phase 3 program with risankizumab demonstrated efficacy for improvement in signs and symptoms of UC and the safety results were consistent with those known to be associated with mechanism of action or other appropriate safety findings. Risankizumab (Skyrizi®) has been approved for use in moderate to severe UC.

As with many immune modulating agents, risankizumab and vedolizumab may impair immune function, resulting in a risk of infection. This will be monitored by collection of all AEs during the study treatment and observation periods. In addition, subjects with active systemic infections or a clinically important infection will not be included in the study. For both study treatments, risankizumab and vedolizumab, screening for TB will be completed before initiation of treatment and according to the local practice.

Published literature indicates that inhibition of IL-23 is unlikely to increase the risk for cancer. Expression of IL-23 is increased in human tumors.[3,8,9] Moreover, preclinical data have demonstrated a beneficial effect of IL-23 p19 inhibition in animal models, both for pre-existing and tumor-induction models.[6] There is a theoretical risk possibility of decreased immune surveillance against malignancies with alteration of immune pathways; however, the weight of evidence assessment from clinical trials suggests a low risk of malignancy from chronic dosing with risankizumab in humans.

Elevations of transaminase and/or bilirubin were reported with use of risankizumab and vedolizumab. Therefore, this study includes timely detection, evaluation, and follow-up of alterations in selected liver laboratory parameters to ensure subjects' safety.

Increases in MACE events, including MI, cerebrovascular accident, and cardiovascular death, which were reported initially with anti-IL-12/23 agents, such as ustekinumab, have not been observed in longer term studies with risankizumab. While the likelihood of increased MACE is small, all suspected cardiovascular or cerebrovascular events (serious or nonserious) observed in this study will be adjudicated by an independent CAC. The committee will remain blinded to treatment allocation (Section 9.3).

Local reactions to subcutaneously or intravenously administered biologic therapies are usually limited to redness, swelling, or induration at the injection or infusion site. Manifestations of systemic hypersensitivity reactions may include anaphylaxis, generalized urticaria, hypotension, and respiratory distress. Serious hypersensitivity reactions, including anaphylaxis, have been reported with use of risankizumab. Both local and systemic hypersensitivity reactions are readily detectable, transient in nature, and manageable with standard medical treatment. Subjects will be closely monitored during study treatment administration on site (Section 8.11).

In conclusion, the benefit-risk profile of risankizumab is considered appropriate for this head-to-head study.[7] Based on data from the integrated safety analyses, risankizumab is safe and well tolerated and demonstrates a favorable benefit-risk profile.

For further details, please see findings from completed studies, including safety data in the current risankizumab IB.

Integrin antagonists like vedolizumab inhibit tumor growth by affecting both tumor cells and tumor associated host cells, most notably the angiogenic endothelium. Overall, the number of malignancies in the clinical trials with vedolizumab was small; however, long-term exposure was limited.[8] Serious infections including TB were reported in patients treated with vedolizumab.[8] Infusion-related reactions and hypersensitivity reactions have been reported, including anaphylaxis. Although unlikely, a risk of PML during treatment with vedolizumab cannot be ruled out. Monitoring of patients for any new or worsening neurological signs or symptoms is required while treated with vedolizumab.[8,9] Caution should be exercised when considering the use of vedolizumab in patients previously treated with rituximab Overall, reported safety data from vedolizumab reveal a favorable safety profile with low incidence rates of serious infections, opportunistic infections, infusion-related reactions and malignancies over an

extended treatment period. Details regarding the risks and benefits of vedolizumab can be found in the locally-approved product label. The benefit-risk profile of vedolizumab is considered appropriate for this head-to-head study.[10]

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

The objective of this study is to compare the efficacy and safety of risankizumab versus vedolizumab over 48 weeks for the treatment of adult subjects with moderate to severe UC who are naïve to TaTs.

Primary Efficacy

The primary efficacy objective of this study is to demonstrate a superior rate of endoscopic improvement at Week 48 in the risankizumab group as compared to the vedolizumab group in adult subjects with moderate to severe UC who are naïve to TaTs.

The hypothesis corresponding to the primary efficacy objective is:

- The proportion of subjects treated with risankizumab achieving endoscopic improvement (per central reading) at Week 48 is greater than that in subjects treated with vedolizumab.

The estimand corresponding to the primary efficacy objective is defined as follows:

- Difference in the proportion of subjects achieving endoscopic improvement at Week 48 regardless of premature discontinuation of study treatment, without initiation or dose escalation of UC-related corticosteroids, and without UC-related surgery in the risankizumab group in comparison with the vedolizumab group in adult subjects with moderate to severe UC who are naïve to TaTs.

Secondary Efficacy

The secondary efficacy objective of this study is to demonstrate a non-inferior or superior rate of clinical remission per mMS at Week 48 in the risankizumab group as compared to the vedolizumab group in adult subjects with moderate to severe UC who are naïve to TaTs.

The two hypotheses corresponding to the secondary efficacy objective are:

- The proportion of subjects treated with risankizumab achieving clinical remission per mMS at Week 48 is non-inferior to that in subjects treated with vedolizumab.
- The proportion of subjects treated with risankizumab achieving clinical remission per mMS at Week 48 is superior to that in subjects treated with vedolizumab.

The estimand corresponding to the secondary efficacy objective is defined as follows:

- Difference in the proportion of subjects achieving clinical remission per mMS at Week 48 regardless of premature discontinuation of study treatment, without initiation or dose escalation of UC-related corticosteroids, and without UC-related surgery in the risankizumab group in comparison with the vedolizumab group in adult subjects with moderate to severe UC who are naïve to TaTs.

3.2 Primary Endpoint

The primary endpoint is the achievement of endoscopic improvement at Week 48, defined as a centrally read endoscopy subscore of 0 or 1 (score of 1 modified to exclude friability): superiority of risankizumab vs. vedolizumab.

3.3 Secondary Endpoints

The achievement of clinical remission per mMS at Week 48, defined as SFS ≤ 1 and not greater than Baseline, RBS = 0, and a centrally read endoscopy subscore of 0 or 1 (score of 1 modified to exclude friability): non-inferiority of risankizumab vs. vedolizumab test first followed by superiority test.

3.4 [redacted]

[redacted]

3.5 Safety Endpoints

Safety evaluations include AE monitoring, physical examinations, vital sign measurements, and clinical laboratory testing (hematology and chemistry) as measures of safety and tolerability for the entire study duration.

3.6 Pharmacokinetic Endpoints

Serum risankizumab concentrations, serum ADA and serum NAb (if applicable) will be determined from samples collected in case of hypersensitivity reactions only and only for subjects randomized to risankizumab treatment. No other predefined PK or immunogenicity sampling is planned for the study.

3.7 Biomarker Research

Optional biospecimens (e.g., blood, stool, and tissue biopsies) will be collected at specified time points (Section 1.3) throughout the study, to evaluate known and/or novel disease-related or treatment-related biomarkers in circulation or at tissue sites. Biospecimen sample analysis may be used to generate prognostic, predictive, pharmacodynamic, or surrogate biomarkers. Types of biomarkers may include nucleic acids, proteins, lipids, and/or metabolites, either free or in association with particular cell types. The samples may also be used to develop new therapies, research methods, diagnostic tests or technologies and may be analyzed as part of a multi-study assessment of factors influencing the subjects' response to the study treatment (or treatments of the same or similar class) or the development and progression of the subjects' disease or related conditions. The analyses may include but are not limited to immunohistochemistry, immunofluorescence, transcriptomics, proteomics, epigenetics, and metabolomics.

This research may be exploratory in nature, as such the results should not be used for patient management, may not be included with the clinical study report, and may be performed at a non-GLP laboratory. Further details regarding the biomarker research sampling and collection are located in Section 8.6. Provision of biospecimens for biomarker research is optional and contingent upon signed biomarker collection consent form. Samples will not be collected from sites where local regulations do

not allow for the collection, use, and storage of samples as described in the protocol. The samples may be retained for up to 20 years after study completion or per local requirements.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase 3b, multicenter, randomized, open label study to compare efficacy and safety of risankizumab versus vedolizumab for the treatment of adult subjects with moderate to severe UC who are naïve to TaTs.

The duration of the study is approximately 69 weeks for subjects randomized to risankizumab and 71 weeks for subjects randomized to vedolizumab. This includes up to a 35-day screening period followed by a primary treatment period of 44 weeks for risankizumab and 46 weeks for vedolizumab, and a 140-day follow-up visit/call after the last dose of study treatments if required (see details below).

Subjects who meet eligibility criteria will be randomized into a 1:1 ratio to risankizumab or vedolizumab. Randomization will be stratified by steroid use at Baseline (yes/no) and mMS at Baseline (≤ 7/> 7) per central reading.

Subjects randomized to risankizumab at Baseline will receive risankizumab 1200 mg induction dose IV administered at Baseline and Weeks 4 and 8. At Week 12, depending on the clinical remission status per mMS based on the local reader, subjects will receive a risankizumab maintenance dose of either 180 mg (clinical remission: Yes) or 360 mg (clinical remission: No) SC every 8 weeks with last dose of risankizumab SC at Week 44.

For countries where no commercial risankizumab or local access mechanism is available, subjects randomized to risankizumab at Baseline may participate in an optional PTE (Section 16) upon completion of the Week 48 visit, until commercial risankizumab or local access mechanism is available or until the end of the PTE at Week 196, whichever comes first.

The 140-day follow-up visit/call is to obtain information on any new or ongoing AEs for those subjects who do not initiate commercial risankizumab or who are not eligible to continue risankizumab through the optional PTE. The 140-day follow-up visit/phone call following the last dose of risankizumab study treatment during the trial will not be required for any subject who initiates commercially available risankizumab upon the study Completion Visit or Premature Discontinuation visit.

Subjects randomized to vedolizumab at Baseline will receive vedolizumab 300 mg IV at Baseline, Weeks 2 and 6, and every 8 weeks with last dose of vedolizumab IV at Week 46. At Week 48, the investigator can identify the preferred treatment options for these subjects once they have completed the study.

For subjects in vedolizumab group, the 140-day follow-up visit/phone call following the last dose of study treatment is required regardless of the treatment options decided by the investigator.

A subset of sites will perform abdominal IUS at Baseline, and Weeks 4, 12, 28, and 48 for subjects randomized to risankizumab and at Baseline, and Weeks 6, 12, 30, and 48 for subjects randomized to vedolizumab. See Section 8.15 for information regarding abdominal IUS.

A ± 7-day window is allowed for all study visits.

The end-of-study is defined in Section 4.4.

4.2 Discussion of Study Design

This is an open-label study. Given this is a head-to-head study (i.e., no placebo and all subjects know that they are receiving active drug), and the IV dose is prepared by an unblinded pharmacists, the risk of a biased interpretation of the study results is low. In addition, the subject self-selection bias from the open-label design is anticipated to be low since both treatments are approved. Furthermore, the primary endpoint is endoscopic improvement based on blinded central reading scores, the endpoint measure is totally objective, and no reporting bias is expected.

Choice of Control Group

An active treatment concurrent control was chosen for this study to compare the efficacy and safety of risankizumab versus the approved biologic vedolizumab for the treatment of adult subjects with moderate to severe UC who are naïve to TaTs for UC.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study and are generally accepted. All efficacy and safety-related measurements in this study are standard for assessing disease activity in subjects with moderate to severe UC. 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.

Suitability of Subject Population

The target subject population for this study represents adult male and female subjects with moderately to severely active UC who meet all eligibility criteria for enrollment. A subject population with UC which is 100% naïve to available TaTs for UC represents a homogenous patient population to compare the efficacy and safety of two established treatment options for UC within this head-to-head study design.

Selection of Doses in the Study

The dose selection in this study is based on the locally approved doses for risankizumab and vedolizumab for the treatment of adults with moderate to severe UC.

4.3 Treatment After End of Study

As the subject nears study completion of the Primary Treatment Period (Week 48), the investigator will discuss the appropriate subsequent treatment with the subject. Subjects randomized to risankizumab at Baseline in countries where no commercial risankizumab or local access mechanism is available will be

able to participate in an optional PTE for up to 144 weeks after study completion of the Primary Treatment Period (Week 48). Details on the optional PTE are in Section 16.

4.4 Start and Completion of the Study

The start-of-study is defined as the date of the first site activated.

The end-of-study is defined as the date of end-of-study participation by the last subject in the last country for the Primary Treatment Period (Weeks 0 to 48) (i.e., the last subject last visit; applicable 140-day follow-up visit/phone call).

The completion of the Primary Treatment Period for a subject is defined as one of the following:

- The date of the follow-up visit/call (140 days after the last dose), as applicable
- The date of the Week 48 visit (for subjects who initiate commercial risankizumab or who enter the optional PTE).
- The date of the last study visit (for subjects who prematurely discontinue and do not consent and/or complete the 140-day follow-up visit/call)

PTE visits for purposes of continued treatment are considered optional and do not preclude a subject from completing the study as defined by the end-of-study definition (See also Section 7.1 and Section 16).

5 STUDY POPULATION

5.1 Eligibility Criteria

Subjects are eligible to be included in the study if they meet all of the inclusion criteria and none of the exclusion criteria specified in this protocol.

Inclusion Criteria

1. Subjects must voluntarily sign and date an informed consent, approved by an IEC/IRB, prior to the initiation of any screening or study-specific procedures.
2. Individuals at least 18 years old to ≤ 80 years old at the Baseline visit. Subject must also meet the legal age of majority per local law.
3. Subjects are willing and able to comply with procedures required in this protocol.
4. Subjects must not be incarcerated and must be freely willing and able to provide informed consent. Examples of subjects unable to freely provide informed consent may include some adults under legal protection measure (e.g., under guardianship/curatorship) or unable to express their consent and select adults under psychiatric care. Investigator's discretion should be applied.

5. Subject is judged to be in good general health, as determined by the investigator based upon the results of a medical history, physical examination, laboratory profile, and a 12-lead ECG performed during the Screening period.
6. Subject has confirmed diagnosis of UC for at least 3 months prior to Baseline. Documentation of biopsy results consistent with the diagnosis of UC as assessed by the Investigator must be available.
7. Subject has active UC with an mMS of 5 to 9 points and endoscopic subscore of 2 to 3 (confirmed by central reader).
8. Subject has 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), and immunomodulators.
    - 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 ≤ 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 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:
                - Azathioprine: ≥ 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-mercaptopurine: ≥ 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 SC or 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 Taiwan and other countries in Asia with local treatment guidelines that include tacrolimus) documented trough level 5 to 10 ng/mL

9. Pregnancy testing in females of childbearing potential/individuals of childbearing potential; the subject must meet the criteria as stated in Section 5.2 Contraception Recommendations of this protocol:
   - Females of childbearing potential/Individuals of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at Baseline prior to the first dose of study treatment (local practices may require serum pregnancy testing at Baseline).
   - Subjects with a borderline serum pregnancy test at Screening must have absence of clinical suspicion of pregnancy or other pathological causes of borderline results and a serum pregnancy test ≥ 3 days later to document continued lack of a positive result (unless prohibited by local requirements).
   - Subjects with a urine pregnancy test at Baseline that is borderline or ambiguous must have a serum pregnancy test. In such cases, the subject must be excluded from participation if the serum pregnancy result is positive.
10. Female subjects of childbearing potential/Individuals of childbearing potential must practice at least 1 protocol-specified method of birth control, from Baseline Visit through at least 140 days (20 weeks or as guided by the local risankizumab label [if approved], whichever is longer) after the last dose of study treatment (local practices may require 2 methods of birth control; refer to Section 5.2 for more details on change in childbearing potential of female subjects/individual subjects and contraception).
11. Female subjects/Individual subjects who are not pregnant, breastfeeding, or considering becoming pregnant during the study or for approximately 140 days (20 weeks or as guided by the local risankizumab label [if approved], whichever is longer) after the last dose of study treatment.
12. Subject must meet the following guidelines for discontinuing or maintaining stable doses of concomitant medications prior to the first dose of study treatment (i.e., Baseline visit):
    - Oral/intramuscular anti-infectives (non-UC related) must be discontinued ≥ 14 days prior to Baseline; an exception is made for TB prophylaxis;
    - Exclusive enteral nutrition or any parenteral nutrition must be discontinued ≥ 35 days prior to Baseline;
    - Oral cyclosporine, oral tacrolimus, or mycophenolate mofetil must be discontinued ≥ 35 days prior to Baseline;

- Fecal microbial transplantation must be discontinued ≥ 35 days prior to Baseline;
- Cannabis use, either for recreational or medical reasons, must be discontinued ≥ 14 days prior to Baseline;
- Doses of UC-related antibiotics must be kept stable for ≥ 14 days prior to Baseline (subjects may discontinue UC-related antibiotics, but must occur ≥ 14 days prior to Baseline);
- Dose of oral aminosalicylates must be kept stable ≥ 14 days prior to Baseline (subjects may discontinue oral aminosalicylates, but must occur ≥ 14 days prior to Baseline);
- Doses of IMMs (i.e., azathioprine, 6-mercaptopurine, MTX) must meet all of the following conditions:
  - The current course of IMMs must have initiated ≥ 42 days prior to Baseline, and;
  - Doses must be kept stable for ≥ 35 days prior to Baseline (subjects may discontinue IMMs, but must occur ≥ 35 days prior to Baseline).

Exclusion Criteria

1. Employees of the sponsor and/or study sites and their family members may not be enrolled in this study.
2. Laboratory values meeting the following criteria within the screening period prior to the first dose of study treatment:
   - Serum AST > 2 × ULN;
   - Serum ALT > 2 × ULN;
   - Serum total bilirubin > 2.0 mg/dL; except for subjects with isolated elevation of indirect bilirubin relating to Gilbert syndrome;
   - Total WBC count < 3,000/µL;
   - ANC < 1,500/µL;
   - Platelet count < 100,000/µL;
   - Hemoglobin < 8.0 g/dL (80 g/L)
3. History of clinically significant (per investigator's judgment) drug or alcohol abuse within the last 6 months.
4. Subject with a current diagnosis of CD or IBD-unclassified or a history of radiation colitis or ischemic colitis.
5. Subjects with any history of an allergic reaction or significant sensitivity to constituents of the study treatments (and their excipients) and/or other products in the same class.
6. Subject has received any TaTs for UC, including but not limited to infliximab, etanercept, adalimumab, natalizumab, golimumab, ozanimod, ustekinumab, etrolizumab, vedolizumab, tofacitinib, filgotinib, etrasimod, guselkumab, mirikizumab, upadacitinib, and risankizumab.

7. 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.
8. Subject who received IV/intramuscular corticosteroids within 14 days prior to Screening or during the Screening period.
9. 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
10. 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
11. 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.
12. Subjects has any of the following medical disorders:
    - History of GI perforation (other than due to appendicitis or mechanical injury), diverticulitis, or significantly increased risk for GI perforation per investigator judgment including history of volvulus and/or intussusception (telescoping of bowels);
    - Diagnosis of CD or indeterminant colitis;
    - Current known complications of UC such as: fulminant colitis and/or toxic megacolon, acute severe UC, previous colectomy (total or subtotal), or any other manifestation that might require surgery while in the study;
    - Current diagnosis of short bowel syndrome;
    - Known or suspected primary immune deficiency;
    - Ostomy or ileoanal pouch;
    - Current or history of dysplasia of the GI tract or the presence of dysplasia, other than completely removed low-grade dysplastic lesions, in any biopsy performed during the Screening endoscopy.
13. Subjects who have had major surgery performed within 12 weeks prior to randomization or planned during the conduct of the study (e.g., hip replacement, aneurysm removal, stomach ligation).
14. Subjects with the following chronic or active infections:
    - Active HBV or HCV infection, defined as:

- HBV: HBs Ag positive (+) test or detected sensitivity on the HBV DNA PCR qualitative test for subjects who are HBc Ab positive (+) (and for HBs Ab positive [+] subjects where mandated by local requirements).
- HCV: HCV RNA detectable in any subject with HCV Ab.

- Are infected with HIV, defined as confirmed positive anti-HIV antibody (HIV Ab) test. Note: In case a screened subject has a confirmed positive HIV Ab test, Inclusion Criterion 5 should be selected in eCRF for documentation of screening failure.
- Active TB. For subjects with latent TB, please see Section 8.12.

15. Active systemic infection/Clinically important infection during the last 2 weeks prior to Baseline Visit as assessed by the investigator.
16. Subjects with infection with *Clostridium difficile* or other intestinal pathogens during Screening.
17. Subject has used any of the following drugs or therapies prior to or during the Screening period. Subject has not met the minimum washout period for list drug prior to the Screening period is specified below or at least 5 times the mean terminal elimination half-life of a drug:
    - At least 60 days for apheresis (e.g., Adacolumn apheresis);
    - At least 14 days for a combination of 2 or more of the following oral budesonide, or oral beclomethasone and/or oral prednisone (or equivalent) simultaneously, with the exception of inhalers;
    - At least 14 days for IV/intramuscular corticosteroids;
    - At least 14 days for therapeutic enema or suppository, other than required for endoscopy.
18. Subjects who have any of the following medical diseases or conditions:
    - Recent (within past 6 months) cerebrovascular accident or MI;
    - History of an organ transplant which requires continued immunosuppression;
    - Active or suspected malignancy or history of any malignancy within the last 5 years except for successfully treated NMSC or localized carcinoma in situ of the cervix.
    - Active, chronic, or recurrent infection that based on the Investigator's clinical assessment makes the subject unsuitable candidate for the study;
19. Subjects with severe, progressive, or uncontrolled renal, hepatic, hematological or endocrine disorders or symptoms thereof.
20. Subjects with a history of or current lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly.
21. Subject has previously received rituximab.
22. Subjects who received any live vaccine (with the exception of replication deficient viral vaccines, e.g., JYNNEOS (also known as Imvamune® or Imvanex®) for the prevention of monkeypox disease) within 4 weeks prior to the first dose of study treatment or expect the need for live vaccination during study participation including at least 140 days (20 weeks or as guided by the

local risankizumab label [if approved], whichever is longer) after the last dose of study treatment.

23. Subject treated with any investigational treatment within 30 days or 5 half-lives of the treatment (whichever is longer) prior to the first dose of study treatment or is currently enrolled in another clinical study or was previously enrolled in this study.

5.2 Contraception Recommendations

Contraception Requirements for Females/Subjects

Subjects must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential/Individuals, Non-Childbearing Potential

  Females/Individuals do not need to use birth control during or following study treatment if considered of non-childbearing potential due to meeting any of the following criteria:

  1. Female/Individual with permanent sterility or permanent infertility due to one of the following:
     - Permanent sterility due to a hysterectomy, bilateral salpingectomy, bilateral oophorectomy
     - Non-surgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals.
  2. Postmenopausal female/individual
     - 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 a FSH level ≥ 30 IU/L.

If a female/individual does not meet the above definition of a female/individual of non-childbearing potential, the subject would be considered to be a female of childbearing potential/individual of childbearing potential.

- Females, of Childbearing Potential/Individuals, of Childbearing Potential
  - Females of childbearing potential/Individuals of childbearing potential must avoid pregnancy while taking study treatment(s) and for at least 140 days (20 weeks or as guided by the local risankizumab label [if approved], whichever is longer) after the last dose of study treatment.
  - Females of childbearing potential/Individuals of childbearing potential must commit to use a contraceptive method listed below that is highly effective (with a failure rate of < 1% per year, when used consistently and correctly):

- Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1
- Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1
- Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
- IUD
- IUS
- Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
- Practice true abstinence, defined as: Refraining from intercourse with a sperm-producing partner 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).

- If required per local regulations, a barrier method (preferably a male condom with or without spermicide; other barrier options are female condom, cap, diaphragm or sponge with spermicide) should be used in addition to one of the birth control methods listed above (excluding true abstinence).
- Contraception recommendations related to use of concomitant therapies prescribed should be based on the local label.

5.3 Prohibited Medications and Therapy

Biologic Therapies and Small Molecules

Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility. Subjects must have no prior exposure to TaTs for UC (Exclusion Criterion 5).

Therapies including but not limited to the following biologic therapies and small molecules are prohibited medications through Week 48 visit/last on-site study visit or through discontinuation of study drug:

- Abatacept
- Adalimumab
- Anakinra
- Belimumab
- Certolizumab
- Etanercept
- Golimumab
- Infliximab
- Ixekizumab
- Natalizumab
- Rituximab
- Secukinumab
- Tocilizumab
- Ustekinumab
- Ozanimod
- Etrasimod
- Mirikizumab
- Tofacitinib
- Baricitinib
- Filgotinib
- Guselkumab
- Upadacitinib

Live vaccines (except non-replicating live vaccines e.g., JYNNEOS [also known as Imvamune® or Imvanex®] monkeypox vaccine) are not permitted during study participation and including up to 140 days (20 weeks or as guided by the local risankizumab label [if approved], whichever is longer) after the last dose of study treatment. Examples of live vaccines include, but are not limited to, the following:

- Adenovirus
- BCG
- Cholera
- Zoster vaccine live (Zostavax®)
- Measles-mumps-rubella or measles mumps rubella varicella
- Monovalent live attenuated influenza A (intranasal)
- Oral polio vaccine
- Rotavirus
- Seasonal trivalent live attenuated influenza (intranasal)
- Smallpox
- Oral typhoid vaccine
- Varicella (chicken pox)
- Yellow fever
- Dengue (Dengvaxia®)

5.4 Prior and Concomitant Therapy

Stable doses of other concomitant therapies for chronic conditions, for which neither the condition nor the treatment are judged by the investigator to exclude the subject from participation, are permissible. All concomitant medications should be carefully evaluated by the investigator.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject has received from 4 weeks prior to screening 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 on the appropriate eCRF.

For sites in China, subjects must record concomitant medication on the subject paper diary cards (see Section 15).

Any questions regarding concomitant or prior therapy should be raised to the AbbVie medical emergency contact. Information regarding potential drug interactions with risankizumab can be located in the risankizumab IB. Information regarding potential drug interactions with vedolizumab can be located in the approved product insert.

Non-live vaccines may be administered during screening or treatment period, if not contraindicated or medically inappropriate.

Subjects taking corticosteroids at Baseline must continue the Baseline dose for 2 weeks and then must initiate a taper according to the taper schedule outlined in Table 3 below. If a subject should experience an inadequate response during the corticosteroid taper, the subject may have the corticosteroid dose increased per the Investigator's discretion up to the dose used at Baseline. Initiation of systemic and/or UC-related corticosteroids during the entire study is prohibited. Decreasing doses of corticosteroids is prohibited during the first 2 weeks, except in the event of moderate-to-severe treatment related toxicities and after discussion with the AbbVie Study MD.

Table 3. Corticosteroid Taper Schedule

Drug Name	Dose	Taper Rate
Prednisone (or equivalent)	> 10 mg/day	5 mg/day per week
	≤ 10 mg/day	2.5 mg/day per week
Budesonide	≤ 9 mg/day	3 mg/day per week

5.5 Screen Failures

A screen failure occurs when a subject who has consented to participate in the clinical study is not subsequently assigned to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographics, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened subjects will not be assigned a new subject number for every screening/rescreening event.

6 STUDY TREATMENTS

6.1 Treatments Administered

Study treatments refer to treatments that are used in this study (Table 4). Investigators will assess the relationship of AEs to the use of study treatments.

Risankizumab will be administered IV at Baseline and Weeks 4 and 8. Risankizumab will be administered SC at Weeks 12, 20, 28, 36, and 44. Subjects who continue in the PTE will follow the schedule in Section 16.

Vedolizumab will be administered IV at Baseline, and Weeks 2, 6, 14, 22, 30, 38, and 46.

Table 4. Description of Study Treatment

Study Treatment	Dosage Form	Strength	Route of Administration	Storage Conditions
Risankizumab (ABBV-066)	Concentrate for solution for infusion	600 mg/10 ml (vial)	IV infusion	Store at 2°C to 8°C (36°F to 46°F)
	Solution for injection	180 mg/1.2 mL (PFS)	SC injection	Store at 2°C to 8°C (36°F to 46°F)
Vedolizumab	Injection, Powder, Lyophilized, for Solution or powder for concentrate for solution for infusion*	300 mg (vial)	IV infusion	Refer to clinical label

* Or as locally sourced/available.

AbbVie will provide study treatment for risankizumab. AbbVie provided study treatment should not be substituted or alternately sourced unless otherwise directed by AbbVie.

Vedolizumab will be provided by AbbVie or sourced locally by the sites (if applicable), depending on country regulations. Presentation might vary depending on country of origin.

Upon completion of or discontinuation from study treatment, all original study treatment units (containing unused study treatments)/devices will be returned to the sponsor (or designee) or destroyed on site. All return or destruction procedures will be according to instructions from the sponsor and according to local regulations following completion of treatment/device accountability procedures.

6.2 Packaging and Labeling

Risankizumab and vedolizumab will be packaged with quantities sufficient to accommodate study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study treatment should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via IRT and encodes the appropriate study treatment to be dispensed at the subject's corresponding study visit. Site staff will complete all blank spaces on the label before dispensing to subjects. Study treatment will only be used for the conduct of this study.

6.3 Storage and Disposition of Study Treatment

Risankizumab must be stored at 2° to 8°C (36° to 46°F). For detailed storage conditions for risankizumab refer to clinical label. For vedolizumab refer to the clinical label for storage conditions.

The investigational products are for investigational use only and are to be used only within the context of this study. The study treatment 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 on site as appropriate.

Sites are responsible for maintaining the investigational study treatment and devices according to the storage conditions specified on the clinical label and monitoring for temperature excursions with the use of a calibrated continuous temperature monitoring device (for example, chart recorders and/or acceptable calibrated min/max thermometers) or continuous monitoring systems. Specific guidance on appropriate temperature monitoring and temperature excursions reporting requirements will be provided separately.

6.4 Preparation/Reconstitution of Dosage Form

Written instructions for the preparation of study treatment for infusion will be provided as a separate document from the protocol.

6.5 Selection and Timing of Dose for Each Subject

Subjects will have study treatment administered by study site personnel as specified in Section 1.3.

Subjects randomized to risankizumab at Baseline will receive risankizumab 1200 mg induction dose IV administered at Baseline and Weeks 4 and 8. At Week 12, depending on the clinical remission status per mMS per local reading, the subjects will receive a risankizumab maintenance dose of either 180 mg (clinical remission: Yes) or 360 mg (clinical remission: No) SC every 8 weeks, with last dose of risankizumab SC at Week 44.

Subjects randomized to vedolizumab at Baseline will receive vedolizumab 300 mg IV at Baseline, Weeks 2, 6, and every 8 weeks with last dose of vedolizumab IV at Week 46.

The last study visit will occur at Week 48.

Subjects who continue in the PTE will follow the schedule in Section 16.

6.6 Randomization/Treatment Assignment

All subjects will be assigned a unique identification number by the IRT at the screening visit. For subjects who rescreen, the screening number assigned by the IRT at the initial screening visit should be used. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule.

For subjects who do not meet the study selection criteria, the site personnel must contact the IRT system and identify the subject as a screen failure.

Subjects who are enrolled will retain their subject number assigned at the screening visit throughout the study. Upon receipt of study treatment, the site will acknowledge receipt in the IRT system.

Study treatment must not be dispensed without contacting the IRT system. Study treatment may only be dispensed to subjects enrolled in the study through the IRT system. At the end of the Treatment Period or at the Premature D/C visit, the site will contact the IRT system to provide visit date information and study treatment return information for each kit.

Randomization will be stratified by steroid use at Baseline (yes/no) and mMS at Baseline (≤ 7/> 7) per central reading.

Contact information and user guidelines for IRT use will be provided to each site.

7 DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Withdrawal of Subjects and Discontinuation of Study

For subjects who prematurely discontinue from the study, the required PD visit procedures should be conducted as soon as possible, preferably within 2 weeks, and the 140-day follow-up visit/phone call should occur.

Subjects who have shown no evidence of therapeutic benefit after 14 weeks of treatment for vedolizumab and 24 weeks of treatment for risankizumab must be discontinued from study drug.

A subject can be withdrawn from the study for reasons including, but not limited to, the following:

- The subject requests withdrawal from the study.
- The investigator believes it is in the best interest of the subject.
- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study treatment, as determined by the investigator or the Sponsor.
- Subject is non-compliant with TB prophylaxis (if applicable) or develops active TB at any time during the study.
- Subject develops any malignancy, except for a localized NMSC or a carcinoma in-situ of the cervix where discontinuation is at the discretion of the Investigator.
- The subject becomes pregnant while on study treatment.
- Eligibility criteria violation was noted after the subject started study treatment and continuation of the study treatment would place the subject at risk as determined by the AbbVie TA MD.
- Introduction of prohibited medications or dosages when continuation of the study treatment would place the subject at risk.

- The investigator determines the subject is significantly noncompliant with study procedures.
- Post-Baseline occurrence of one or more of the following hepatic test abnormalities (confirmed on a second separate sample at least 48 hours apart):
  - ALT or AST > 8 × ULN;
  - ALT or AST > 5 × ULN for more than 2 weeks;
  - ALT or AST > 3 × ULN and Total Bilirubin > 2 × ULN or international normalized ratio [INR] > 1.5;
  - ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).
  - Subjects who meet any of the above criteria should be evaluated for an alternative etiology of the ALT or AST elevation and managed as medically appropriate. If applicable, the alternative etiology should be documented in the site source documents. If after clinically appropriate evaluation, no alternative etiology for ALT or AST elevation is found or the ALT or AST elevation has not resolved or is not trending down toward normal, the subject should be discontinued from study treatment.
- Subject who develops a serious hypersensitivity reaction, including anaphylaxis, should be discontinued and appropriate therapy initiated immediately.
- Subject with confirmed PML must discontinue vedolizumab therapy immediately and be discontinued from the study.

All attempts must be made to determine the date of the last study treatment dose and the primary reason for discontinuation of study treatment or study participation. The information will be recorded on the appropriate eCRF page. 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, the subject will be treated in accordance with the investigator's best clinical judgment.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at their site if they have safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

Possible reasons for discontinuation of the study include unacceptable risk, any relevant toxicity, or a negative change in the risk/benefit assessment, request of member state concerned (regulatory agency and/or ethics commission), insufficient recruitment rate, withdrawal of the license to manufacture or of permission to import (for marketed IMPs).

7.2 Follow-Up After Subject Discontinuation of Study Treatment or from Study

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits, unless subjects have decided to discontinue the study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

If the subject has started a new TaT approved for UC after study drug discontinuation and the subject chooses to continue study participation, then only safety data are required to be collected (efficacy data should not be collected including endoscopy). If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the premature discontinuation visit should be completed as soon as possible, preferably within 2 weeks. In addition, if the subject is willing, a 140-day follow-up visit/phone call after the last dose of study treatment should be completed to ensure all treatment-emergent AEs/SAEs have been resolved. The 140-day (20 week) follow-up visit/phone call following the last dose of risankizumab study treatment during the trial will not be required for any subject who initiates commercially available risankizumab upon the study Completion Visit or Premature Discontinuation visit. For subjects in vedolizumab group, the 140-day follow-up visit/phone call following the last dose of study treatment is required regardless of the treatment options decided by the investigator.

In the event a subject withdraws consent from the clinical study, biomarker research will continue unless the subject explicitly requests analysis to be stopped. When AbbVie is informed the subject has withdrawn and no longer wishes biomarker samples research to continue, samples will not be analyzed and no new biomarker analysis data will be collected for the withdrawn subject or added to the existing data or database(s). A subject may withdraw consent for optional biomarker research at any time and remain in the clinical study. Data generated from the clinical study and/or optional biomarker research, before subject withdrawal of consent, will remain part of the study results.

8 STUDY PROCEDURES

Information regarding specific procedures is provided in this section. The timing of the activities for this study is presented in tabular form in Section 1.3 Activity Schedule.

8.1 Medical History

A complete medical history including demographics, history of tobacco, alcohol, and drug use will be taken at screening. The subject's medical history will be updated at the Baseline visit. This updated medical history will serve as the baseline for clinical assessment.

8.2 Adverse Event Assessment

Please refer to Section 9.2.

8.3 Mayo Score

The following Mayo Score will be collected in this study:

- mMS (also known as Adapted Mayo Score): A composite of SFS, RBS, and endoscopy subscores

Modified Mayo Score by Category

Stool Frequency	
0	Normal number of stools for this patient
1	1-2 more stools than normal
2	3-4 more stools than normal
3	5 or more stools more than normal
Rectal Bleeding	
0	No blood seen
1	Stool with streaks of blood
2	Stool with more than streaks of blood
3	Blood alone passed
Endoscopy	
0	Normal appearance mucosa
1	Mild disease (erythema, decreased vascular pattern), no friability
2	Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3	Severe disease (spontaneous bleeding, ulcerations)

Source: Food and Drug Administration. Ulcerative Colitis: Developing Drugs for Treatment Guidance for Industry. 2022.

Stool Frequency Subscore

- The subject should be asked to identify at the screening visit how many bowel movements (when a subject passed stool, blood alone, blood and mucus, or mucus only) he or she had in a 24-hour period when their UC is not active. This value will serve as the reference stool frequency and must be a full number of at least 1.
- The SFS is calculated by comparing the stool frequency to the reference stool frequency.
- Subjects will record the daily number of bowel movements throughout the trial. Using these numbers, the SFS 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 SFS during days which the subject received anti-diarrheal medication will be scored as a 3.
- The SFS based on 7 days prior to each study visit will be averaged and used for the SFS for each study visit.
- A minimum of 3 consecutive days of completed diary entries or 4 nonconsecutive days are necessary. Otherwise, the SFS should be considered missing.
- For visits that have endoscopies, the calculation of the 7-day average should exclude the subscores from non-applicable days, which is defined as the day of bowel preparation and the day of endoscopy. Daily diary entries will be used accordingly to provide the most recent data for 7 days prior to the respective study visit.

Rectal Bleeding Subscore

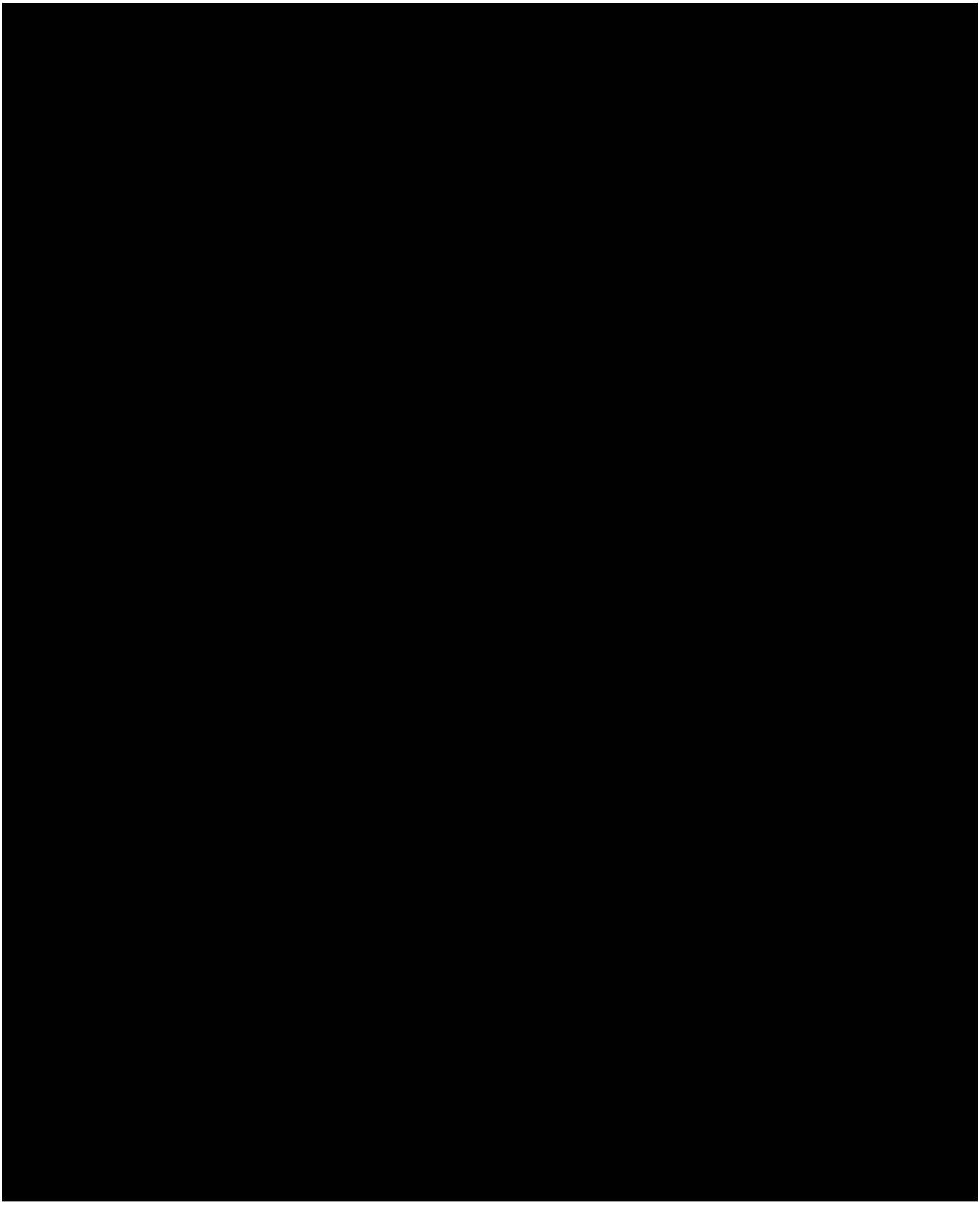
- Subjects will be assigned a daily RBS value as follows:
  - No visible blood with stool during the respective day should be scored as 0.
  - Stool with streaks of blood during the respective day should be scored as 1.
  - Stool with more than streaks of blood during the respective day should be scored as 2.
  - Blood alone passed during the respective day should be scored as a 3.
- The RBS based on 7 days prior to each study visit will be averaged and used for the RBS for each study visit.
- A minimum of 3 consecutive days of completed diary entries or 4 nonconsecutive days are necessary. Otherwise, the RBS should be considered missing.
- For visits that have endoscopies, the calculation of the 7-day average should exclude the subscores from non-applicable days, which is defined as the day of bowel preparation and the day of endoscopy. Daily diary entries will be used accordingly to provide the most recent data for 7 days prior to the respective 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 appearance of mucosa
  - 1 = Mild disease (erythema, decreased vascular pattern, no friability)
  - 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
  - 3 = Severe disease (spontaneous bleeding, ulcerations)

- 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.

8.4 Patient-Reported Outcomes



[redacted]

8.5 Pharmacokinetic Sampling

Blood samples for analysis of serum risankizumab, serum ADA, and NAb will be collected only in the event of a suspected post-dose systemic hypersensitivity reaction, and only from subjects randomized to the risankizumab treatment group as specified in Section 1.3.

Additional information on the collection, handling/processing and disposition can be found in the laboratory manual.

8.6 Biomarker Research Sampling

Biomarker research sample collection including the pharmacogenetic sample may be used to conduct exploratory investigations into known and novel biomarkers. Biomarker samples should be collected at the visits specified in Section 1.3. Stool samples should not be collected while the subject is taking bowel preparation or on the day of endoscopy. One optional whole blood sample for pharmacogenetics will be collected at Baseline from each subject who consents to optional biomarker analysis. If the optional pharmacogenomic biomarker sample is not collected at Baseline visit, it may be collected at any other visit during the study. All other biomarker samples should be collected at the visits specified in Section 1.3.

All samples may be stored for up to 20 years. AbbVie (or its designee) will store the samples and data in a secure storage space with adequate measures to protect confidentiality. Specific instructions for collection, handling, processing, storage, and shipment of samples will be provided by the central laboratory, AbbVie, or its designee.

8.7 12-Lead Electrocardiogram

12 Lead Electrocardiogram (Single Only)

Resting 12-lead ECGs will be obtained in single as specified in Section 1.3.

When an ECG is scheduled at the same time as a blood collection, the ECG will be obtained prior to the blood collection.

ECGs will be acquired after the subject has been in the supine position for at least 5 minutes. Subjects will be instructed to remain completely stationary (no talking, laughing, deep breathing, sleeping, or swallowing) for approximately 10 seconds during the ECG recording. While ECGs are being acquired, subjects and staff are prohibited from having devices (e.g., cellular telephones, fans, heaters, etc.) that emit electrical interference in the room.

For subjects with a normal ECG taken within 90 days of Screening, a repeat ECG at Screening will not be required, provided all protocol-required documentation is available and nothing has changed in the subject's health status since the time of the test that warrants a repeat test.

ECG Safety Review

Each ECG will be evaluated by an appropriately trained medical practitioner at the study site (the "local reader"). The local reading of the ECG will be used by the investigator for subject safety assessment.

The local reader will sign and date all the ECGs collected in this study and provide a global interpretation for each ECG using the following categories:

- Normal ECG
- Abnormal ECG Not clinically significant (NCS)
- Abnormal ECG Clinically significant (CS)
- Unable to evaluate

Clinically significant ECG findings noted at screening will be captured in Medical History.

All local reader evaluations of ECGs will be entered into the source documents. If the global interpretation is Abnormal (NCS or CS), the local reader will provide further information (e.g., sinus bradycardia, arrhythmia). The QTcF will be calculated and documented for all ECGs.

All ECG source documentation will be retained at the study site. The automatic cardiograph reading (i.e., cardiograph-generated measurements and interpretations) will not be collected for analysis.

8.8 Height and Weight

Height will be measured at screening only. Body weight will be measured at scheduled visits as specified in Section 1.3. The subject will wear lightweight clothing and no shoes during weighing.

8.9 Vital Signs

Vital sign determinations of systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature will be obtained at visits as specified in Section 1.3. Blood pressure, pulse rate, and respiratory rate should be measured before blood draws are performed. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes.

Measurements should be assessed consistently throughout the study. Vital signs measurements determined prior to dosing on Day 1 will serve as baseline.

8.10 Physical Examination

A complete physical examination, including height (at Screening only) and weight, or targeted physical exam will be performed at the designated study visits as specified in Section 1.3. The physical examination performed at Baseline visit will serve as the baseline physical examination for the entire study. Physical examination abnormalities noted at the Baseline Visit prior to the first dose of study treatment should be recorded in the subject's medical history. Any significant physical examination

findings after the first dose will be recorded as AEs. All findings, whether related to an AE or part of each subject's medical history, will be captured on the appropriate eCRF page.

At any time, a symptom-directed physical examination can be performed as deemed necessary by the investigator.

8.11 Administer Study Treatment

Study treatment will be dispensed to subjects beginning at Baseline (Day 1) and as specified in Section 1.3. All SC or IV doses of risankizumab or vedolizumab will be administered by designated and qualified study site personnel under the direction of the investigator. Date and exact time (to the nearest minute) of study treatment administration will be recorded on eCRFs. The first dose of study treatment will be administered after all other Baseline procedures are completed. Study treatment administration instruction for risankizumab PFS and /or vials will be provided to the site.

Each site will be responsible for maintaining treatment accountability records including product description, manufacturer, and lot numbers for all non-investigational products dispensed by the site.

Monitoring for Hypersensitivity Reactions

Therapeutic protein products, such as biologics, may elicit a range of acute effects, from symptomatic discomfort to sudden, fatal reactions and may encompass a wide range of clinical events, including anaphylaxis and other events that may not be directly related to Ab responses, such as cytokine release syndrome.

Serious hypersensitivity reactions, including anaphylaxis, have been reported with use of risankizumab and vedolizumab. Subjects should be closely monitored at the site for signs and symptoms of hypersensitivity reactions according to the product label of the study drugs, including allergic reactions and anaphylaxis, after all SC or IV dosing of study treatment have been administered at each dosing visit. A medical person qualified in the treatment of acute hypersensitivity reactions must be present during the injections.

All appropriate medical support measures (e.g., antihistamines, 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 injection should be monitored for appropriate resolution prior to leaving the site. Subjects are encouraged to report any symptoms related to a possible injection-related reaction 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 subjects.

Subjects will be monitored throughout the study for signs and symptoms suggestive of hypersensitivity reactions, including allergic reactions and anaphylaxis. In the event of a suspected anaphylactic/systemic hypersensitivity reaction, in addition to the standard AE eCRF, the supplemental Hypersensitivity Reaction Signs and Symptoms eCRF should also be completed by the site. The clinical criterion for diagnosing anaphylaxis is provided in Section 17 for reference; symptoms of anaphylactic reactions usually occur within minutes to 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.

In the event of a suspected anaphylactic reaction, blood and serum samples should also be collected as described in Section 8.12.

8.12 Clinical Laboratory Tests

The blood samples for serum chemistry tests (glucose, total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides) will be collected following a minimum 8-hour fast at the Baseline visit. If a subject is not able to fast at those visits, due to unforeseen circumstances, the non-fasting status will be recorded in study source documentation and lab requisition. Blood samples at other visits can be drawn without prior fast. The Baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study treatment.

Blood draws should be performed, as much as possible, after all questionnaires, clinical efficacy assessments, and vital sign determinations are obtained and before study treatment administration during a visit. Unscheduled clinical labs may be obtained at any time during the study if deemed appropriate per investigator's discretion.

A certified laboratory will be used to process and provide results for the clinical laboratory tests. Laboratory reference ranges will be obtained prior to the initiation of the study.

Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory.

If a laboratory test value is outside the reference range and the investigator considers the laboratory result to be clinically significant, the investigator will:

- repeat the test to verify the out-of-range value;
- follow the out-of-range value to a satisfactory clinical resolution; or
- discontinue the subject from the study and/or initiate the treatment in this subject; in this case, the laboratory result will be recorded as an AE.

<table>
<tr><th colspan="3">Clinical Laboratory Tests</th></tr>
<tr><th>Hematology</th><th>Clinical Chemistry</th><th>Urinalysis</th></tr>
<tr><td>Hematocrit
Hemoglobin
WBC count/
Leukocytes
Platelet count/Thrombocytes
Diff. Automatic (absolute count):
Neutrophils
Eosinophils
Basophils
Monocytes
Lymphocytes
Manual Differential (ONLY IF Automated Differential is abnormal):
Neutrophils, bands (Stabs)
Neutrophils, polymorphonuclear
Eosinophils
Basophils
Monocytes
Lymphocytes
<u>Coagulation</u>:
PT/INR[a]</td><td><u>Enzymes</u>:
ALT
AST
AP
GGT
<u>Electrolytes</u>:
Sodium
Potassium
Chloride
Bicarbonate
Calcium
Phosphorus
<u>Substrates</u>:
Glucose
BUN/Urea
CKD-EPI[b,c]
Bilirubin total
Bilirubin direct (if total is elevated)
Bilirubin indirect (if total is elevated)
Albumin
hsCRP
Cholesterol, total
LDL-C
HDL-C
Triglycerides
FSH[d]</td><td><u>Dipstick Urinalysis</u>[b]
Urine nitrite
Urine protein
Urine glucose
Urine ketone
Urobilinogen
Urine bilirubin
Urine RBC/erythrocytes
Urine WBC/leukocytes
Urine pH

ONLY IF urine analysis abnormal:
Urine Sediment (microscopic examination)</td></tr>
<tr><th>Additional Testing</th><td></td><th>Pregnancy Testing[f]</th></tr>
<tr><td>N/A</td><td></td><td>Urine pregnancy test (local)[g]
Serum pregnancy test[h]</td></tr>
<tr><td></td><td></td><th>Anaphylaxis Testing[i]</th></tr>
<tr><td></td><td>Infection Screening</td><td>Serum risankizumab concentration
Serum ADA
Serum NAb
Tryptase</td></tr>
<tr><td></td><td>HBs Ag (qualitative)[e]
HBs Ab (qualitative)[e]
Anti-HBc total (qualitative)[e]
HBV DNA (quantitative)[e]
Anti-HCV (qualitative)[e]
HCV RNA (quantitative)[e]
HIV-1 and HIV-2 Ab (qualitative)[e]
QuantiFERON®-TB (or IGRA equivalent) and/or purified PPD</td><td></td></tr>
</table>

a. INR test only performed if ALT or AST > 3 × ULN (upper limit of normal).

b. Only done at screening.

c. Calculated by the central laboratory.

d. FSH testing is to be done at Screening in all women aged ≤ 55 years with no menses for 12 or more months without an alternative medical cause.

e. Performed only at Screening. Per regional requirements: for subjects with HBs Ab (+) and/or HBc Ab (+) at Screening, the HBV-DNA PCR test should be performed again as noted in Section 8.12. Retesting is not necessary for subjects that have a history of HBV vaccine and are HBs Ab (+).

f. Pregnancy testing is not required for female subjects of non-childbearing potential/individuals of non-childbearing potential (defined in Section 5.2).
g. Urine pregnancy test will be performed at every dosing visit and the Week 48/PD Visit and must be conducted prior to study treatment dosing. Negative urine pregnancy test results must be confirmed prior to study treatment dosing.
h. Serum pregnancy test is conducted at Screening and at other visits only if urine pregnancy test is positive. Negative serum pregnancy test results must be confirmed prior to study treatment dosing.
i. Only performed in case of a suspected anaphylactic reaction. Risankizumab PK, ADA and NAb samples are to be collected only from subjects randomized to the risankizumab treatment group. Refer to anaphylaxis testing below.

Urinalysis

Dipstick urinalysis will be completed by the central laboratory at visits specified in Section 1.3. Specified abnormal macroscopic urinalyses defined as leukocytes, nitrite, protein, ketones, or blood greater than negative, or glucose greater than normal will be followed up with a microscopic analysis at the central laboratory.

Pregnancy Tests (Serum and Urine)

Determination of postmenopausal status will be made during the Screening period based on the subject's history and confirmed by FSH, if appropriate.

A pregnant or breastfeeding female/individual will not be eligible for participation or continuation in this study.

Pregnant subjects must discontinue from study treatment. Refer to Section 7.1 for additional details.

Serum Pregnancy Test

A serum pregnancy test will be performed for all female subjects of childbearing potential/individuals of childbearing potential (defined in the protocol) at 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, the serum pregnancy test should be repeated ≥ 3 days later to determine eligibility.

If the repeat serum pregnancy test is:

- Positive, the subject is considered a screen failure;
- Negative, the subject can be enrolled into the trial;
- Still borderline ≥ 3 days later: If no clinical suspicion of pregnancy and there are other pathological causes of borderline results, the borderline results will be considered documentation of continued lack of a positive result and the subject can be enrolled into the study.

Urine Pregnancy Test

A urine pregnancy test (or serum per local guidelines) will be performed for all females of childbearing potential/individuals of childbearing potential at the Baseline Visit prior to the first dose of study treatment. Additional urine pregnancy tests for female subjects of childbearing potential/individuals of

childbearing potential will be performed at visits indicated in Section 1.3. More frequent pregnancy tests will be performed throughout the study if required per local/country requirements. Use of highly sensitive urine pregnancy tests (detection of at least 25 IU/L hCG) at baseline and post-baseline are preferable.

- If the urine pregnancy test (which is performed at the site) is negative, dosing may begin or continue.
- If the urine pregnancy test is ambiguous or positive, dosing should be withheld, and a serum pregnancy test performed. In such cases, the subject must be excluded from participation if the serum pregnancy result is positive.

Follicle Stimulating Hormone

FSH should be tested at Screening if the female subject/individual is ≤ 55 years of age AND has had no menses for ≥ 12 months AND has no history of permanent surgical sterilization.

Hepatitis B and C Testing

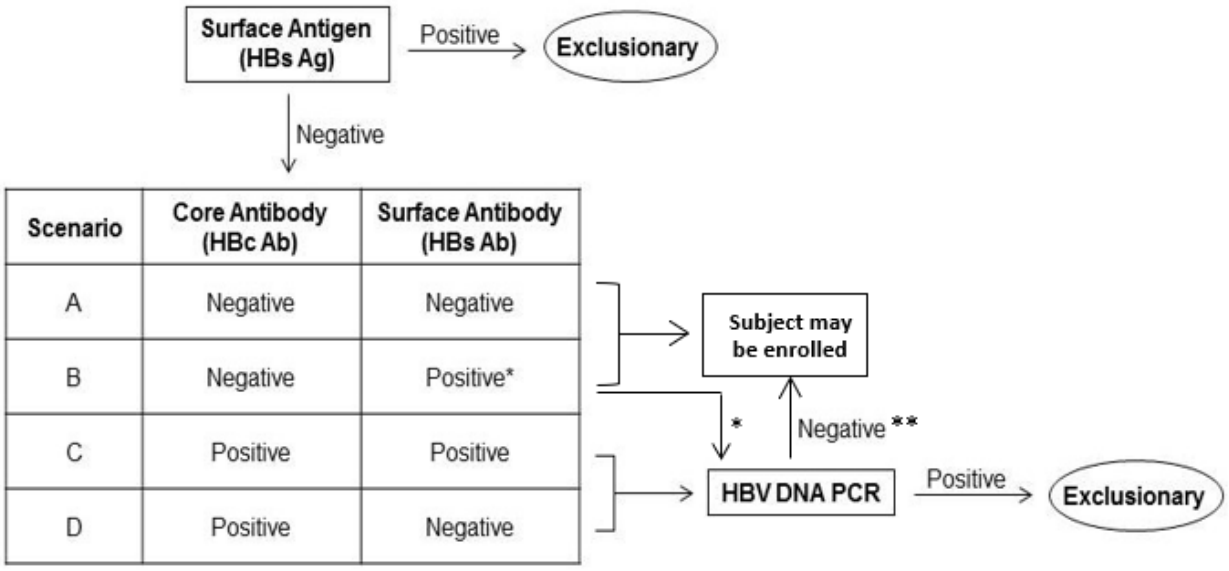
All subjects will be tested for the presence of HBV and HCV at Screening (Figure 2). Subjects with hepatitis B (HBs Ag positive [+] or detected sensitivity on the HBV DNA PCR qualitative test) or hepatitis C (HCV RNA detectable in any subject with anti-HCV Abs) will be excluded. Subjects who have been vaccinated against hepatitis B and are HBs Ab positive may be enrolled. If HBs Ag is negative but HBc Ab total is positive, HBV DNA will be quantified. If HBV DNA level is undetectable at Screening, the subject can participate in this trial.

Where mandated by local requirements, subjects with HBs Ab+ and/or HBc Ab+ and negative HBV DNA at screening should have HBV DNA PCR testing performed approximately Q12W. HBV DNA PCR testing Q12W is not necessary when the subject has a history of HBV vaccine and is HBs Ab+ and HBc Ab .

Per regional requirements: for subjects with HBs Ab (+) and/or HBc Ab (+) at Screening, the HBV DNA PCR test should be performed as outlined in the Section 1.3. A positive result for HBV DNA PCR testing will require immediate interruption of study treatment. Subjects may remain in the study pending further work up, consultation with a hepatologist (or a physician with a special interest in viral hepatology) and sponsor TA MD. Consultation should ideally occur as soon as possible and prior to the next scheduled study treatment dose. Retesting is not necessary for subjects that have a history of HBV vaccine and are HBs Ab (+).

If HCV Abs are positive, HCV RNA will be quantified. If HCV RNA level is undetectable at Screening, the subject can participate in this trial.

Figure 2. Interpretation and Management of HBV Serologic Test Results



* A positive test result for HBs Ab is expected for subjects who have had a HBV vaccination. For subjects without a history of HBV vaccination (and where mandated by local requirements), a positive result for HBs Ab requires HBV DNA PCR testing.

** Where mandated by local requirements, subjects with HBs Ab+ and/or HBc Ab+ and negative HBV DNA at Screening should have HBV DNA PCR testing performed approximately every 12 weeks. HBV DNA PCR testing every 12 weeks is not necessary when the subject has a history of HBV vaccination and is HBs Ab+ and HBc Ab-. If necessary, HBV DNA PCR may be tested at unscheduled visits.

HIV Testing

HIV testing will be performed at Screening. The Investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report confirmed positive 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 receive or be referred for clinical care promptly.

A subject will not be eligible for study participation if test results indicate a positive HIV infection. In case a screened subject has a confirmed positive HIV Ab test, Inclusion Criterion 5 should be selected in eCRF for documentation of screening failure.

Tuberculosis Screening

All subjects will be tested for TB by either the QuantiFERON-TB Gold Test (or IGRA equivalent) or a TB Skin Test (PPD) at the Screening visit. Signs and symptoms of active TB will be closely monitored and assessed by the investigator during each visit. Any additional work-up tests and procedures for TB monitoring and diagnosis can be performed per the investigator's medical judgment.

At Screening, all subjects will be assessed for evidence of TB and TB risk factors. At Screening the site staff will complete the TB risk assessment questionnaire in its entirety (Part I and Part II) and enter the data into the appropriate eCRF. Subjects who have had a TB test performed within 90 days of the

Screening Visit will not need to have the test repeated, provided all of the protocol required documentation is available at the site, and no new TB risk factors have been identified. If a chest x-ray or other diagnostic tests are required to assess TB per local guidelines, these diagnostic measures should be performed prior to enrolling the subject.

The QuantiFERON®-TB Gold test (or IGRA equivalent) will be supplied and analyzed by the central laboratory. (QuantiFERON-TB test is preferred over TB Skin Test.) Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

- If the **QuantiFERON-TB Gold Test (or IGRA equivalent) is NOT possible** or if both the QuantiFERON-TB Gold Test [or IGRA equivalent] and the PPD Skin Test are required per local guidelines, the PPD Skin Test will be performed according to standard clinical practice.
    - The PPD Skin Test should be read by a licensed healthcare professional between 48 and 72 hours after administration. A subject who does not return within 72 hours will need to be rescheduled for another skin test.
    - The reaction will be measured in millimeters (mm) of induration and induration ≥ 5 mm is considered a positive reaction. The absence of induration will be recorded as "0 mm," not "negative."
- If subject had a positive QuantiFERON-TB Gold (or IGRA equivalent) or PPD test at Screening, the test should not be repeated. 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.
- If the **TB screening test** (either PPD or the QuantiFERON-TB Gold test [or IGRA equivalent]) **is positive, or** if there is a **repeat indeterminate** QuantiFERON-TB Gold test (or IGRA equivalent) upon retesting, subjects may participate (or continue participation) in the study if **further work-up** (according to local practice/guidelines) establishes conclusively that the patient has **NO** evidence of active TB. If presence of **latent TB** is established, subjects are not required to be treated with prophylactic anti-TB therapy prior to or during the study, if the subject is considered low risk (i.e., no risk factors identified using the TB risk assessment questionnaire or defined by local guidelines or investigator judgment) for reactivation. However, for subjects to be randomized to vedolizumab, the treatment of latent TB should be conducted in accordance with the local vedolizumab label.
- If the subject is diagnosed with **active TB**, the subject should not be randomized in the study and should not receive study treatment. Subject will be considered as a **screening failure**.
- If the subject is diagnosed with **active TB** after being randomized, the subject should not receive any further study treatment and follow the PD Visit procedure (Section 1.3).
- If **TB (latent or active)** is diagnosed during the study, it is also necessary to report it as an AE in the source documents and eCRFs. In the case of a TB-related AE, a TB supplemental form that provides additional information will be completed by the investigator or designee.

Suspected Anaphylactic/Systemic Hypersensitivity Reaction Testing

Clinical criteria for diagnosing anaphylaxis are provided in Section 17. Blood tests to be conducted in the event of a suspected systemic hypersensitivity/anaphylactic reaction:

- For subjects randomized to the risankizumab treatment group: Serum risankizumab PK and ADA/NAb samples drawn in context of a suspected anaphylactic reaction are collected if an anaphylactic reaction occurs while subject is at the study site. The samples should be collected once within 24 hours of the suspected reaction.
- For subjects in either treatment groups: tryptase samples should be collected
  - Serum tryptase: 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);
  - A follow-up tryptase level should be collected a minimum of 2 weeks after the recorded event or at the next study visit.

Subjects will be closely monitored on site during study treatments administration at all visits. A medical person qualified in the treatment of acute hypersensitivity reactions must be present during the injections.

In the event that a suspected anaphylactic reaction occurs while the subject is not on site at the study clinic, please advise the treating facility to perform serum tryptase testing to help better understand and characterize the diagnosis.

hs CRP

Blood samples for hs-CRP will be obtained as indicated in Section 1.3.

Fecal Calprotectin

FCP will be performed for all subjects as indicated in Section 1.3. If subjects are unable to provide a sample at the site visit, subjects will be sent home with a stool sample supply kit and the site will give instructions to assist with collection procedures. All stool samples should be collected before any bowel preparation for endoscopy is started and returned to the site per the instructions provided outside of this protocol. The central laboratory will be utilized to process and provide results for these laboratory tests.

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-tested.

8.13 Endoscopy

A full colonoscopy is required prior to baseline and for all follow-up visits. All endoscopies performed will be recorded at the site in a video format and will be reviewed/scored by a blinded central reader. The same endoscopist should, where possible, perform all endoscopies for an individual subject throughout the study. In addition, where possible, the investigator or sub investigator should be the endoscopist for the study.

For the screening colonoscopy, this procedure may be completed at any time prior to baseline except the date the subject is enrolled as the blinded central reader review of the endoscopy video is required for study entry. Sites must wait to receive a copy of the score from the blinded central reader for the screening colonoscopy before a subject can be enrolled in order to confirm eligibility, however for all subsequent endoscopies clinical response status/clinical decisions will be determined based on local scores (sites will not receive a copy of the blinded central reader score). The local endoscopy subscores by segment will be noted in the subject's source documents and in the database. The blinded central reader's endoscopy subscore will be used for the efficacy analyses.

Endoscopies associated with scheduled visits should be performed up to 7 days prior to or on the day of the scheduled visit (the endoscopy may not occur after the visit, only on the day of or in advance of the scheduled visit). This up to 7 days timeframe prior to the scheduled visit may be extended as necessary after consultation with the AbbVie TA MD in case of external, not subject-related circumstances (e.g., scheduling conflict).

An endoscopy may be performed at unscheduled visits to confirm inadequate response. The endoscopy may be a full colonoscopy or sigmoidoscopy at the investigator's discretion and should be sufficient to accurately determine the Mayo endoscopic sub-score.

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

1. Biopsy confirmation of the diagnosis is available (see biopsy requirements below).
2. The endoscopic procedure took place within 45 days prior to Baseline visit.
3. The endoscopic procedure was recorded in a video format to allow determination of endoscopic eligibility by the blinded central reader.

Biopsy During Endoscopy

Appropriate documentation of biopsy results consistent with the diagnosis of UC, in the assessment of the investigator, must be available 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 local pathologist and the results reviewed by the investigator; the central laboratory will not provide a pathology report during the screening endoscopy to document UC diagnosis. 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 a local pathologist.

During all study endoscopies indicated in Section 1.3, a mandatory set of biopsies should be collected for histological assessment and analyzed by the blinded central reader. Each set of biopsies for histologic assessment should consist of 2 samples, obtained from the rectosigmoid colon (approximately 15 30 cm from the anal verge). For each set of 2 samples, one should be taken from the area of most inflammation (if the area is ulcerated, the sample should be obtained from the edge of the ulcer), and one from an area that is representative of the general degree of mucosal inflammation present in that segment. For all histology biopsies, the location of the biopsy specimen (distance from the anal margin) should be recorded. If any biopsy sample(s) are obtained, it should also be recorded on the endoscopy video. Any biopsy sample(s) obtained should be collected from the respective bowel segment during the withdrawal of the endoscope and after sufficient recording for the blinded central reader to calculate the Endoscopy Subscore.

Subjects should not be enrolled if high grade colonic dysplasia or colon cancer is discovered at the Screening endoscopy. 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 is completely removed. In the case of rescreening, an endoscopy with biopsy will not be required to be repeated, provided the conditions noted above are met and the endoscopy was performed within 45 days of the Baseline Visit.

Biopsies sent to the central laboratory will not be returned to sites and will be retained for study use only. AbbVie (or people or companies working with AbbVie) will store the biopsy samples in a secure storage space with adequate measures to protect confidentiality. The samples taken for endpoint analyses may also be used for additional research related to risankizumab and vedolizumab. The samples will be retained while research on risankizumab (or drugs of this class), vedolizumab (or drugs of this class) or UC and related conditions continues, but for no longer than 20 years after study completion. Only the protocol required biopsies for histologic assessment will be collected and sent to the central laboratory for storage, no additional samples will be collected and/or stored.

The signed pathology report will be monitored by the responsible clinical research associate and kept with the subject's source documents onsite.

Biopsy Sample Collection, Storage and Shipping:

Using routine forceps for tissue collection, obtain the required number of biopsy specimens and process the specimens following the instructions in the study-specific laboratory manual.

8.14 Unscheduled Visits

An Unscheduled Visit should be performed when the subject comes in for a medical visit for evaluation and assessment. During Unscheduled Visits, blood and urine samples may be obtained for the laboratory tests listed in Section 8.12, or for other tests, at the investigator's discretion.

Visits for dispensing new study treatment in case of temperature excursion, loss or damage are not considered an Unscheduled Visit. In addition, visits to only retest a lab will not be considered an Unscheduled Visit.

8.15 Abdominal IUS

Abdominal IUS will be performed only at selected sites who meet the experience and expertise specifications. Training and detailed instructions will be provided by the central imaging vendor. IUS sites selected by the sponsor should have (i) an IUS machine and (ii) a qualified sonographer and (iii) provide a test case, all reviewed and approved by the central imaging vendor.

Abdominal IUS will be performed using site's owned equipment.

IUS sites must ensure all enrolled subjects complete the abdominal IUS and study activities according to the activities schedule. Sites will transfer subject abdominal IUS images and videos to the central imaging vendor to be read by a blinded central imaging reader. Abdominal IUS data will be maintained and managed by the central imaging vendor. Results will be made available to the site through the central imaging vendor.

9 SAFETY CONSIDERATIONS

9.1 Complaints and Adverse Events

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. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the biologic or treatment component of the product or to the medical device component(s).

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 (e.g., printing illegible), missing components/product, device damage or not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event.

Reporting will be done via EDC. The date the product complaint details are entered into EDC and the form is saved represents the date reported to AbbVie. A back-up paper form will be provided for reporting complaints related to unassigned product or in the event of an EDC system issue. If a back-up

paper form is used, the date the form is emailed to RD_PQC_QA@abbvie.com represents the date reported to AbbVie.

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

Medical Complaints/Adverse Events and Serious Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE 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 treatment as stipulated in the protocol or labeling, as well as from "special situations" such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, treatment abuse, treatment misuse, or treatment withdrawal, all which must be reported whether associated with an AE or not. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meets protocol-specific criteria, and/or if the investigator considers them to be clinically significant.

The investigators will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and/or 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 AE.

If an AE, whether associated with study treatment or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance as a SAE within 24 hours of the site being made aware of the SAE (refer to Section 9.2 for reporting details and contact information):

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). 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 treatment dependency or treatment abuse. Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event, along with any suspected transmission of an infectious agent via a medicinal product if no other serious criterion is applicable.

The following definitions will be used for SAR and SUSAR:

SAR	Defined as all noxious and unintended responses to an IMP related to any dose administered that result in an SAE as defined above.
SUSAR	Refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the sponsor or the investigator, is unexpected (not listed in the applicable Reference Safety Information) and meets one of the above serious criteria.

AbbVie will be responsible for SUSAR reporting for the IMP in accordance with global and local requirements, including reporting to Eudravigilance database in accordance with EU Clinical Trial Regulation.

AEs will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

Adverse Events of Special Interest

The following AESIs will require additional eCRFs:

- Hepatic Events:
  - Discontinuation or interruption of study treatment due to a hepatic-related AE
  - Hepatic-related SAE
  - ALT or AST > 8 × ULN
  - ALT or AST > 3 × ULN with a total bilirubin > 2 × ULN
- Suspected Anaphylaxis Reactions
- TB
- Herpes Zoster Infection
- Cardiac events
- Death

Adverse Event Severity and Relationship to Study Treatment

The investigator will rate the severity of each AE according to the NCI CTCAE Version 5.0.

The investigator will use the following definitions to assess the relationship of the AE to the use of study treatment:

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.

Pregnancy

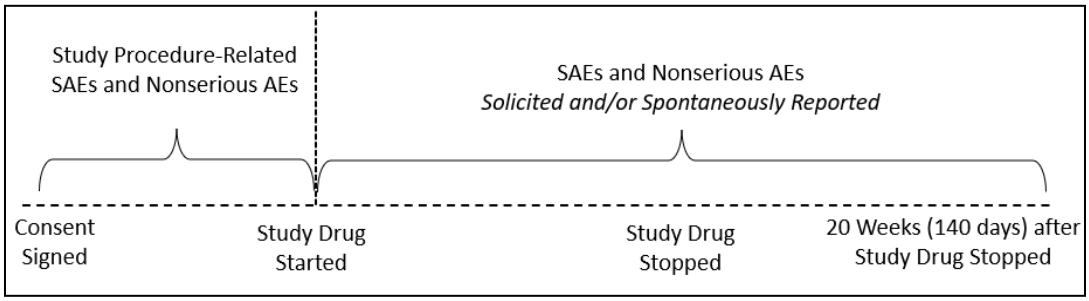
While not an AE, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 7.1). If a pregnancy occurs in a study subject, information regarding the pregnancy and the outcome will be collected.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

9.2 Safety Manual

Methods and Timing of Safety Assessment

All AEs will be collected from the time of study treatment administration until 140 days (20 weeks) after the last dose of study treatment, whether solicited or spontaneously reported by the subject. After the 140-day follow-up visit/call, only spontaneously reported SAEs will be collected. In addition, study procedure-related serious and nonserious AEs (e.g., contusion secondary to blood draw during screening) will be collected from the time the subject signs the study-specific ICF. If a subject prematurely discontinues study participation and begins commercially available risankizumab (Skyrizi®), the 140-day (20 week) follow-up visit/phone call following the last dose of risankizumab study treatment during the study will not be required.



Reporting Adverse Events and Intercurrent Illnesses

In the event of an SAE, whether associated with study treatment or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the EDC system. SAEs that occur prior to the site having access to the EDC, or if the EDC system is not operable, should be documented on the SAE nonCRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

Email: PPDINDPharmacovigilance@abbvie.com
FAX to: +1-847-806-2062 Backup: +1-847-935-2844

For safety questions, contact the Immunology Safety Team at:

Immunology Safety Team
Email: SafetyManagement_immunology@abbvie.com

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

Primary Therapeutic Area Medical Director
EMERGENCY MEDICAL CONTACT:
[redacted] **MD**
AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen, Germany

Contact Information:

Office: [redacted]
Mobile
Email:

In emergency situations involving study subjects when the primary 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:

HOTLINE: +1 (973) 784-6402

SUSAR Reporting

AbbVie will be responsible for SUSAR reporting for the IMP in accordance with global and local requirements, including EU Clinical Trial Regulation, and Appendix A of the IB will serve as the RSI. The RSI in effect at the start of a DSUR reporting period will be used to determine expectedness until the RSI that was submitted at the time of the DSUR becomes approved by all applicable regulatory authorities. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' SAR will be used to assess expectedness.

9.3 Cardiovascular Adjudication Committee

An independent adjudication committee will adjudicate 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 CAC Charter.

In addition, the site may be contacted for additional source documentation for relevant events.

10 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

10.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on primary and secondary analyses. Complete and specific details of the statistical analysis will be described in the SAP.

The primary analysis of clean, in-scope, EDC and vendor data will be conducted after all subjects have completed the Week 48 visit or prematurely discontinued from the study prior to Week 48. This is the only and final efficacy analysis for the study. When all subjects complete their Week 48/PD visit, the database will be locked and all planned analyses at Week 48 will be performed. Data collected in the optional PTE period of the study will not be included in the clinical study report and safety data will be reported separately.

10.2 Definition for Analysis Populations

The ITT population includes all randomized subjects in the study. For all efficacy analyses, subjects will be included in the treatment group to which they are randomized.

The SA population includes all subjects who received at least 1 dose of study treatment. In all safety analyses, subjects will be analyzed according to treatment received regardless of randomization.

10.3 Handling Potential Intercurrent Events

The primary and secondary endpoints (defined in Section 3.2 and Section 3.3) will be analyzed on the ITT population and subjects following potential ICEs will be addressed as described below:

ICE1: premature discontinuation of the study treatment.

ICE2: initiation or dose escalation of UC-related corticosteroids.

ICE3: UC-related surgery (ileostomy, colectomy, or proctocolectomy).

- Treatment policy strategy will be used to handle ICE1 that data collected after ICE1 will be included in the analysis (up until the initiation of any new TaTs) as is.
- For binary endpoints, composite strategy will be used to handle ICE2/ICE3 that subjects will be categorized as "not achieved" on or after ICE2 or ICE3.
- For continuous endpoints, composite strategy will be used that any value on or after ICE2 or ICE3 will be excluded, and imputed by an unfavorable value.

Additional details will be provided in the SAP.

10.4 Statistical Analyses for Efficacy

Analyses of the primary and secondary efficacy endpoints will be conducted in the ITT population based on randomized treatment groups. For both the primary and secondary efficacy endpoints, NRI will be the primary approach to handle missing data. In cases data missing at random can be reasonably assumed, NRI-MI, where those missing data at random will be imputed by multiple imputation, will be used. Additional details will be provided in the SAP.

Summary and Analysis of the Primary Endpoint

The primary efficacy endpoint is achievement of endoscopic improvement at Week 48.

Point estimate and 95% confidence interval of the response rate of the primary endpoint will be summarized for each randomized treatment group and for the treatment difference. The point estimate and its 95% confidence interval for the treatment difference (risankizumab vedolizumab) will be based on the Mantel-Haenszel method after adjusting for the actual values of stratification factors (Baseline steroid use [yes or no] and Baseline mMS [≤ 7 vs > 7]). The superiority test of risankizumab vs vedolizumab will be performed using CMH test stratified by Baseline steroid use [yes or no] and Baseline mMS (≤ 7 versus > 7) based on central reading. The primary efficacy endpoint will be tested at a two-sided significance level of 0.05.

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

Summary and Analysis of Secondary Endpoint

The secondary efficacy endpoint is achievement of clinical remission per mMS at Week 48. Non-inferiority of risankizumab vs vedolizumab will be tested first followed by superiority test.

Point estimate and 95% confidence interval of the response rate for the achievement of clinical remission per mMS at Week 48 will be summarized for each randomized treatment group and for the treatment difference. The point estimate and its 95% confidence interval for the treatment difference (risankizumab vedolizumab) will be based on the Mantel-Haenszel method after adjusting for the actual values of stratification factors (Baseline steroid use [yes or no] and Baseline mMS [≤ 7 vs > 7] based on central reading). The superiority test of risankizumab vs vedolizumab will be performed using CMH test stratified by Baseline steroid use (yes or no) and Baseline mMS (≤ 7 vs > 7) based on central reading. Non-inferiority test and superiority test will be performed sequentially. Specifically, for the non-inferiority test, if the lower limit of 95% confidence interval for the risk difference between risankizumab and vedolizumab groups (risankizumab vedolizumab) is greater than the negative 12% non-inferiority margin then non-inferiority is demonstrated for clinical remission per mMS at Week 48. If non-inferiority is demonstrated for clinical remission per mMS at Week 48, then the superiority of risankizumab vs vedolizumab for the clinical remission per mMS at Week 48 will be sequentially tested at two-sided significance level of 0.05 using the CMH test. The 12% non-inferiority margin was determined from the Varsity Trial and a meta-analysis for placebo based on data in INSPIRE and COMMAND for risankizumab, U-ACHIEVE and U-ACCOMPLISH for upadacitinib, and ELEVATE UC for etrasimod.[11] The margin preserved 50% of the active control (vedolizumab)'s effectiveness.

Summary and Analysis of Additional Efficacy Endpoints

Additional efficacy endpoints (defined in Section 3.4) include both categorical variables and continuous variables. Categorical variables will be analyzed using the same CMH test as the primary endpoint.

For continuous variables, missing data will be imputed via MI and intercurrent events will be handled as described in Section 10.3. Data will be analyzed using Analysis of Covariance (ANCOVA) model.

Additional details will be provided in the SAP.

10.5 Statistical Analyses for Safety

Safety analyses will be carried out in the SA population as defined in Section 10.2 based on the treatment actually received, regardless of the treatment randomized. Incidence of AEs including those related to study treatment, changes in vital signs, physical examination results, and clinical laboratory values will be analyzed.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Treatment-emergent AEs are defined as AEs that begin or worsen in severity either on or after initiation of study treatment and within 140 days after the last dose of the study treatment. An overview of treatment-emergent AEs, including AEs of special interest such as serious infection, malignancies, MACEs, systemic hypersensitivity reactions/infusion reactions, hepatic events, AEs leading to death and AEs leading to early termination (see details in the SAP), AEs by MedDRA preferred term and system organ class, AEs by maximum relationship to study treatment, and AEs by maximum severity will be summarized by number and percentage.

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

10.6 Interim Analysis

No formal interim analysis is planned for this study.

10.7 Overall Type I Error Control

The type I error will be controlled strongly across the primary and secondary endpoints. The primary endpoint will be tested first, if significant (i.e., risankizumab is superior to vedolizumab), the secondary endpoint will be tested sequentially according to the order specified in Section 3.3 and Section 10.4. Further details on the overall type I error control will be provided in the SAP.

10.8 Sample Size Determination

Endoscopic improvement rate assumptions were informed by the published results from the Varsity Trial[12] for vedolizumab and by M16-067/M16-066 study results for risankizumab.

Assuming a Week 48 endoscopic improvement rate of 59% for the risankizumab group and 43% for the vedolizumab group among TaTs naïve patients, a sample size of 265 subjects per arm (planned total sample size N = 530) will have at least 95% power to detect at least a 16% treatment difference between risankizumab and vedolizumab groups in endoscopic improvement at Week 48 using a Fisher's exact test at 2-sided significance level of 0.05. Sample size calculation was conducted in SAS Version 9.4 (SAS Institute Inc., Cary, NC 27513).

10.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified), the investigator is responsible for notifying IEC/IRB, regulatory authorities (as applicable), and AbbVie.

11 GENERAL CONSIDERATIONS: REGULATORY, ETHICS, AND STUDY OVERSIGHT

11.1 Independent Ethics Committee/Institutional Review Board

The protocol, ICF(s), recruitment materials, and all subject materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the ICF(s) must be obtained before any subject is screened. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

11.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, EU Clinical Trial Regulation, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Section 13.

11.3 Subject Confidentiality

Before subject data are shared with AbbVie, the study investigator and staff will replace the subject's name, address, and contact information with a generic code which AbbVie cannot link to that subject's identity to protect the confidentiality of the data.

For the personal data that AbbVie Deutschland GmbH & Co KG acting as sponsor of the submitted study ("AbbVie Deutschland") controls and maintains, AbbVie Deutschland has developed a robust security program focused on due diligence in design, managed change, and information security governance. Information Security policies govern the Information Security functions including identity and access management, operations, infrastructure, application, and third-party security requirements. The risk-based AbbVie Data Classification Tool dictates the level of scrutiny and control required for the relevant activities per AbbVie's Information Security policies taking into account the sensitivity of the data.

AbbVie Deutschland has a data protection impact assessment program to ensure and document the appropriate controls and safeguards stated above are in place for clinical trial data that it controls and maintains, and these processing activities respect privacy of clinical trial subjects. AbbVie Deutschland also maintains robust security incident response policies and procedures, including requirements for the containment of any data-related incidents, the mitigation measures where needed, and notification to authorities or affected individuals where required.

AbbVie Deutschland as the sponsor shall document any personal data breaches for which it is a controller and notify where required the competent national supervisory authority without undue delay and at the latest within 72 hours after becoming aware of such an incident. AbbVie Deutschland shall create and maintain appropriate records of such an incident.

11.4 Study Subject Information and Informed Consent

The investigator or their representative will explain the nature of the study to the subject, the benefits and risks anticipated from participation in the study, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject or any medications being discontinued by the subject in order to participate in this study, the informed consent statement will be reviewed, signed, and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. This may be done electronically, in accordance with local regulations and where permitted. A legally authorized representative is not permitted to sign on behalf of subjects. A copy of the signed informed consent will be provided to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

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

Samples for optional pharmacogenetic analyses or other exploratory analyses will only be collected if the subject has voluntarily signed and dated a separate written consent form for this testing that has been approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The separate written consent may be part of the main consent form. If the subject does not consent to the testing, it will not impact the subject's participation in the study.

11.5 Publication Policy

AbbVie as the sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and sponsor personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final clinical study report of the multicenter study except as agreed with the sponsor.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.

Investigators are NOT employed by the organization sponsoring the study. There is an agreement between investigators and the sponsor (or its agents) that restricts the investigator's rights to discuss or publish study results after the study is completed.

AbbVie requests that any investigator or institution that plans on presenting/publishing results, provide written notification of their request 60 days prior to their presentation/publication. AbbVie requests that no presentation/publication will be instituted until 12 months after a study is completed or after the first presentation/publication, whichever occurs first. A delay may be proposed for a presentation/publication if AbbVie needs to secure patent or proprietary protection.

12 GENERAL CONSIDERATIONS: RISK MANAGEMENT AND QUALITY ASSURANCE

12.1 Source Documents and Case Report Form Completion

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH GCP, and applicable local regulatory requirement(s), including EU Clinical Trial Regulation.

12.2 Data Quality Assurance

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP and applicable regulatory requirements, including EU Clinical Trial Regulation.

13 APPENDIX A. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M25-540: A Phase 3b, Multicenter, Randomized, Open-Label Study of Risankizumab Compared to Vedolizumab for the Treatment of Adult Subjects With Moderate to Severe Ulcerative Colitis Who are Naïve to Targeted Therapies

Protocol Date: 08 July 2025

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP), as well as applicable laws, regulations, and guidelines. Certain laws, regulations, or guidelines may apply to conduct of the study at investigator's site even if such laws, regulations, or guidelines originate in a foreign jurisdiction. The investigator agrees and acknowledges that applicable laws or regulations may require AbbVie to submit inspection reports, instances of significant non-compliance with the study protocol, or other documents regarding conduct of the study at the investigator's site to regulatory authorities, and such documents may be publicly disclosed by such authorities. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the treatments are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
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 protocol and all of its amendments.
9. Reporting the following to AbbVie within 1 calendar day of becoming aware:
   - Any unanticipated problems involving risks to human subjects
   - Any departure from relevant clinical trial regulation, GCP, or the trial protocol that has affected or is likely to affect to a **significant** degree the following:
     - Rights, safety, physical or mental integrity of the subjects in the clinical trial
     - Scientific value of the clinical trial, reliability or robustness of data generated

   Where required by local regulation, inform relevant Ethics Committees / Institutional Review Boards and other appropriate individuals (e.g., Co-ordinating Investigator, Institution Director).
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)	

14 APPENDIX B. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]		Clinical Development
		Statistics

15 APPENDIX C. COUNTRY-SPECIFIC REQUIREMENTS

Any coded data (as defined under General Data Protection Requirements) that is transferred to AbbVie's parent company, AbbVie Inc., in the United States, or other AbbVie affiliates is done under internal agreements, which include an EU approved model contract pertaining to data transfers to controllers. A copy can be obtained by sending an email to privacyoffice@abbvie.com. Any transfers of Coded Data to AbbVie's research partners outside the EU will be done in compliance with the international data transfer restrictions that apply under EU data protection laws.

For Sites in China

For sites in China, a paper diary card will be provided at the indicated visit in Section 1.3. Subjects will be trained on how to complete the diary cards by site staff during the indicate the visit. If subjects require re-training during the study, the site staff will accommodate this requirement.

All subjects should complete their paper diary cards throughout the entire study. Subjects will be instructed to bring their paper diary cards back to the site to be reviewed and collected at each visit, including at any visit at which a dose level change may be required. If COVID-19 circumstances warrant a virtual visit, diary cards should be reviewed virtually with the subject and site should collect the paper diary card at the next on-site visit. Subjects will be instructed to record the date and time each dose of study treatment is taken (if self-administered or not administered at the site or by site personnel), (indicating if any doses of study treatment are missed).

Subjects will also be instructed to record AE symptoms and concomitant medications in the paper diary cards. At each visit, the paper diary cards are to be reviewed by the investigator, assessed for any updates needed, and collected from the subject by study staff. Relevant information will be recorded in existing AE, treatment administration, and concomitant medication forms in the eCRF as applicable. At each visit after Screening, including the Final/Premature Discontinuation visit, the paper diary cards are to be returned to the site and appropriately filed with the subject's source documents for this study. At each visit, after the paper diary card is initially dispensed (except the Final/Premature Discontinuation visit), the subject will be provided a new diary card.

In case of missing diary card information, or when discrepancies are discovered, site personnel should discuss with the subject and document changes to data in site records and eCRF forms, if applicable. The need for completion of the paper diary card will be reinforced with the subject during study visits, as necessary, by the site personnel.

Certified Clinical Laboratories for Sites in China:

Labcorp Pharmaceutical Research & Development (Shanghai) Co., Ltd.,
Building 9. No. 338 Jialilue Road, Zhangjiang Hi-Tech Park,
Shanghai 201203, China
Phone Number: +86 (0) 21 6192 5800

16 APPENDIX D. OPTIONAL PRIMARY-TRIAL EXTENSION FOR APPLICABLE COUNTRIES

Directions are found throughout this appendix for sites in countries that require continued treatment in accordance with local regulations until such time when risankizumab is commercially available and/or the subject can access treatment locally. Access is defined as investigational product that is commercially available and/or reasonably accessible to the patient (including but not limited to through insurance or reimbursement coverage, or local access mechanism).

As subjects approach the Week 48 visit, the investigator will discuss the appropriate subsequent treatment with the subject. If the subject and investigator determine continued therapy with risankizumab remains the best course of treatment, subjects may continue to receive open-label treatment with risankizumab in the PTE for up to an additional 144 weeks to bridge the gap between completion of the Primary Treatment Period (Week 48) and commercial availability and/or local treatment access to risankizumab.

When risankizumab is commercially available and/or the subject can access treatment locally, subjects will be brought in for a final visit. In the event regulatory approval, local reimbursement, or the decision to discontinue pursuit of regulatory approval/reimbursement occurs at a time point earlier than the Week 196 visit, subjects should then be brought in for their termination visit based on the actual date as provided by AbbVie. AbbVie reserves the right to terminate the PTE at any time.

Overall Study Design and Plan

Subjects who complete the Primary Treatment Period may continue to receive open-label risankizumab in the PTE starting at Week 52. See Section 4.1 for additional details on the Primary Treatment Period.

Subjects participating in the PTE will be evaluated per standard of care and will return Q24W (or depending on the local regulations) up to an additional 144 weeks (refer to the PTE Study Activities Table below for further visit details). During the PTE, open-label risankizumab 180 mg or 360 mg will be administered SC every 8 weeks by the staff or, if locally permissible, self-administered at home, starting at Week 52. Subjects will continue receiving the same dose they received at the end of the Primary Treatment Period. Subjects who prematurely discontinue the study will have a 140-day follow-up visit/call after the last dose of study treatment. The 140-day follow-up phone visit/call will not apply for subjects who receive risankizumab through various continued treatment options at the end of the PTE.

Open-label 180 mg or 360 mg risankizumab SC maintenance dosing will be administered Q8W during PTE, starting at Week 52.

If risankizumab treatment is not commercially available and/or the subject cannot access treatment locally, the PTE may continue for up to an additional 144 weeks. Subjects who no longer derive benefit from receiving risankizumab and are to be withdrawn, should have a PTE Withdrawal visit and complete the procedures outlined in the PTE Study Activities table below.

The 140-day (20-week) follow-up visit/phone call following the last dose of risankizumab in the PTE will be required for subjects who do not continue risankizumab through continued treatment options (e.g., initiates commercial risankizumab) upon the end of PTE.

PTE visits for purposes of continued treatment are optional, do not preclude a subject from being considered as completing the study.

Note: If an alternate program for risankizumab treatment becomes available, subjects will be informed of possible entry.

Concomitant Medication

For subjects who receive open-label treatment with risankizumab 180 mg or 360 mg SC every 8 weeks after Week 48, addition or modification of concomitant UC medications can be made per Investigator judgment regardless of the disease activity status.

Paper Diary Cards in China

For sites in China, a paper diary card will be provided at the beginning of subject participation in the PTE. Subjects will be trained on how to complete the diary cards by site staff during the first PTE visit. If subjects require re-training during the study, the site staff will accommodate this requirement. All subjects should complete their paper diary cards throughout participation in the PTE. Subjects will be instructed to bring their paper diary cards back to the site to be reviewed and collected at each visit, including at any visit at which a dose level change may be required. Subjects will be instructed to record the date and time each dose of study treatment is taken (if self-administered or not administered at the site or by site personnel), indicating if any doses of study treatment are missed as trained by site staff.

Subjects will also be instructed to record AEs, symptoms and concomitant medications in the paper diary cards. At each visit, the paper diary cards are to be reviewed by the investigator, assessed for any updates needed, and collected from the subject by study staff. Relevant information will be recorded in existing AE and concomitant medication forms in the eCRF as applicable. At each visit after the first PTE visit, including the Final/PD Visit, the paper diary cards are to be returned to the site and appropriately filed with the subject's source documents for this study. At each visit, after the paper diary card is initially dispensed, (except the Final/PD Visit), the subject will be provided a new diary card.

In case of missing diary card information, or when discrepancies are discovered, site personnel should discuss with the subject and document changes to data in site records and eCRF forms, if applicable. The need for completion of the paper diary card will be reinforced with the subject during study visits, as necessary, by the site personnel.

Withdrawal and Discontinuation of Subjects

Subjects will be withdrawn from the PTE if any of the following occur in addition to what is stated in Section 7.1:

- A subject no longer derives benefit from risankizumab per investigator assessment.
- Subject has reasonable access to commercial risankizumab in the country of participation per investigator and/or sponsor assessment.

Drug Assignment

Subjects who enter the PTE will continue to use the same randomization number assigned by IRT during the Primary Treatment Period.

Safety Considerations

Safety information will continue to be collected for subjects who enter the PTE. CAC is not applicable in the PTE. Overall management and monitoring of safety during the PTE is the responsibility of the investigator.

If any urine pregnancy test is positive, a serum pregnancy test will be performed locally. If the serum pregnancy test is positive, study treatment must be permanently discontinued. If the serum pregnancy test is borderline, it should be repeated ≥ 3 days later. If the repeat serum pregnancy test is:

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

A pregnant or breastfeeding female/individual will not be eligible for continuation or be allowed to continue study treatment.

Statistical Analysis for Safety

Safety data collected during the PTE will be reported through the safety reporting process for the product (e.g., DSUR, PSUR, and IB).

Completion of the PTE

The completion for the PTE is defined as last subject last visit in the PTE (e.g., the date of withdrawal from the PTE; applicable 140-Day Visit/Follow-up call).

PTE Study Activities Table for Applicable Study Subjects

Activity	Every 24 Weeks[a] starting at Week 52	PTE Withdrawal/ Completion Visit[b]	Unscheduled Visit	140-Day Follow-Up Visit/Call[b]
Informed Consent[c]	X			
Prior/concomitant therapy	X	X	X	X
Adverse Event Assessment	X	X	X	X
For China sites only, dispense and/or review and collect the subject paper diary cards adverse events symptoms and concomitant therapy	X	X	X	X
Dispense and/or review subject Paper pregnancy and Dosing Diary cards	X	X	X	
Dispense urine pregnancy tests for home testing (for all female subjects of childbearing potential)	X			
Urine Pregnancy Test (for all female subjects of childbearing potential/individuals of childbearing potential)[d]	X	X		
Dispense/administer Study treatment[e]	X			

a. Visit intervals for the PTE are to be scheduled starting from the Week 52 visit date based on the schedule established by baseline date for up to 144 weeks.

b. Subjects who end study participation due to either an option available for continued treatment or no longer deriving benefit from receiving risankizumab, will have a PTE Withdrawal visit and complete the procedures outlined in the PTE Study Activities table. Subjects will be contacted 140 days following last dose of study treatment prior to PTE withdrawal for an assessment of any new or ongoing AEs. For subjects withdrawing from the PTE and receiving risankizumab through various continued treatment options at the end of the PTE a 140-day follow-up visit/call is not required.

c. Informed consent should be obtained prior to performing PTE procedures.

d. Urine pregnancy test should be performed at all study visits where a dose is being administered and at home prior to dosing (if applicable) for all WOCBP. The urine pregnancy test must be negative prior to administering risankizumab. The results of the at home pregnancy tests will be communicated to the site. If any urine pregnancy test is positive, a serum pregnancy test will be performed by a local laboratory.

e. At Week 52, subjects will continue to be supplied OL risankizumab. Dosing should continue per the previously determined schedule. with the last dosing at Week 196. If required locally, subjects may return to the site to receive their risankizumab.

17 APPENDIX E. CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS

Anaphylaxis[1] is highly likely when any one of the following 3 criteria is 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):

   Systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline.

PEF = peak expiratory flow; BP = blood pressure

Serious Systemic Hypersensitivity Reaction: A drug hypersensitivity reaction is an objectively reproducible clinical sign or symptom, or constellation of signs or symptoms, caused by exposure to a drug at a dose tolerated by normal individuals. A systemic hypersensitivity reaction is a hypersensitivity reaction that does not only occur at the local site of study treatment administration (e.g., not an injection site reaction). A serious systemic hypersensitivity reaction is a systemic hypersensitivity reaction that fulfills criteria for a SAE.

In the event of an anaphylactic reaction, blood samples will be drawn per Section 8.12 after the onset of the reaction. This will include: tryptase. Blood samples for PK, ADA and NAb assessment will also be collected along with 1 hour blood samples for above assessments. Separate instructions for the collection, handling, storage and shipping of these labs will be provided outside of the study protocol.

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18 APPENDIX F. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
Ab	antibody
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
Ag	antigen
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BCG	bacilli Calmette-Guérin
BP	blood pressure
BWT	bowel wall thickness
CD	Crohn's Disease
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease - 2019
CS	clinically significant
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EU	European Union
FACIT	Functional Assessment of Chronic Illness Therapy
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FCP	fecal calprotectin
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HB	hepatitis B
HBV	hepatitis B virus
hCG	human chorionic gonadotropin

Abbreviation	Definition
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HIV Ab	HIV antibody
HRQOL	health-related quality-of-life
hs-CRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICEs	intercurrent events
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
Ig	immunoglobulin
IL	interleukin
IM	intramuscular
IMP	Investigational Medicinal Product
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
ITT	Intent-to-Treat
IUD	intrauterine device
IUS	intestinal ultrasound
IV	intravenous
LDL	low-density lipoprotein
mAb	monoclonal antibody
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mMS	modified Mayo Score
MTX	methotrexate

Abbreviation	Definition
N/A	not applicable
NAb	neutralizing antibody
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCS	not clinically significant
NMSC	nonmelanoma skin cancer
NRI	non-responder imputation
PCR	polymerase chain reaction
PFS	prefilled syringe
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PPD	purified protein derivative (tuberculin)
PRO	patient-reported outcome
PSUR	Periodic Safety Update Report
PT	prothrombin time
PTE	primary-trial extension
Q12W	once every 12 weeks
Q8W	once every 8 weeks
QoL	quality-of-life
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
RBS	rectal bleeding subscore
RNA	ribonucleic acid
RSI	Reference Safety Information
RZB	risankizumab
SA	Safety analysis population
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAR	serious adverse reaction
SC	subcutaneous
SF	short form
SF-36	36-Item Short Form Health Survey
SFS	stool frequency subscore

Abbreviation	Definition
SUSAR	suspected unexpected serious adverse reaction
TA MD	therapeutic area medical director
TaT	targeted therapy
TB	tuberculosis
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
VDO	vedolizumab
WBC	white blood cell
WPAI-UC	Work Productivity and Impairment Questionnaire - UC

19 APPENDIX G. REFERENCES

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20 APPENDIX H. PROTOCOL SUMMARY OF CHANGES

Protocol	Date
Version 1.0	18 December 2024
Version 2.0	18 June 2025

The purpose of this version is to make revisions in response to regulatory feedback. Changes include the following:

- In Section 7.1, it was clarified that subjects who have shown no evidence of therapeutic benefit after 14 weeks of treatment for vedolizumab and 24 weeks of treatment for risankizumab must be discontinued from study drug. Deleted text in the second bullet indicating that consideration should be given to discontinuing treatment in subjects who have shown no therapeutic benefit after 14 weeks of treatment for vedolizumab and 24 weeks of treatment for risankizumab.

  Rationale: Added in response to regulatory feedback.

- In Section 8.12, in the "Tuberculosis Screening" section, added text in Bullet #4 to clarify that, for subjects to be randomized to vedolizumab, the treatment of latent TB should be conducted in accordance with the local vedolizumab label. Deleted the last bullet indicating that treatment of latent TB should be conducted in accordance with the local product label.

  Rationale: Added for clarity regarding treatment of latent TB in subjects to be randomized to vedolizumab to address regulatory feedback.

Document Approval

Study M25540 - A Phase 3b, Multicenter, Randomized, Open-Label Study of Risankizumab Compared to Vedolizumab for the Treatment of Adult Subjects With Moderate to Severe Ulcerative Colitis Who are Naïve to Targeted Therapies - Protocol Version 2-1 (EU Only) - EU CT 2024-518998-33 - 08Jul2025

Version: 1.0 **Date:** 08-Jul-2025 **Company ID:** 08Jul2025-b775281d-4ac9-4a3d-83de-03fce1b09da4-1.0-en

Signed by:	Date:	Meaning of Signature:
[redacted]	[redacted]	Approver - Statistics
		Approver