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Protocol for Study M15-722

Ulcerative Colitis: Ravagalimab (ABBV-323) in Subjects with Moderately to Severely Active UC Who Failed Prior Therapy

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SPONSOR:	For Non-European Countries:* AbbVie 1 North Waukegan Road Bldg. AP31 North Chicago, IL 60064 USA	For European Countries:* AbbVie Deutschland GmbH & Co. KG (AbbVie) Knollstrasse 67061 Ludwigshafen Germany
NUMBER OF SITES:	Approximately 35 sites	
ABBVIE INVESTIGATIONAL PRODUCT:	Ravagalimab (ABBV-323)	EUDRACT: 2018-000930-37

FULL TITLE: A Multicenter, Single Arm, Open-label Study to Investigate the Efficacy and Safety of Ravagalimab (ABBV-323) in Subjects with Moderate to Severe Ulcerative Colitis Who Failed Prior Therapy

Incorporating Versions 1.0, 2.0, 3.0, 4.0, 5.0 and 6.0

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1 SYNOPSIS

Title: A Multicenter, Single Arm, Open-label Study to Investigate the Efficacy and Safety of Ravagalimab (ABBV-323) in Subjects with Moderate to Severe Ulcerative Colitis Who Failed Prior Therapy	
Background and Rationale:	Ulcerative colitis (UC) is a chronic, relapsing inflammatory disease of the rectum and/or large intestine characterized by inflammation and ulceration of the mucosal and submucosal intestinal layers. Despite increasingly available therapies, currently approved UC therapies have limited efficacy and have a potential for significant safety events. Thus, a large unmet need continues to exist for the treatment of UC. CD40 is a tumor necrosis factor (TNF) receptor family member that plays an important role in lymphocyte activation and antigen presenting cell (APC) function. CD40 expression on epithelium, leukocytes, and vascular endothelium is elevated in systemic inflammatory diseases (e.g., Crohn's disease [CD], UC, rheumatoid arthritis [RA], and systemic lupus erythematosus [SLE]). Ravagalimab is a proprietary monoclonal antibody (mAb) that is a potent CD40 antagonist with no evidence of agonist activity. Evidence from in vitro studies, preclinical models, and human disease suggests that CD40 signaling is important in the pathogenesis of UC and inhibition of CD40 mediated signaling may be a potential treatment for patients with UC.
Objective(s) and Endpoint(s):	Objective: To explore the efficacy, safety, and tolerability of ravagalimab as treatment in subjects with moderately to severely active UC. Primary Efficacy Endpoint: The proportion of subjects with endoscopic improvement (Mayo endoscopic subscore of 0 or 1) at Week 8.
Investigator(s):	Multi-center.
Study Site(s):	Approximately 35 sites; countries such as, but not limited to Canada, France, Germany, Hungary, Italy, Netherlands, South Korea, Spain, United Kingdom, and United States.
Study Population and Number of Subjects to be Enrolled:	The study population consists of adults with moderate to severe UC who failed prior therapy. Up to approximately 40 subjects will be enrolled.
Investigational Plan:	Study M15-722 is a Phase 2a, multicenter, single arm, open-label study to investigate the efficacy and safety of ravagalimab in subjects with moderate to severe UC who failed prior therapy. The study contains a 35-day screening period, 2 treatment periods, and an 84-day follow up period from the last dose of study drug. The induction period is an open-label (OL) 12-week treatment period to evaluate the efficacy, safety, tolerability, pharmacokinetics (PK) and receptor occupancy (RO) of ravagalimab for inducing endoscopic improvement at Week 8. Subjects who achieve clinical response per Partial Adapted Mayo score at Week 12 may continue into the maintenance period. The maintenance period is an OL 92-week treatment period to assess efficacy and safety for maintenance of response with ravagalimab. An internal data monitoring committee (DMC) will review safety at regular intervals.

Key Eligibility Criteria:	• Subjects must understand and personally voluntarily sign and date an informed consent, approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures. • Adult male or female, between 18 and 75 years of age, inclusive, at time of the Baseline visit. • Diagnosis of UC for at least 3 months prior to Baseline. Appropriate documentation of biopsy results consistent with the diagnosis of UC in the assessment of the Investigator, must be available. • Subject meets the following disease activity criteria: Active UC with an Adapted Mayo score of 5 to 9 points and endoscopic subscore of 2 to 3 (confirmed by central review). • History of inadequate response, loss of response, or intolerance to one or more of the approved therapies: infliximab, adalimumab, golimumab, vedolizumab, ustekinumab and/or tofacitinib. Dose and duration requirements are specified in Section 5.1.
Study Drug and Duration of Treatment:	Ravagalimab (100 mg/mL) Induction Period: • OL ravagalimab 600 mg intravenous (IV) Week 0; ravagalimab 300 mg subcutaneous (SC) Weeks 2, 4, 6, 8, and 10 Maintenance Period: • Open-label ravagalimab 300 mg SC every other week (eow) from Week 12 to Week 102
Date of Protocol Synopsis:	04 December 2020

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

Ulcerative colitis (UC) is a chronic, relapsing inflammatory disease of the rectum and/or large intestine characterized by inflammation and ulceration of the mucosal and submucosal intestinal layers. The hallmark clinical symptoms include bloody diarrhea associated with rectal urgency and tenesmus. The clinical course is marked by exacerbation and remission. Extraintestinal complications include arthritis, erythema nodosum, pyoderma gangrenosum, uveitis, and primary sclerosing cholangitis. Conventional therapies for the induction of remission include 5-aminosalicylic acid (5-ASA) derivatives, corticosteroids and the immunomodulatory agent cyclosporine. 5-ASA derivatives as well as thiopurines are used for the maintenance of remission.[1] The biological agents infliximab, adalimumab, golimumab, vedolizumab, and ustekinumab as well as the Janus kinase (JAK) inhibitor tofacitinib are indicated for the induction and maintenance of remission in subjects with moderate to severe UC. Despite increasingly available therapies, currently approved UC therapies have limited efficacy[2-4] and have a potential for significant safety events.[5-8] Thus, a large unmet need continues to exist for the treatment of UC.

CD40 is a tumor necrosis factor (TNF) receptor family member that plays an important role in lymphocyte activation and antigen presenting cell (APC) function. CD40 expression on epithelium, leukocytes, and vascular endothelium is elevated in systemic inflammatory diseases (e.g., Crohn's disease [CD], UC, rheumatoid arthritis [RA], and systemic lupus erythematosus [SLE]). Ravagalimab is a proprietary monoclonal antibody (mAb) that is a potent CD40 antagonist with no evidence of agonist activity.

Evidence from in vitro studies, preclinical models, and human disease suggests that CD40 signaling is important in the pathogenesis of UC and inhibition of CD40 mediated signaling may be a potential treatment for patients with UC.[9] For further details, please see ravagalimab Investigator's Brochure.[10]

Clinical Hypothesis

Ravagalimab is safe and well tolerated in subjects with moderate to severe UC and leads to endoscopic improvement at Week 8.

2.2 Benefits and Risks to Subjects

Despite the availability of various UC therapies, including biologic and small molecule therapies, many patients still do not respond adequately to these treatments, gradually lose response over time or discontinue treatment due to significant adverse events (AEs). Thus, there remains a large unmet medical need for additional therapeutic options in UC for patients with inadequate response or intolerance to available therapies. Based on pre-clinical, clinical, and translational evidence, ravagalimab could potentially demonstrate efficacy with a favorable safety profile in the treatment of patients with moderately to severely active UC who have failed or have intolerance to approved biologics and/or tofacitinib.

In the Phase 1 studies ravagalimab was safe and well tolerated with no serious or severe AEs observed in healthy adult subjects. The dose regimen in Study M15-722 will not exceed the doses evaluated in the Phase 1 studies.

As with any immune modulating agent, ravagalimab has the potential to impair immune function resulting in a potential risk of infection, including opportunistic infections. The role of ravagalimab in tumor immunity is not well established at this time, but an increased risk of cancer associated with ravagalimab treatment cannot be excluded. Though the completed Phase 1 studies did not suggest a potential for drug-induced liver injury (DILI) with ravagalimab, DILI is under constant surveillance by sponsors and regulators and any suspected event of DILI in this study requires timely detection, evaluation, and follow-up of laboratory parameters. Local reactions to intravenous (IV) infusions or subcutaneous (SC) administered biologic therapies are uncommon, and are usually limited to redness, swelling, or induration at injection site. In Phase 1 studies, 1 subject on ravagalimab each experienced injection site reaction and injection site pain. The aforementioned safety risks were taken into account with the establishment of the safety monitoring measures in the eligibility criteria for this study. Furthermore, an internal data monitoring committee (DMC) will monitor safety at regular intervals (Section 6.3).

Blood sampling, IV infusions, and subcutaneous SC injections can cause local bruising, inflammation, and pain. The preparation for endoscopy, and the endoscopy and biopsy procedure itself, although generally well tolerated, can be associated with diarrhea, abdominal pain, and in more severe cases, perforation, bleeding, effects from anesthetic medications, and infection.

In view of the coronavirus disease of 2019 (COVID-19) pandemic, the benefit-risk profile of various immunomodulatory therapies on COVID-19 is being evaluated. At this time, the effects of ravagalimab on the course of COVID-19 is not known.

The benefit-risk profile of ravagalimab is considered appropriate for an experimental therapy at this stage of clinical development in an especially refractory patient population.

Taken together, the data support further development of ravagalimab in Phase 2 for subjects with moderate to severe UC who have failed prior biologic therapy and/or tofacitinib. For further details, please see findings from completed studies, including safety data in the ravagalimab Investigator's Brochure.[10]

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

To explore the efficacy, safety, and tolerability of ravagalimab as treatment in subjects with moderately to severely active UC.

3.2 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with endoscopic improvement (Mayo endoscopic subscore of 0 or 1) at Week 8. Note that evidence of friability during endoscopy in subjects with a Mayo endoscopic subscore of 0 or 1 will confer an endoscopic subscore of 2.

3.3 Secondary Efficacy Endpoints

Definitions of Efficacy Endpoints:

Clinical Remission per Adapted Mayo Score: stool frequency subscore (SFS) ≤ 1, and not greater than baseline, rectal bleeding subscore (RBS) = 0, and endoscopic subscore ≤ 1

Clinical Response per Adapted Mayo Score: decrease from Baseline ≥ 2 points and ≥ 30%, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1

Clinical Response per Partial Adapted Mayo Score: decrease from Baseline ≥ 1 points and ≥ 30%, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1

Clinical Remission per Full Mayo Score: Full Mayo score ≤ 2 with no subscore > 1

Clinical Response per Full Mayo Score: decrease from Baseline ≥ 3 points and ≥ 30%, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1

Endoscopic Improvement: Mayo endoscopic subscore of 0 or 1

Endoscopic Remission: Mayo endoscopic subscore = 0

Histologic Remission: Geboes score of < 2.0

Mucosal Healing: endoscopic and histologic remission

Modified Baron Score: The modified Baron score, which represents an endoscopic classification, ranges from 0 to 4, with 0 denoting normal mucosa, 1 granular mucosa with an abnormal vascular pattern, 2 friable mucosa, 3 microulceration with spontaneous bleeding, and 4 gross ulceration.

Note that evidence of friability during endoscopy in subjects with a Mayo endoscopic subscore of 0 or 1 will confer an endoscopic subscore of 2.

For this study, Baseline is defined as Week 0.

Key Secondary Efficacy Endpoints for Induction Period (Weeks 0 to 12)

- Proportion of subjects with clinical remission per Adapted Mayo score at Week 8
- Proportion of subjects with clinical response per Adapted Mayo score at Week 8
- Proportion of subjects with clinical response per Partial Adapted Mayo score over time
- Proportion of subjects with clinical remission per Full Mayo score at Week 8 in subjects with a Full Mayo score of 6 to 12 at Baseline

- Proportion of subjects with Endoscopic remission at Week 8

3.4 Additional Efficacy Endpoints

- Change from Baseline in modified Baron score over time (at visits with endoscopy)
- Proportion of subjects with achievement of SFS = 0, RBS = 0, and Mayo endoscopic subscore = 0 over time (at visits with endoscopy)
- Time to clinical response per Partial Adapted Mayo score
- Proportion of subjects with endoscopic improvement over time (at visits with endoscopy)
- Proportion of subjects with clinical remission per Adapted Mayo score over time (at visits with endoscopy)
- Proportion of subjects with clinical response per Adapted Mayo score over time (at visits with endoscopy)
- Proportion of subjects with clinical response per Partial Adapted Mayo score over time
- Proportion of subjects with achievement of clinical remission per Adapted Mayo score over time among subjects who were taking corticosteroids at Baseline and subsequently discontinued corticosteroids for ≥ 90 days prior to the respective visit.
- Proportion of subjects with discontinuation of corticosteroid use for subjects taking corticosteroids at Baseline at all visits over time
- Proportion of subjects with endoscopic remission over time (at visits with endoscopy)
- Proportion of subjects with clinical remission per Full Mayo score over time in subjects with a Full Mayo score of 6 to 12 at Baseline (at visits with endoscopy)
- Proportion of subjects with clinical response per Full Mayo score over time in subjects with a Full Mayo score of 6 to 12 at Baseline (at visits with endoscopy)
- Proportion of subjects with SFS ≤ 1 over time
- Proportion of subjects with RBS = 0 over time
- Change from Baseline in RBS over time
- Change from Baseline in SFS over time
- Change from Baseline in fecal calprotectin (FCP) over time
- Change from Baseline in high sensitivity C-reactive protein (hs-CRP) over time
- Change from Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) over time
- Proportion of subjects with UC-related Hospitalizations (yes/no) over time
- Proportion of subjects with UC-related surgery (yes/no) over time
- Proportion of subjects reporting no bowel urgency over time
- Change from Baseline in weekly abdominal pain score over time

- Proportion of subjects with achievement of ≥ 30% reduction from Baseline in weekly abdominal pain score over time
- Proportion of subjects with weekly abdominal pain score = 0 over time
- Change from Baseline in number of extraintestinal manifestations (EIM) over time (as captured in the EIM electronic case report form [eCRF])
- Proportion of subjects with histologic remission over time (at visits with endoscopy)
- Proportion of subjects with mucosal healing (endoscopic and histologic remission) over time (at visits with endoscopy)
- Change from Baseline in Ulcerative Colitis Endoscopic Index of Severity (UCEIS) over time (at visits with endoscopy)
- Change from Baseline in UC-100 score over time (at visits with endoscopy)

3.5 Safety Endpoints

Safety evaluations include AE monitoring, physical examinations, vital sign measurements, electrocardiogram (ECG) variables (as needed), and clinical laboratory testing (hematology, chemistry, and urinalysis) as measures of safety and tolerability. An internal DMC will monitor safety at regular intervals (Section 6.3).

3.6 Pharmacokinetic Endpoints

Serum ravagalimab concentrations will be obtained at the visits indicated in Appendix D and will be summarized at each sampling time point using descriptive statistics. A nonlinear mixed-effects modeling approach may be used to estimate the population central value and the empirical Bayesian estimates of the individual values for ravagalimab apparent clearance (CL/F) and volume of distribution at steady-state (Vss/F). Ravagalimab anti-drug antibody (ADA) development will also be determined at specific visits during the study (Appendix D) and will be summarized using descriptive statistics. Additional parameters and relationships (e.g., exposure-receptor occupancy, exposure-efficacy, or exposure-safety) may be evaluated if useful for the interpretation of study results.

3.7 Biomarker Endpoints

Biospecimens (blood and tissue biopsy) will be collected at specified time points (Appendix D) throughout the study to evaluate known and/or novel disease-related or drug-related biomarkers. Types of biomarkers may include nucleic acids, proteins, lipids, and/or metabolites. Biopsies for biomarker analysis will be done when performing endoscopies. Up to 4 biopsies will be taken from the site of general inflammation at each visit with an endoscopy for biomarker research as outlined in Appendix D: 1 biopsy for histologic assessment by central review, 1 biopsy for gene expression analysis (including CD40 signature), and 2 biopsies for tissue RO (where applicable). Biopsies for tissue RO will only be collected at sites located in the United States. Additional biopsies may be collected at the Investigator's discretion to confirm disease diagnosis, and/or to rule out dysplasia, colon cancer and infection.

Blood samples will be used to evaluate ravagalimab RO and change in T cells, NK cells, B cells, and plasmablast cell numbers.

Blood samples may be used for exploratory research to assess and generate prognostic, predictive, pharmacodynamic, or surrogate biomarker signatures. Mandatory intestinal biopsy tissue samples may also be used for exploratory research to assess and generate prognostic, predictive, pharmacodynamic, or surrogate biomarker signatures. These assessments may be explored in the context of UC or related conditions and/or ravagalimab or drugs of similar classes.

The results from these analyses are exploratory in nature and may not be included with the clinical study report. Biomarker samples will be collected and analyzed from all subjects, unless precluded by local regulations or restrictions.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

Study M15-722 is a Phase 2a, multicenter, single arm, open-label (OL) study to investigate the efficacy and safety of ravagalimab in subjects with moderate to severe UC who failed prior therapy. The study contains a 35-day screening period, 2 treatment periods, and an 84-day follow up period from the last dose of study drug. The induction period is an open-label 12-week treatment period to evaluate the efficacy, safety, tolerability, PK and RO of ravagalimab for inducing endoscopic improvement at Week 8. Subjects who achieve clinical response per Partial Adapted Mayo score at Week 12 may continue into the maintenance period. The maintenance period is an OL 92-week treatment period to assess efficacy and safety for maintenance of response with ravagalimab.

Prior to protocol version 4.0 the study had a double-blind (DB) placebo-controlled induction period. Ongoing subjects enrolled prior to version 4.0 continued their treatment as randomized during the induction period and, in case of clinical response at Week 12, their OL treatment during the maintenance period.

Induction Period

Up to approximately 40 subjects will be enrolled in the induction period to receive the following treatment:

- Ravagalimab 600 mg intravenous (IV) Week 0; ravagalimab 300 mg subcutaneous (SC) Weeks 2, 4, 6, 8, and 10.

Once the 30th subject completes Week 8 assessments an interim analysis will occur. This interim analysis will inform the planning of future Phase 2b and 3 studies. Enrollment into the induction period may continue until approximately 40 subjects have enrolled, or enrollment may be terminated if the study objectives are determined to have been met.

An endoscopy is required at Screening, and evaluation of endoscopic improvement will occur at Week 8. In order to explore the time-course of ravagalimab efficacy, subjects will continue through Week 12 and

will be assessed for clinical response per Partial Adapted Mayo score at Week 12. Subjects who complete the induction period and achieve clinical response per Partial Adapted Mayo score at Week 12 will be given the opportunity to continue into the maintenance period. Subjects not achieving clinical response per Partial Adapted Mayo score at Week 12 will be discontinued and have a follow-up visit (or call if a visit is not possible) 84 days from the last dose of study drug to obtain information on any new or ongoing AEs.

Maintenance Period

Subjects who enter the maintenance period will receive OL ravagalimab 300 mg SC every other week (eow) from Week 12 through Week 102.

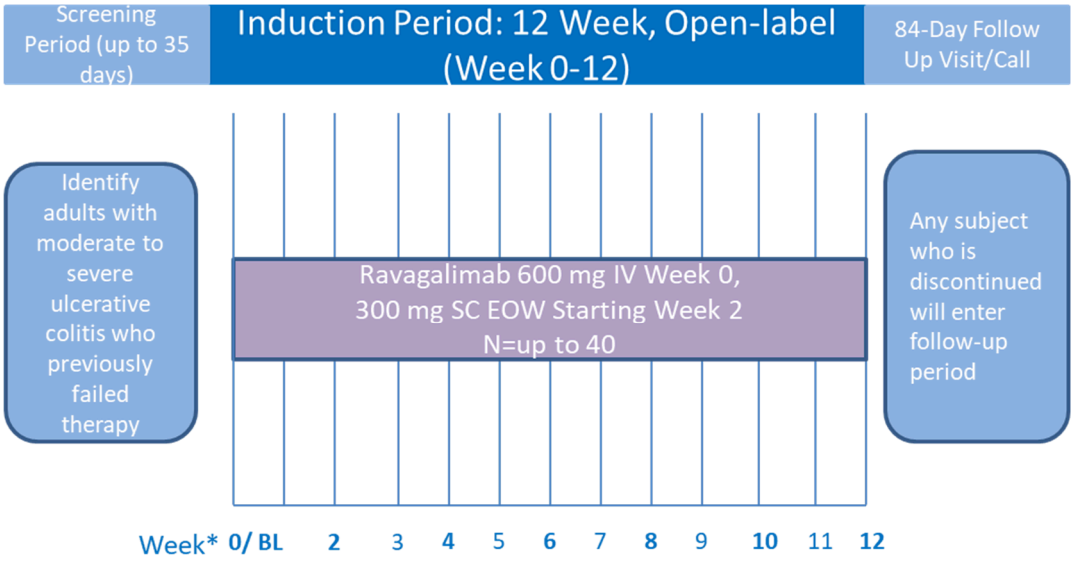
At Weeks 52 and 104 subjects will undergo endoscopy. Clinical response and remission, as well as other exploratory endpoints will be evaluated throughout the study at specified time points. Patients who complete the maintenance period will have a follow-up visit (or call if a visit is not possible) 84 days from the last dose of study drug to obtain information on any new or ongoing AEs.

The schematic of the study is shown in Figure 1. Further details regarding study procedures are located in the Operations Manual.

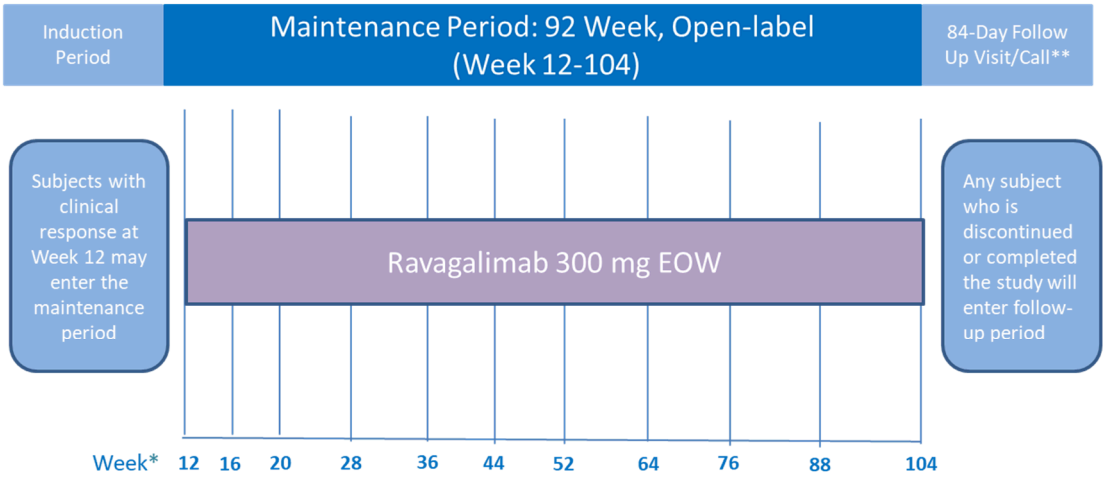
See Section 5.1 for information regarding eligibility criteria.

All video endoscopies and mandatory biopsies for histologic assessment will be centrally reviewed.

Figure 1. Induction and Maintenance Period Schematic



***Bold**= Study Visits +/- 7 days



***Bold**= Study Visits +/- 7 days
**84-day follow up visit/call from last study drug administration
Study Drug Administration Visits ONLY not listed in the schematic above and will occur at:
Week 14, 18, 22, 24, 26, 30, 32, 34, 38, 40, 42, 46, 48, 50, 54, 56, 58, 60, 62, 66, 68, 70, 72, 74, 78, 80, 82, 84, 86, 90, 92, 94, 96, 98, 100, 102

BL = Baseline; EOW = every other week; IV = intravenous; SC = subcutaneous

Note: Prior to protocol version 4.0 the study had a double-blind (DB) placebo-controlled induction period.

4.2 Discussion of Study Design

Choice of Control Group

The efficacy of ravagalimab will be evaluated through comparison with historical control. The control group for this study is placebo data derived from meta-analysis of recent clinical studies that used central review of endoscopies and that are aligned in terms of endpoint definition and time point of analysis. The objective nature of the centrally read endpoint, as well as the low placebo rate of endoscopic improvement, makes the use of historical placebo control a feasible method to assess the effect of ravagalimab. Subjects will therefore not be enrolled into a concurrent control group within the study.

Prior to Version 4.0, a concurrent placebo control arm was used in this study.

Appropriateness of Measurements

Standard data collection, clinical, statistical, endoscopy-related and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard or are derived from commonly used efficacy measurements for assessing disease activity in clinical studies of subjects with UC. All clinical and laboratory procedures in this study are standard and generally accepted. Central review of endoscopy will increase study rigor and ensure enrollment of subjects with moderately to severely active UC.

Suitability of Subject Population

The specific population chosen was based on the unmet medical need of those subjects who have failed prior therapy as defined in Section 5.1.

Selection of Doses in the Study

The dose selection in this study is based on analysis of PK, pharmacodynamics, and safety data from Phase 1 studies in healthy volunteers as well as safety data from pre-clinical animal studies. The Phase 1 ravagalimab single and multiple ascending dose studies, Study M15-726 and Study M15-730, evaluated ravagalimab single doses of 10 - 300 mg SC and 100 - 600 mg IV, and multiple doses of 50 and 150 mg SC weekly for 3 weeks following IV loading doses of 50 mg and 300 mg, respectively. Partial peripheral blood B cell CD40 RO was achieved with SC doses of 10 and 30 mg; whereas full peripheral blood B cell CD40 RO (i.e., > 90%) was achieved with IV or SC doses ≥ 100 mg. In Study M15-730, full peripheral blood B cell RO was achieved with weekly SC doses of 50 and 150 mg and was maintained for at least 14 days after the last ravagalimab dose.

In Study M16-641 the impact of ravagalimab on T helper dependent B cell responses following keyhole limpet hemocyanin (KLH) administration was evaluated. Preliminary results from the study showed that a single 300 mg SC dose of ravagalimab achieved near full suppression of IgM and IgG response to KLH antigen. On the other hand, a single 100 mg SC dose and multiple 100 mg SC doses given once every two weeks (total of three doses) resulted in minimal to no suppression of immune response to KLH, despite prolonged maximal peripheral blood B cell CD40 RO.

Given the results from the KLH immunization study and the uncertainty in correlation between peripheral blood B cell CD40 RO and efficacy in UC patients and the potential for a tissue sink in UC

patients, for this proof-of-concept (POC) study, a 600 mg IV loading dose followed by 300 mg eow SC dose was selected for induction to enable rapid achievement of serum steady state ravagalimab concentrations as well as presumably high levels of tissue RO. Such dosing is predicted to provide at least a 20-fold safety margin relative to no-observed-adverse-effect-level (NOAEL) exposures observed at a dose of 50 mg/kg in the 13-week GLP-compliant toxicology study in cynomolgus monkeys. Given the high inflammatory burden for UC patients, a 300 mg eow SC maintenance dose was selected for subjects who demonstrate clinical response after induction. Furthermore, 300 mg eow SC dosing with ravagalimab is predicted to result in serum ravagalimab exposures that are approximately 4-fold lower than the NOAEL exposures observed at a dose of 5 mg/kg in 26-week toxicology studies in cynomolgus monkeys.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

- 1. Subjects must understand and personally, voluntarily **sign and date an informed consent**, approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.

Demographic and Laboratory Assessments

- 2. Adult **male or female**, between 18 and 75 years of age, inclusive, at time of the Baseline visit.
- 3. **Laboratory values** meeting the following criteria within the screening period prior to the first dose of study drug:
  - Serum aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2 × upper limit of normal (ULN);
  - Total white blood cell (WBC) count ≥ 3.0×10^9/L;
  - Absolute neutrophil count (ANC) > 1,200 cells/µL;
  - Absolute lymphocyte count (ALC) > 750 cells/µL;
  - Total bilirubin < 2 mg/dL, except for subjects with isolated elevation of indirect bilirubin relating to Gilbert's syndrome;
  - Estimated glomerular filtration rate (GFR) by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula ≥ 40 ml/min/1.73 m^2;
  - Hemoglobin ≥ 9 g/dL;
  - Platelet count ≥ 100,000/µL.
- 4. Are willing or able to comply with procedures required in this protocol.

- 5.Subject must not have an active, chronic, or recurrent infection that based on the Investigator's clinical assessment makes the subject an unsuitable candidate for the study, or the following:
  - Subject must not be currently infected with C. difficile toxin as identified during Screening or another known intestinal pathogen.
  - Subject must not be infected with human immunodeficiency virus (HIV)
  - Subject must not have active hepatitis B or hepatitis C (as defined in Appendix F)
  - Subject must not have active tuberculosis (TB). Subjects with a positive QuantiFERON TB / or Purified Protein Derivative (PPD) skin test during Screening may participate in the study if further workup (including a mandatory chest X-ray [CXR] and other testing according to local country guidelines) establishes conclusively that the subject has no evidence of active TB. If latent TB is established, the subject must initiate and complete a minimum of 2 weeks (or per local guidelines, whichever is longer) of an ongoing TB prophylaxis/treatment or have documented completion of a full course of TB prophylaxis, prior to Baseline. Subjects with active TB or a history of active TB who have documented completion of a full course of anti-TB therapy may be allowed to enter the study after consultation with the AbbVie Therapeutic Area Medical Director (TA MD).
  - Confirmed COVID-19: the Baseline visit must be at least 14 days from onset of signs/symptoms or positive SARS-CoV-2 test; symptomatic subjects must have recovered, defined as resolution of fever without use of antipyretics and improvement in symptoms;
  - Suspected COVID-19: subjects with signs/symptoms suggestive of COVID-19, known exposure, or high risk behavior should undergo molecular (e.g., PCR) testing to rule out SARS-CoV-2 infection or must be asymptomatic for 14 days from a potential exposure.

Disease Activity

- 6. Diagnosis of UC for at least 3 months prior to Baseline. Appropriate documentation of biopsy results consistent with the diagnosis of UC in the assessment of the Investigator, must be available.
- 7. Subject meets the following disease activity criteria: Active UC with an Adapted Mayo score of 5 to 9 points and endoscopic subscore of 2 to 3 (confirmed by central review).
- 8. No current diagnosis of CD or inflammatory bowel disease-unclassified (IBD-U).
- 9. No extent of inflammatory disease limited to the rectum as assessed by screening endoscopy.
- 10. No currently known complications of UC such as:
  - fulminant colitis,
  - toxic megacolon,
  - previous colectomy (total or subtotal),
  - or any other manifestation that might require surgery while enrolled in the study
- 11. Subjects must not have an ostomy or ileoanal pouch.

Subject History

- 12. History of inadequate response, loss of response, or intolerance to one or more of the following:
  - Demonstration of intolerance requires no minimum dose or duration of use.
  - Inadequate response is defined as outlined below:
    - Signs and symptoms of persistently active disease despite a history of one or more of the following:
      - Infliximab: At least one 6-week induction regimen of infliximab (≥ 5 mg/kg intravenous [IV] at Weeks 0, 2, and 6),
      - Adalimumab: At least one 4-week induction regimen of adalimumab (one 160 mg SC dose at Week 0, followed by one 80 mg SC dose at Week 2),
      - Golimumab: At least one 4-week induction regimen of golimumab (200 mg SC at Week 0 and 100 mg SC at Week 2),
      - Vedolizumab: At least one 6-week induction regimen of vedolizumab (300 mg IV at Weeks 0, 2, and 6),
      - Tofacitinib: At least one 8-week induction regimen of tofacitinib (10 mg PO twice a day) or
      - Ustekinumab: At least an induction regimen of a single weight-based infusion dose of ustekinumab (260 mg IV with body weight [bw] ≤ 55 kg, 390 mg with bw > 55 kg to 85 kg, 520 mg with bw > 85 kg).
    - Recurrence of symptoms during scheduled maintenance dosing following demonstration of clinical benefit of the above biologics or tofacitinib.
- 13. No history of radiation or ischemic colitis.
- 14. No history of **any malignancy** except for successfully treated non metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix.
- 15. No history of clinically significant (per investigator's judgment) **drug or alcohol abuse** within the last 12 months.
- 16. No history of clinically significant medical conditions or any other reason that the investigator determines would **interfere with the subject's participation** in this study or would make the subject an unsuitable candidate to receive study drug.
- 17. No history of **dysplasia** of the gastrointestinal tract or evidence of dysplasia in any biopsy performed during the Screening endoscopy, other than completely removed low-grade dysplastic lesions (historically or during Screening).
- 18. No history of **lymphoproliferative disease**, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly.
- 19. No history of an **allergic reaction** or significant sensitivity to excipients of the study drug or the ingredients of Chinese hamster ovary (CHO) cells.

- 20. No severe, progressive, or uncontrolled renal, hepatic, hematological, endocrine, disorder or symptoms thereof.

Contraception

- 21. For all females of childbearing potential, a **negative serum pregnancy test** at the Screening Visit and a negative urine pregnancy test at baseline prior to the first dose of study drug. Procedures in the case of a borderline serum pregnancy test are described in Appendix F.
- 22. Female subjects of childbearing potential must practice at least 1 protocol-specified **method of birth control** (Section 5.2), that is effective from Study Day 1 through at least 84 days after the last dose of study drug. Female subjects of non-childbearing potential do not need to use birth control.
- 23. Females must not be **pregnant, breastfeeding, or considering becoming pregnant** during the study or for at least 84 days after the last dose of study drug.

Concomitant Medications

- 24. Subject must not receive IV anti-infectives within 35 days prior to Baseline visit or oral/intramuscular (IM) anti-infectives (non-UC-related) within 14 days prior to the Baseline visit.
- 25. Subject must not receive any parenteral nutrition within 35 days prior to Baseline.
- 26. Subject must not receive cannabis for either recreational or for medical reasons within 14 days prior to Baseline.
- 27. Subject must not receive cyclosporine, tacrolimus, or mycophenolate mofetil (unless for ocular application) within 35 days prior to Baseline.
- 28. Subject must not receive fecal microbial transplantation within 35 days prior to Baseline.
- 29. Subject must not have been treated with **any approved biologic agent** (e.g., infliximab, adalimumab, golimumab, vedolizumab) within 8 weeks prior to Baseline, or with tofacitinib within 14 days prior to Baseline, or any investigational biologic or other agent or procedure within 35 days or 5 half-lives prior to Baseline, whichever is longer. Subject must not have been treated with ravagalimab at any time prior to Baseline.

  Note: If there is proper documentation of an undetectable drug level measured by a commercially available assay for any of the approved biologics above, there is no minimum washout prior to Baseline.
- 30. Subject must not have received **any live vaccine** within 35 days prior to Baseline.
- 31. Subject must not receive oral UC-related antibiotics or oral aminosalicylates within 14 days prior to Baseline unless they have been on stable doses for greater than 14 days prior to Baseline.

- 32. Subjects must not have received oral corticosteroids, unless they have been on that corticosteroid for at least 14 days prior to Baseline and on a stable dose for at least 7 days prior to Baseline. Subjects taking oral corticosteroids must not be taking oral corticosteroids at the following doses: budesonide > 9 mg/day, beclomethasone > 5 mg/day, prednisone or equivalent > 20 mg/day.
- 33. Subject must not be on immunomodulators (azathioprine [AZA], mercaptopurine [6-MP], methotrexate [MTX]) unless they have been on the course for at least 42 days prior to Baseline and have been on a stable dose for at least 35 days prior to Baseline.
- 34. Subject must not receive the following therapies within 14 days prior to Screening or during Screening:
  - A combination of 2 or more of the following: oral budesonide, oral beclomethasone, and/or oral prednisone (or equivalent) simultaneously, with the exception of inhalers
  - IV corticosteroids
  - Therapeutic enema or suppository (i.e., rectal aminosalicylates/corticosteroids), other than required for endoscopy
- 35. Subject must not have received apheresis (e.g., Adacolumn apheresis) within 60 days prior to Screening or during Screening.

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential

  Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:
  - Postmenopausal, age > 55 years with no menses for 12 or more months without an alternative medical cause.
  - Postmenopausal, age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level > 40 IU/L.
  - Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy)
- Females, of Childbearing Potential

  Females of childbearing potential must avoid pregnancy while taking study drug and for at least 84 days after the last dose of study drug. Females must commit to one of the following methods of birth control:
  - 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).
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is/are the sole sexual partner(s) of the trial subject).
- Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

If required per local practices, male or female condom with or without spermicide OR 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 the use of concomitant therapies should be based on the local label.

5.3 Prohibited Medications and Therapy

Except as listed in the eligibility criteria, the following medications are prohibited throughout the duration of the study:

- All biologics or small molecule medication (e.g., JAK inhibitors, sphingosine-1-phosphate [S1P] receptor modulators) with potential impact on UC
- Initiation of oral aminosalicylates, immunomodulators, IV or oral corticosteroids, and/or UC-related antibiotics through Week 12
- Cyclosporine, tacrolimus, or mycophenolate mofetil (unless for ocular application)
- Cannabis
- Rectal therapy with any therapeutic enemas or suppositories, with the exception of those required for endoscopy
- Apheresis
- Any parenteral nutrition
- Any investigational agent
- Any fecal microbial transplant

Vaccines

Live or attenuated vaccines are prohibited within 35 days prior to Baseline, during the study, and for 84 days after the last dose of study drug. Vaccines recommended by local guidelines should be considered. If the Investigator chooses to administer a vaccine, this should be completed before first dose of study drug with appropriate precautions and time interval. It is recommended that subjects be up to date for recommended inactivated, toxoid or biosynthetic vaccines, such as injectable flu vaccine, pneumococcal, and pertussis (tetanus, diphtheria, pertussis vaccine [Tdap]).

5.4 Prior and Concomitant Therapy

Subjects taking oral aminosalicylates, immunomodulators, oral corticosteroids, and/or UC-related antibiotics at Baseline must continue their concomitant treatment for the duration of the induction period (through Week 12). Initiating and/or increasing doses of oral aminosalicylates, immunomodulators, oral corticosteroids, and/or UC-related antibiotics during the study is prohibited through Week 12. Decreasing doses of oral aminosalicylates, immunomodulators, oral corticosteroids, and/or UC-related antibiotics during the induction period is prohibited, except in the event of moderate-to-severe treatment related toxicities and after discussion with the AbbVie TA MD. Starting at Week 12 (maintenance period), oral aminosalicylates, immunomodulators, and/or UC-related antibiotics may be decreased or discontinued at the discretion of the Investigator. Starting at Week 12, initiating and/or increasing doses of oral aminosalicylates, immunomodulators, oral corticosteroids, and/or UC-related antibiotics is permissible after discussion with the AbbVie TA MD.

During the maintenance period, subjects can initiate an optional steroid taper at Week 12. While stopping the taper is permitted, increasing doses above the Baseline dose is permitted only after discussion with the AbbVie TA MD. Below is a suggested tapering schedule.

	Dose	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

Any questions regarding concomitant or prior therapy should be raised to the AbbVie emergency contact. Information regarding potential drug interactions with ravagalimab can be located in the ravagalimab Investigator's Brochure.[10]

5.5 Withdrawal of Subjects and Discontinuation of Study Drug or from Study Participation

A subject may voluntarily withdraw or be withdrawn from study participation, or be discontinued from study drug, at any time for reasons including, but not limited to, the following:

- Disease progression or lack of response to treatment.

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator or the AbbVie TA MD.
- The investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study. This includes if a subject would like to discontinue after completion of the Week 52 visit.
- Eligibility criteria violation was noted after the subject started study drug and continuation of the study drug would place the subject at risk.
- Introduction of prohibited medications or dosages and continuation of the study drug would place the subject at risk.
- The subject becomes pregnant while on study drug.
- Subject has a malignancy, except for localized non-melanoma skin cancer. Discontinuation for carcinoma in situ of the cervix is at the discretion of the Investigator.
- Subject is significantly noncompliant with study procedures, which would put the subject at risk for continued participation in the trial.

Subjects who complete the induction period and do not achieve clinical response per Partial Adapted Mayo score at Week 12 will be discontinued.

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 his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

During states of emergency or pandemic situations, it may be necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. Acceptable mitigation strategies are identified and included in the Operations Manual in Appendix F.

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

5.6 Follow-Up After Subject Discontinuation of Study Drug or from Study Participation

To minimize missing data for efficacy and safety endpoints, 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 by withdrawal of informed consent, in which no further study procedures or study activities can be performed. Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

If a subject prematurely discontinues from the study/study drug, the procedures outlined for the Premature Discontinuation visit (PD visit) should be completed as soon as possible, preferably within 2 weeks. In addition, if subject is willing, an 84-day follow-up visit after the last dose of study drug may be completed to ensure all treatment-emergent AEs/serious adverse events (SAEs) have been resolved.

If a subject withdraws from study follow up or withdraws permission for the collection of their personal data, the study staff may still use available public records to obtain information about survival status only, as appropriate per local regulations.

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 that samples are withdrawn from research, samples will not be analyzed, no new biomarker analysis data will be collected for the withdrawn subject or added to the existing data or database(s), and the samples will be destroyed. Data generated for biomarker research before subject withdrawal of consent will remain part of the study results.

5.7 Study Drug

Information about the study drug used in this study is presented in Table 1.

Table 1. Description of Study Drug

	Investigational Product	Investigational Product Placebo
Investigational product name	Ravagalimab (ABBV-323)	Placebo
Active ingredient	Ravagalimab (ABBV-323)	N/A
Dosage Form	Lyophilized powder for solution for injection/infusion in vials	Lyophilized powder for solution for injection/infusion in vials
Strength	100 mg/mL, when reconstituted	N/A, when reconstituted
Frequency of administration	Induction: IV × 1 dose then SC eow Maintenance: SC eow	Induction period only: for IV line flush only

IV = intravenous; eow = every other week; N/A = not applicable; SC = subcutaneous

The study drugs will be supplied in cartons containing one vial with quantities sufficient to accommodate study design. Each vial contains 100 mg ravagalimab lyophilized powder for solution for injection/infusion, or placebo. Each carton and vial label will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be administered at the subject's corresponding study visit. Each carton and vial will be labeled as required per country requirements. The labels must remain affixed to the cartons and vials. All blank spaces should be completed by site staff prior to dispensing to subject. Study drug will only be used for the conduct of this study.

AbbVie will provide instructions for drug preparation.

5.8 Randomization/Drug 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. No randomization will be used in the single arm, open-label study.

5.9 Protocol Deviations

The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. Protocol deviations are prohibited except when necessary to eliminate an immediate hazard to study subjects. If a protocol deviation occurs (or is identified, including those that may be due to cases of state of emergency or pandemic situations), the investigator is responsible for notifying independent ethics committee (IEC)/independent review board (IRB), regulatory authorities (as applicable), and AbbVie.

6 SAFETY CONSIDERATIONS

6.1 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 drug 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 not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 1 business day of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events

An adverse event 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 adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use

of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

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

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

If an adverse event, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance or CRO (as appropriate) as a serious adverse event within 24 hours of the site being made aware of the serious adverse event (refer to Section 4.3 of the Operations Manual [Appendix F] 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). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All adverse events reported from the time of study drug administration until 84 days after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events and protocol-related nonserious adverse events will be collected from the time the subject signs the study-specific informed consent.

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local requirements.

Adverse events 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

Below is a list of adverse events of special interest. Related supplemental eCRFs, if applicable, should be filled out in response to an event.

- Serious infections and opportunistic infections
- Active TB (TB screening eCRF in all subjects and supplemental TB eCRF as appropriate)
- Malignancies (all types) (Malignancy eCRF);
- Hepatic events (Hepatic AE eCRF):
  - Discontinuation or interruption of study drug due to a hepatic-related AE;
  - A hepatic-related SAE;
  - ALT/AST > 8 × ULN or ALT/AST > 3 × ULN with a total bilirubin > 2 × ULN;
- Hematologic disorders;
- Hypersensitivity reactions (Hypersensitivity Reaction Signs and Symptom eCRF).

Adverse Event Severity and Relationship to Study Drug

The investigators will rate AEs according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0, which can be accessed at: https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.[11]

For AEs not captured by the CTCAE, the following should be used:

Grade 1	The adverse event is transient and easily tolerated by the subject (mild).
Grade 2	The adverse event causes the subject discomfort and interrupts the subject's usual activities (moderate).
Grade 3/4	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening (severe).
Grade 5	The adverse event resulted in death of the subject (severe).

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

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

Pregnancy

While not an adverse event, pregnancy in a study subject must be reported to AbbVie within 1 working day after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.5). If a pregnancy occurs in a study subject or in the partner of a study subject, information regarding the pregnancy and the outcome will be collected.

In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained prior to collection of any such information. AbbVie will provide a separate consent form for this purpose. Pregnancy in a subject's partners will be collected from the date of the first dose through 84 days following the last dose of study drug.

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.

6.2 Toxicity Management

The management of specific AEs and laboratory parameters is described in Table 2.

The toxicity management of AEs including AEs of special interest consists of safety monitoring (review of AEs on an ongoing basis, and periodical/ad hoc review of safety issues by a DMC), interruption of study drug dosing with appropriate clinical management if applicable, and discontinuation of the subjects from study drug. There are no time limits for study drug interruption as long as no permanent study discontinuation criteria have been met. The management of specific AEs and laboratory parameters is described below.

For subjects who discontinue study drug but continue study participation and are on standard of care therapies, these toxicity management requirements do not apply (including alerts from the central lab) and any intolerability to standard of care therapies should be managed by the prescribing physician.

Serious Infections: Subjects should be closely monitored for the development of signs and symptoms of infection during and after treatment with study drug. Study drug should be interrupted if a subject develops a serious infection or an opportunistic infection. A subject who develops a new infection during treatment with study drug should undergo prompt diagnostic testing appropriate for an immunocompromised subject. As appropriate, antimicrobial therapy should be initiated, and the subject should be closely monitored. Study drug may be restarted once the infection has been successfully treated or resolved. Subjects who develop active TB or experience Hepatitis B reactivation must be discontinued from study drug. For subjects who develop TB during the study, the supplemental eCRF should be completed.

COVID-19: Interrupt study drug in subjects with a confirmed diagnosis of COVID-19. Consider interrupting study drug in subjects with signs and/or symptoms and suspicion of COVID-19. The COVID-19 eCRF must be completed. If a subject has a confirmed or suspected SARS-CoV-2 infection and study drug was interrupted, the investigator should contact the AbbVie TA MD before reintroducing study drug.

Malignancy: Subjects who develop malignancy other than NMSC or carcinoma in situ of the cervix must be discontinued from study drug. Information including histopathological results should be queried for the confirmation of the diagnosis. The supplemental eCRF should be completed.

ECG Abnormality: Subjects must be discontinued from study drug for an ECG change considered clinically significant and with reasonable possibility of relationship to study drug OR a confirmed absolute QTcF value > 500 msec.

Surgery: Subjects who undergo emergency surgery should have study drug interrupted at the time of the surgery. After emergency surgery, reintroduction of study drug is allowed once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

Management of Select Laboratory Abnormalities: For any given laboratory abnormality, the Investigator should assess the subject, apply the standard of care for medical evaluation and treatment following any local guidelines. Specific toxicity management guidelines for abnormal laboratory values are described in Table 2 and may require an appropriate supplemental eCRF be completed. All

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abnormal laboratory tests that are considered clinically significant by the Investigator will be followed to a satisfactory resolution. If a repeat test is required per Table 2, the repeat testing must occur as soon as possible. Subjects who meet any of the criteria for ALT and/or AST listed in Table 2 should be evaluated for an alternative etiology and managed as medically appropriate per local guidelines. The investigator should contact the AbbVie TA MD to discuss the management of a subject when an alternative etiology has been determined. The alternative etiology should be documented appropriately in the eCRF; study drug should be discontinued if no alternative etiology can be found.

Table 2. Specific Toxicity Management Guidelines for Abnormal Laboratory Values

	Laboratory Parameter	Value	Toxicity Management Guideline
All Subjects	Hemoglobin	< 8 g/dL	• If alternative etiology cannot be identified, interrupt study drug dosing and redraw lab with a new sample. • If value is confirmed, continue to withhold study drug until value returns to normal reference range or baseline value.
		Decrease ≥ 3.0 g/dL from baseline	• If an alternative etiology is known or the hemoglobin value remains in the normal reference range, the subject may continue study drug dosing at the investigator's discretion. • If alternative etiology cannot be identified, interrupt study drug dosing and redraw lab with a new sample. • If value is confirmed, continue to withhold study drug until value returns to normal reference range or baseline value.
	Absolute neutrophil count (ANC)	< 1000 cells/µL	• Interrupt study drug dosing and redraw lab with a new sample. • If value is confirmed, continue to withhold study drug until value returns to normal reference range or baseline value.
		< 500 cells/µL	• Interrupt study drug dosing and redraw lab with a new sample. • If value is confirmed, discontinue study drug.
	Absolute lymphocyte counts (ALC)	< 500 cells/µL	• Interrupt study drug dosing and redraw lab with a new sample. • If value is confirmed, continue to withhold study drug until value returns to normal reference range or baseline value.
	Total white blood cell count	< 2,500 cells/µL	• Interrupt study drug dosing and redraw lab with a new sample. • If value is confirmed, continue to withhold study drug until value returns to normal reference range or baseline value.

	Laboratory Parameter	Value	Toxicity Management Guideline
All Subjects (continued)	Platelet count	< 50,000 cells/µL	• Interrupt study drug dosing and redraw lab with a new sample. • If value is confirmed, continue to withhold study drug until value returns to normal reference range or baseline value.
	ALT or AST	ALT or AST > 8 × ULN	• Interrupt study drug dosing and redraw lab with a new sample. • If value is confirmed, discontinue study drug and complete supplemental hepatic eCRF.
		ALT or AST > 5 × ULN	• Interrupt study drug dosing and redraw lab with a new sample. • If value is confirmed for > 2 weeks of duration, discontinue study drug and complete supplemental hepatic eCRF.
		ALT or AST > 3 × ULN	• Interrupt study drug dosing and redraw lab with a new sample. • If value is confirmed and patient has appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%) discontinue study drug and complete supplemental hepatic eCRF. • If value is confirmed and total bilirubin > 2 × ULN or international normalized ratio (INR) > 1.5, discontinue study drug and complete supplemental hepatic eCRF.
	Serum Creatinine	> 1.5 × the baseline value and > ULN	• Interrupt study drug dosing and redraw lab with a new sample. • If value is confirmed, continue to withhold study drug until value returns to normal reference range or baseline value.
		≥ 2 mg/dL	• Interrupt study drug dosing and redraw lab with a new sample. • If value is confirmed, continue to withhold study drug until value returns to normal reference range or baseline value.
Subjects who are HBc Ab+ and HBV DNA negative at Screening	ALT or AST	ALT or AST > 5 × ULN	• Interrupt study drug dosing and redraw lab with a new sample. • If value is confirmed, send HBV DNA by PCR. • If HBV DNA by PCR is positive, discontinue study drug and complete supplemental hepatic eCRF.

6.3 Data Monitoring Committee

An internal DMC will review safety data. A separate DMC charter will be approved before the first subject is enrolled into the study. The DMC is responsible for monitoring safety data, alerting AbbVie to possible safety concerns related to the conduct of the study, and recommending appropriate actions for study conduct and management.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

Complete and specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the Week 12 database lock for the primary analysis. The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA).

7.2 Definition for Analysis Populations

The Full Analysis Set (FAS) includes all enrolled subjects who received at least 1 dose of ravagalimab (including subjects randomized to ravagalimab prior to Version 4.0). The FAS will be used for all efficacy and baseline analyses.

Subjects enrolled prior to version 4.0 will be unblinded after they finish Week 8 assessments. Subjects who were randomized to and received ravagalimab will be included in the FAS.

The Safety Analysis Set consists of all subjects who received at least 1 dose of study drug. Subjects randomized to the study prior to Version 4.0 will be analyzed along with subjects enrolled after Version 4.0 for safety analysis. Subjects will be grouped based on the treatment received.

Depending on the magnitude of missing data due to COVID-19, additional appropriate analysis may be performed with details included in the SAP.

7.3 Statistical Analyses for Efficacy

Primary Analysis

The primary analysis will be performed after all subjects completed the study induction period (i.e., completed Week 12 assessments). The final analysis will be performed after all subjects completed the study maintenance period. Additional analysis may be performed to support program development or health authority requests. There will be no multiplicity test alpha-adjustment for this proof of concept study.

The primary efficacy endpoint is the proportion of subjects with endoscopic improvement at Week 8. The null hypothesis is that there is no difference in the proportion of subjects with endoscopic improvement at Week 8 between ravagalimab treated subjects and historical placebo.

Analysis of the primary efficacy endpoint will be conducted on the FAS. Comparison of the primary efficacy endpoint will be performed between the ravagalimab group and the historical placebo group using Bayesian approach with placebo distribution as [redacted] from historical data meta-analysis and prior for ravagalimab Beta (0.5, 0.5), the Jeffrey's prior for binomial distribution. The placebo prior is determined based on available placebo data from similar trials and may be updated if new placebo data from similar trials become available before the primary analysis database lock.

Non-Responder Imputation while incorporating Multiple Imputation to handle missing data due to COVID-19 (NRI-C) will be applied to the primary endpoint analysis.

Details on the primary, secondary, and other efficacy analyses are provided in the SAP.

Interim Analysis

An interim efficacy analysis will be performed after approximately 30 subjects complete Week 8 assessments. This interim analysis will inform the planning of future Phase 2b and 3 studies. Enrollment into the induction period will continue until approximately 40 subjects have been enrolled.

Sample Size Estimation and Decision Probability

The planned sample size is up to approximately 40 subjects.

Meta-analysis for historical placebo data from tofacitinib (OCTAVE1/2),[4] upadacitinib (Phase 2b; data on file) and ustekinumab (UNIFI)[12] studies gives [redacted] endoscopic improvement rate at Week 8. The matched prior distribution for placebo is [redacted]. The prior for ravagalimab treatment group will be set to Jeffreys prior Beta (0.5, 0.5) as non-informative. The probability that the posterior probability of rate difference > 0 is larger than 90% is more than 90% if the endoscopic improvement rate difference is 25% between ravagalimab and historical placebo, given a sample size of 40 subjects for ravagalimab. If ravagalimab has the same endoscopic improvement rate of [redacted] as historical placebo, that probability is approximately 3.1%.

7.4 Statistical Analyses for Safety

Safety analysis will be carried out using the Safety Analysis Set. Incidence of AEs, changes in vital signs, physical examination results, ECGs, and clinical laboratory values will be analyzed. Treatment-emergent AEs will be tabulated by system organ class (SOC) and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) for the treatment group. Mean change from Baseline for laboratory and vital signs data will be summarized. In addition, shift tables and listings will be provided for abnormal values, whereby the normal range of the analyzing laboratory will be used. Vital signs will be analyzed similarly.

Missing safety data will not be imputed. Details for each safety endpoint analysis will be provided in the SAP.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The protocol, informed consent form(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 informed consent form(s) must be obtained before any subject is enrolled. 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.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual (Appendix F), International Council for Harmonisation (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 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 Good Clinical Practice (GCP), and applicable local regulatory requirement(s). In cases of state of emergency or pandemic situations, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10 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.

11 COMPLETION OF THE STUDY

The end-of-study is defined as 84 days after the last subject last dose of ravagalimab.

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APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
5-ASA	5-aminosalicylic acid
6-MP	Mercaptopurine
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine transaminase
APC	Antigen presenting cell
AST	Aspartate transaminase
AZA	Azathioprine
bw	body weight
CD	Crohn's disease
CHO	Chinese hamster ovary
CL/F	Apparent clearance
COVID-19	Coronavirus Disease-2019
CTCAE	Common Terminology Criteria for Adverse Events
CXR	Chest X-ray
DILI	Drug-induced liver injury
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDP	Extemporaneous Dose Preparation
EIM	Extraintestinal manifestation
eow	Every other week
FAS	Full analysis set
FCP	Fecal calprotectin
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
GFR	Glomerular filtration rate
GLP	Good Laboratory Practice
HIV	Human immunodeficiency virus
hs-CRP	High sensitivity C-reactive protein

IBDQ	Inflammatory Bowel Disease Questionnaire
IBD-U	Inflammatory Bowel Disease-unclassified
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IM	Intramuscular
IMP	Investigational Medicinal Product
IRB	Institutional review board
IRT	Interactive response technology
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous(ly)
JAK	Janus kinase
L	Ligand
mAb	Monoclonal antibody
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
nAb	Neutralizing antibody
NOAEL	No-observed-adverse-effect-level
NRI	Non-Responder Imputation
OL	Open-label
PD	Premature discontinuation
PK	Pharmacokinetic(s)
PO	orally (*per os)*
POC	Proof of concept
PPD	Purified protein derivative
PT	Preferred term
QTcF	Fridericia-corrected QT interval
RA	Rheumatoid arthritis
RBS	Rectal bleeding subscore
RO	Receptor occupancy
S1P	Sphingosine-1-phosphate
SAE	Serious adverse event

SAP	Statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous(ly)
SFS	Stool frequency subscore
SLE	Systemic lupus erythematosus
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reactions
TA MD	Therapeutic Area Medical Director
TB	Tuberculosis
Tdap	Tetanus, diphtheria, pertussis vaccine
TNF	Tumor necrosis factor
UC	Ulcerative colitis
UCEIS	Ulcerative Colitis Endoscopic Index of Severity
ULN	Upper limit of normal
Vss/F	Volume of distribution at steady-state
WBC	White blood cell

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M15-722: A Multicenter, Single Arm, Open-label Study to Investigate the Efficacy and Safety of Ravagalimab (ABBV-323) in Subjects with Moderate to Severe Ulcerative Colitis Who Failed Prior Therapy

Protocol Date: 04 December 2020

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation (ICH) Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. 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 operations manual, 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 drugs 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 promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. 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)	

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	Program Lead II	Clinical Program Development
[redacted]	Principal Medical Writer	Medical Writing
[redacted]	Medical Director	Immunology Development
[redacted]	Group Medical Director	Immunology Development
[redacted]	Study Project Manager II	Clinical Program Development
[redacted]	Director	Data and Statistical Sciences
[redacted]	Sr. Director, TA Head	Data and Statistical Sciences
[redacted]	Associate Director	Clinical Pharmacology

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities the subject encounters. The individual activities are described in detail in Appendix F. Allowed modifications due to states of emergency or pandemic situations are detailed within the Operations Manual.

Study Activities Induction Period

Activity	Screening	Induction Period (W0 to W12)							PD	Unscheduled	84-Day Follow Up Visit[a]
		Baseline	W2	W4	W6	W8	W10	W12			
	D –35 to D –1	D1	D15 ± 7 days	D29 ± 7 days	D43 ± 7 days	D57 ± 7 days	D71 ± 7 days	D85 ± 7 days			
INTERVIEWS & QUESTIONNAIRES											
Informed consent	✓										
Eligibility criteria	✓	✓									
Medical/surgical history	✓	✓									
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓		✓		✓	✓	✓	
TB Risk Factor Questionnaire	✓										
Subject questionnaires: IBDQ		✓				✓		✓	✓		
Dispense subject diary	✓										
Review subject diary		✓	✓	✓		✓		✓	✓	✓	
LOCAL LABS, EXAMS & ASSESSMENTS											
Height	✓										
Weight	✓	✓				✓		✓	✓		
12-lead ECG[b]	✓										
Chest X-Ray[c]	✓										
Vital signs	✓	✓	✓	✓		✓		✓	✓	✓	
Physical examination	✓	✓				✓		✓	✓		
Endoscopy	✓					✓			✓[d]		
Partial Adapted Mayo		✓	✓	✓		✓		✓	✓	✓	

Activity	Screening	Induction Period (W0 to W12)							PD	Unscheduled	84-Day Follow Up Visit[a]
	Baseline	W2	W4	W6	W8	W10	W12				
	D –35 to D –1	D1	D15 ± 7 days	D29 ± 7 days	D43 ± 7 days	D57 ± 7 days	D71 ± 7 days	D85 ± 7 days			
Adapted Mayo/Full Mayo		✓				✓			✓		
SARS-CoV-2 molecular test, if applicable	✓										
CENTRAL LABS											
Hepatitis B, Hepatitis C Screening and HIV Test (Note: HBV testing is done every 12 weeks where required)	✓										
C. difficile toxin	✓										
Pregnancy test[e]	✓[f]	✓[g]	✓	✓	✓	✓	✓	✓	✓		
FSH[f]	✓										
QuantiFERON-TB Gold test (and/or local PPD skin test)	✓										
Urinalysis[h]	✓	✓		✓		✓		✓	✓		
Chemistry and hematology[h]	✓	✓[g]	✓	✓		✓		✓	✓		✓
hs-CRP[h]		✓	✓	✓		✓		✓	✓		
Serum ravagalimab		✓	✓	✓		✓		✓	✓		
Serum ADA and neutralizing anti-drug antibodies (nAb)		✓		✓				✓	✓		
Biomarker: CD40 RO and/or T cells, NK cells and B cell subsets (including plasmablasts)[i]		✓		✓		✓		✓	✓		
FCP[h,j]		✓				✓		✓	✓		
Intestinal Biopsies[k]	✓					✓			✓[d]		
Biomarker Sample: Whole Blood Epigenetic (DNA)		✓				✓		✓	✓		

Activity	Screening	Induction Period (W0 to W12)							PD	Unscheduled	84-Day Follow Up Visit[a]
		Baseline	W2	W4	W6	W8	W10	W12			
	D –35 to D –1	D1	D15 ± 7 days	D29 ± 7 days	D43 ± 7 days	D57 ± 7 days	D71 ± 7 days	D85 ± 7 days			
Biomarker Sample: Whole Blood Transcriptomic (RNA)		✓				✓		✓	✓		
Biomarker: Whole Blood Immunoassays (Plasma)		✓				✓		✓	✓		
Biomarker: Whole blood Immunoassays (Serum)		✓				✓		✓	✓		
℞ TREATMENT											
Enrollment		✓									
Administer study drug[l]		✓	✓	✓	✓	✓	✓				
Review subject diary		✓	✓	✓		✓		✓	✓	✓	

a. The 84-day follow up visit (or call if a visit is not possible) will be calculated from the last study drug administration date.

b. Repeat ECG will be performed as needed at the discretion of the investigator throughout the study.

c. CXR will be performed only on those subjects with positive Quantiferon and/or PPD test.

d. If the subject discontinues between Week 4 and Week 8, endoscopy will be performed at the PD visit. If the subject discontinues after Week 8, during the Induction Period, endoscopy will not be performed at the PD visit.

e. Serum pregnancy test will be performed on all females of childbearing potential at Screening. Urine pregnancy test will be performed locally as indicated in the table for all females of childbearing potential. The urine pregnancy test must be negative to receive study drug. If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory.

f. Only for women ≤ age 55, no menses for > 12 months, and no history of permanent surgical sterilization to confirm postmenopausal status.

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

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

i. T cells, NK cells and B cells subsets (including plasmablasts) will be analyzed at all indicated study visits. CD40 RO will only be analyzed at Baseline, Week 8 and Week 52 and PD if prior to Week 52.

j. Stool sample will be collected at each time point indicated in the table. For the visit when endoscopy will be conducted, stool sample should be collected prior to bowel prep and should be returned to the site within 3 days of collection. If a sample cannot be obtained during the site visit, the site will give instructions and a stool sample supply kit.

k. Mandatory intestinal biopsies will be collected for histopathology, gene expression, and tissue RO (where applicable). Additional biopsies may also be collected at the Investigator's discretion to confirm disease diagnosis and/or to rule out dysplasia, colon cancer and infection.

l. Consecutive doses should not be administered less than a week (7 days) apart.

Study Activities Maintenance Period (Weeks 12 - 104)

Activity	Maintenance Period (W12 to W104)											PD	Unscheduled	84-Day Follow Up Visit[b]
	W12[a]	W16	W20	W28	W36	W44	W52	W64	W76	W88	W104			
	D85 ± 7 days	D113 ± 7 days	D141 ± 7 days	D197 ± 7 days	D253 ± 7 days	D309 ± 7 days	D365 ± 7 days	D449 ± 7 days	D533 ± 7 days	D617 ± 7 days	D729 ± 7 days			D813 ± 7 days
INTERVIEWS & QUESTIONNAIRES														
Adverse event assessment		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant therapy		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Subject questionnaires: IBDQ							✓				✓	✓		
TB risk factor questionnaire							✓				✓	✓		
Review subject diary		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
LOCAL LABS, EXAMS, & ASSESSMENTS														
Weight							✓				✓	✓		
Vital signs		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Physical examination				✓			✓		✓		✓	✓		
Endoscopy							✓				✓	✓		
Partial Adapted Mayo		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Adapted Mayo/Full Mayo							✓				✓	✓		

Activity	Maintenance Period (W12 to W104)											PD	Unscheduled	84-Day Follow Up Visit[b]
	W12[a]	W16	W20	W28	W36	W44	W52	W64	W76	W88	W104			
	D85 ± 7 days	D113 ± 7 days	D141 ± 7 days	D197 ± 7 days	D253 ± 7 days	D309 ± 7 days	D365 ± 7 days	D449 ± 7 days	D533 ± 7 days	D617 ± 7 days	D729 ± 7 days			D813 ± 7 days
CENTRAL LABS														
Pregnancy test[c]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Urinalysis[d]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Chemistry and hematology[d]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
hs-CRP[d]				✓			✓		✓		✓	✓		
QuantiFERON-TB-Gold test (and/or local PPD skin test)[e]							✓				✓			
Serum ravagalimab							✓				✓	✓		
Serum ADA and nAb							✓				✓	✓		
Biomarker: CD40 RO and T cells, NK cells and B cell subsets (including plasmablasts)[f]							✓					✓		
FCP[d,g]							✓					✓		
Intestinal Biopsies[h,i]							✓				✓	✓		
Biomarker Sample: Whole Blood Epigenetic (DNA)[i]			✓				✓					✓		
Biomarker Sample: Whole Blood Transcriptomic (RNA)[i]			✓				✓					✓		
Biomarker: Whole Blood Immunoassays (Plasma)[i]			✓				✓					✓		
Biomarker: Whole blood Immunoassays (Serum)[i]			✓				✓					✓		
TREATMENT														
Administer study drug[j]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				

a. Study drug dispensation, the only study activity indicated for the maintenance period Week 12 visit, is only for subjects who continue onto the maintenance period.

b. The 84-day follow up visit (or call if a visit is not possible) will be calculated from the last study drug administration date.

c. Urine pregnancy test will be performed locally as indicated in the table for all females of childbearing potential. The urine pregnancy test must be negative to receive study drug. If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory.

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

e. For subjects with a negative TB test, an annual TB test will be required at Weeks 52 and 104. If the annual TB screen is positive, a CXR will be required for evaluation of active TB. Annual TB screening will not be required for subjects who have been treated for latent, or prior active, TB.

f. T cells, NK cells and B cells subsets (including plasmablasts) will be analyzed at all indicated study visits. CD40 RO will only be analyzed at Baseline, Week 8 and Week 52/PD.

g. Stool sample will be collected at each time point indicated in the table. For the visit when endoscopy will be conducted, stool sample should be collected prior to bowel prep and should be returned to the site within 3 days of collection. If a sample cannot be obtained during the site visit, the site will give instructions and a stool sample supply kit.

h. Mandatory intestinal biopsies will be collected for histopathology, gene expression, and tissue RO (where applicable). Additional biopsies may also be collected at the Investigator's discretion to confirm disease diagnosis and/or to rule out dysplasia, colon cancer and infection.

i. Only to be collected at PD visit if subject discontinues prior to Week 52.

j. Consecutive doses should not be administered less than a week (7 days) apart.

Study Activities Maintenance Period Drug Administration Visits, (Weeks 12 - 50)

Activity	Maintenance Period (W12 to W52)													
	W14	W18	W22	W24	W26	W30	W32	W34	W38	W40	W42	W46	W48	W50
	D99 ± 7 days	D127 ± 7 days	D155 ± 7 days	D169 ± 7 days	D183 ± 7 days	D211 ± 7 days	D225 ± 7 days	D239 ± 7 days	D267 ± 7 days	D281 ± 7 days	D295 ± 7 days	D323 ± 7 days	D337 ± 7 days	D351 ± 7 days
INTERVIEWS & QUESTIONNAIRES														
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CENTRAL LABS														
Pregnancy test[a]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TREATMENT														
Administer study drug[b]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

a. Urine pregnancy test will be performed locally as indicated in the table for all females of childbearing potential. The urine pregnancy test must be negative to receive study drug. If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory.

b. Consecutive doses should not be administered less than a week (7 days) apart.

Study Activities Maintenance Period Drug Administration Visits, Continued (Weeks 52 - 102)

Activity	Maintenance Period (W52 to W104)																				
	W54	W56	W58	W60	W62	W66	W68	W70	W72	W74	W78	W80	W82	W84	W86	W90	W92	W94	W96	W98	W100	W102
	D379 ± 7 days	D393 ± 7 days	D407 ± 7 days	D421 ± 7 days	D435 ± 7 days	D463 ± 7 days	D477 ± 7 days	D491 ± 7 days	D505 ± 7 days	D519 ± 7 days	D547 ± 7 days	D561 ± 7 days	D575 ± 7 days	D589 ± 7 days	D603 ± 7 days	D631 ± 7 days	D645 ± 7 days	D659 ± 7 days	D673 ± 7 days	D687 ± 7 days	D701 ± 7 days	D715 ± 7 days
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pregnancy test[a]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Administer study drug[b]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

a. Urine pregnancy test will be performed locally as indicated in the table for all females of childbearing potential. The urine pregnancy test must be negative to receive study drug. If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory.

b. Consecutive doses should not be administered less than a week (7 days) apart.

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	07 June 2018
Version 2.0	17 August 2018
Administrative Change 1	23 October 2018
Version 3.0	13 February 2019
Version 4.0	29 May 2019
Version 5.0	06 May 2020

The purpose of this version is to correct minor clerical errors for consistency throughout the protocol, to clarify and update statistical methods, and incorporate necessary protocol modifications due to the COVID-19 pandemic as follows:

- Synopsis – addition of Hungary to study country list

  Rationale: *to reflect addition of new study country.*

- Synopsis – addition of ustekinumab to approved therapies list for key eligibility criteria of subject having a history of inadequate response, loss of response, or intolerance to one or more of the approved therapies

  Rationale: *correcting omission of ustekinumab from synopsis in previous version of the protocol.*

- Synopsis – removal of text from key eligibility criterion requiring OL use of tofacitinib if received in a clinical trial

  Rationale: *To permit subject enrollment after inadequate response to, or intolerance of, tofacitinib received in a clinical trial in all scenarios where treatment allocation is known to have been tofacitinib.*

- Section 2.2 – included a statement on the benefit and risk of ravagalimab for subjects participating in the study in light of the SARS-CoV-2 pandemic based on current knowledge

  Rationale: *To update the benefit-risk assessment of ravagalimab with regards to COVID-19 to clearly state that risk related to use of this investigational drug on the course of COVID-19 is not currently known.*

- Section 3.3 – clarified endpoint definitions

  Rationale: *to provide clear definitions for each endpoint planned for evaluation*

- Section 3.4 - in the list of additional efficacy endpoints to remove duplicate endpoints, revise endpoints for clarity, and remove endpoints which are not expected to be informative

  Rationale: *The proportion of subjects with clinical response per Full Mayo score at Week 8 in subjects with a Full Mayo score of 6 to 12 at Baseline was removed as duplicative with an endpoint listed as a key secondary endpoint in Section 3.3. The 2 endpoints related to*

corticosteroid use were revised for clarity. General hospitalizations not informative and already captured in SAEs, UC-related hospitalizations will be summarized over time. UC related surgery will be summarized over time, not only through Week 12.

- Section 4.1 – removed discussion of the data monitoring committee (DMC) from the study design

  Rationale: *DMC review of safety data is not a component of the study design. The use of an internal DMC that will review safety at regular intervals is discussed in Section 6.3.*

- Section 4.1 - revise discussion of changes made in protocol version 4.0

  Rationale: *To remove repetitive text to improve clarity and remove the obsolete text which stated the maintenance period continued until Week 52 as the study was previously extended to include a 92-week OL treatment period*

- Section 4.1 and Section 7.3 - clarified text regarding primary and interim analysis and the timing of termination of study enrollment, and explicitly permit additional statistical analysis if needed

  Rationale: *There are 2 separate analyses planned in the induction period. The primary analysis will occur at the end of the induction period after all 40 subjects reach Week 12. An interim analysis will occur after the first 30 subjects reach Week 8 with the purpose to permit early decision making for subsequent study planning. To provide clarity, these 2 previously planned analyses have been separated.*

  Rationale: Permit additional statistical analysis if needed to support program development or health authority request.

- Section 4.1 Clarified that an endoscopy is required at Screening

  Rationale: *Screening endoscopy has always been required in this protocol and is noted in other sections of the protocol and operations manual. It has been added here for clarity.*

- Section 4.1 and Section 5.6, Appendix D, and Appendix F, Section 2.1 - Specified that a follow-up visit is preferred over a follow-up call and added collection of hematology and clinical chemistry at that visit

  Rationale: *As this is the initial phase 2a study with ravagalimab it is preferred to have a follow-up visit to ensure comprehensive capture of safety data including new or ongoing AEs and collection of hematology and clinical chemistry to ensure resolution/reversibility of any abnormal laboratory data. For subjects in which a visit is not possible, a phone call will be permitted.*

- Section 4.1 and Appendix D, footnote b– Remove text pertaining to subjects on protocol version 5.0

  Rationale: *This text is obsolete as all subjects, regardless of protocol amendment enrolled under, are to continue the visit schedule in the most current IRB/EC approved protocol, inclusive of all activities relative to their Baseline visit, are required to sign the most current IRB/EC approved informed consent form, and there is no enrolled subject at risk of experiencing a delay in dosing based on different protocol versions.*

- Section 5.1 – Update eligibility criterion #5, with details regarding subject eligibility with regards to COVID-19 (coronavirus SARS-CoV-2) infection, eligibility criterion #12 to remove requirement for tofacitinib and ustekinumab to have been given in open label fashion if received in a clinical

trial, and corrected language on eligibility criterion #23, prohibiting pregnancy and breastfeeding.

Rationale: *Modified eligibility criteria to exclude subjects with suspected or confirmed active COVID-19 infection to maintain subject safety. To permit subject enrollment after inadequate response to, or intolerance of, tofacitinib or ustekinumab received in a clinical trial in all scenarios where treatment allocation is known to have been tofacitinib or ustekinumab. Revised language surrounding prohibition of pregnancy and breastfeeding to ensure clarity surrounding requirements as ravagalimab has not been studied in human pregnancy or breastfeeding.*

- Section 5.5 - Appendix D, and Appendix F Section 2, Section 2.1, and Section 4.3 – added instructions for necessary changes to activities or procedures in the event of states of emergency or pandemic situations

  Rationale: *To provide flexibility during state-of emergency or pandemic situations to ensure the safety of subjects, maintain protocol compliance, and minimize risk to the integrity of the study while trying to best manage continued care of study subjects.*

- Section 5.5 – clarified discontinuation of study drug as well as study participation.

  Rationale: *To clarify that PD procedures apply to discontinuation from study and study drug. To clarify handling of subject data accounting for situations when a subject withdraws consent from the clinical study or withdraws samples from research.*

- Section 5.6 – clarified discontinuation of study drug as well as study participation. Also added text regarding collection of personal data and biomarker research in the event a subject withdraws consent.

  Rationale: *To clarify that PD procedures apply to discontinuation from study and study drug. To clarify handling of subject data accounting for situations when a subject withdraws consent from the clinical study or withdraws samples from research.*

- Section 5.8 – deleted the statement that IRT would assign a randomization number

  Rationale: *Not applicable to the open-label study. All subjects are assigned a unique number at screening.*

- Section 5.9 – clarified that modifications to the protocol, including those due to cases of state of emergency or pandemic situations, are considered deviations if not expressly outlined as permitted

  Rationale: *To clarify that unless necessary to eliminate an immediate hazard to study subjects that no prospective protocol modifications are permitted, including those which may be related to cases of cases of state of emergency or pandemic situations.*

- Section 6.1, Appendix D - clarified that active TB is an adverse event of special interest

  Rationale: *Active TB is a separate category from serious infections and opportunistic infections.*

- Section 6.2 - clarified that there are no time limits for study drug interruption as long as no permanent study discontinuation criteria have been met and added guidance regarding study drug interruption in subjects with confirmed diagnosis or suspicion of COVID-19

Rationale: *To provide investigators with guidance regarding permissible duration of drug interruption and to clarify guidelines for interruption of study drug in the event of confirmed or suspected diagnosis of COVID-19 to ensure subject safety.*

- Section 7.1 – clarified the SAP will be finalized prior to the Week 12 database lock for the primary analysis

  Rationale: *The primary analysis timepoint is at Week 12. To maintain statistical rigor the SAP will be finalized prior to Week 12.*

- Section 7.3 - separated discussion of the interim analysis from the primary analysis

  Rationale: *To clarify that the interim analysis will be performed after approximately 30 subjects complete Week 8 assessments is in addition to the primary analysis which is planned after all subjects have completed Week 12.*

- Section 7.3 - removed POC success criterion

  Rationale: *To avoid a purely statistical criterion for POC success claim based on a single endpoint and permit more flexibility in the interpretation of the totality of the clinical data which is more in line with the exploratory nature and objectives of the POC study.*

- Section 7.3 – updated external placebo data and related probabilities

  Rationale: *To update the external placebo data and related probabilities based on data which have become available from other studies during the conduct of this study and after re-evaluation of existing data. In addition, a clarification was made that future updates to the historical placebo data to be used in analyses may occur based on emerging clinical data prior to database lock.*

- Section 7.3 – replaced use of NRI with an imputation method for the primary analysis with missing data handling due to COVID-19 (NRI-C)

  Rationale: *To account for potential missing data due to a contemporary pandemic situation (COVID-19).*

- Section 7.3 – removed sensitivity analysis for the primary efficacy endpoint

  Rationale: *Removed sensitivity analysis to avoid possible inconsistent results between Bayesian approach and frequentist approach.*

- Section 8.2 – Specified that investigators must notify AbbVie if any urgent safety measures are taken due protect subjects from any immediate hazard

  Rationale: *To ensure subject safety.*

- Section 9 – noted that remote monitoring may be employed as needed in cases of state of emergency or pandemic situations

  Rationale: *To permit an alternative method to monitor study activities during cases of state of emergency or pandemic situations if on-site monitoring is not possible.*

- Section 12 – updated reference 12

  Rationale: *to remove reference to the abrilumab study and add reference to the ustekinumab study to align with revisions to Section 7.3.*

- Appendix A – updated definition of ICH to The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

  Rationale: *To provide official updated definition of the abbreviation*

- Appendix A – addition of SARS-CoV-2 to abbreviations list

  Rationale: *To provide definition of abbreviation*

- Appendix F, Appendix A - addition of COVID-19 to abbreviations list

  Rationale: *To provide definition of abbreviation*

- Appendix F, Appendix A - addition of TA MD to abbreviations list

  Rationale: *To provide definition of abbreviation*

- Appendix C - Update list of protocol signatories

  Rationale: *To reflect changes to personnel at sponsor.*

- Appendix D and Appendix F, Section 2.1 – added additional timepoints for physical exam and hsCRP monitoring; added HBV testing every 12 wks where required locally and add administration of the TB risk factor questionnaire at the PD visit

  Rationale: *To monitor inflammatory status, support subject safety and monitor extraintestinal manifestations of disease, clarify HBV testing requirements where mandated locally, and enhance latent TB screening.*

- Appendix F, Section 1 and Section 4.3 - Update sponsor contact information

  Rationale: *To reflect changes to personnel at sponsor*

- Appendix F, Section 3.1 – update requirements for informed consent related to cases of state of emergency or pandemic situations

  Rationale: *In cases of state of emergency or pandemic situations, it is possible that additional protocol modifications not outlined in this protocol may become necessary for which it is necessary to obtain verbal consent if it is not possible to travel to the study site and sign a written form.*

- Appendix F, Section 3.12 – add Hepatitis B screening, Hepatitis C screening, HIV test, and SARS-CoV-2 molecular test to the list of clinical tests which may be performed during the study

  Rationale**:** *Hepatitis B screening, Hepatitis C screening, HIV test* are required for all subjects at the screening visit. The *SARS-CoV-2 molecular test was added to align with the update to eligibility criterion #5 in which testing for SARS-CoV-2 will be required for selected subjects.*

- Appendix F, Section 3.12 – update Figure 1 and footnote

  Rationale: *To provide interpretation of HBV test results in Scenario A and B, clarify when a subject may be enrolled, and clarify when additional screening is required.*

- Appendix F, Appendix B – addition of UC-100 to endpoint definitions

  Rationale: *to provide clear definitions for each endpoint*

APPENDIX F. OPERATIONS MANUAL

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Operations Manual for Clinical Study Protocol M15-722

Ulcerative Colitis: Ravagalimab (ABBV-323) in Subjects with Moderately to Severely Active UC Who Failed Prior Therapy

SPONSOR:	For Non-European Countries: AbbVie 1 North Waukegan Road Bldg. AP31 North Chicago, IL 60064 USA For European Countries: AbbVie Deutschland GmbH & Co. KG (AbbVie) Knollstrasse 67061 Ludwigshafen Germany	ABBVIE INVESTIGATIONAL PRODUCT:	Ravagalimab (ABBV-323)

FULL TITLE: A Multicenter, Single Arm, Open-label Study to Investigate the Efficacy and Safety of Ravagalimab (ABBV-323) in Subjects with Moderate to Severe Ulcerative Colitis Who Failed Prior Therapy

1 CONTACTS

Sponsor/Emergency Medical Contact	[redacted] MD Therapeutic Area Medical Director (TA MD) AbbVie Deutschland GmbH & Co. KG (AbbVie) Knollstrasse 67061 Ludwigshafen Germany **EMERGENCY 24 hour Number:** **+1 (973) 784-6402**	Office: [redacted] Mobile [redacted] Fax: Email: [redacted]
Safety Concerns	Immunology Safety Team 1 North Waukegan Road North Chicago, IL 60064	Toll Free: +1 833-942-2226 Email: GPRD_SafetyManagement_Immunology@abbvie.com
SAE Reporting outside of RAVE	Email: PPDINDPharmacovigilance@abbvie.com	Fax: +1 (847) 938-0660
Protocol Deviations	[redacted] AbbVie 1 North Waukegan Road North Chicago, IL 60064	Phone: [redacted] Email:
Certified Clinical Lab	For sites in North America: Covance 8211 SciCor Drive Indianapolis, IN 46214 USA	Phone: +1 (866) 762-6209 (Toll free) +1 (317) 271-1200 (Local calls) Fax: +1 (317) 616-2362
	For sites in Europe: Covance 7 rue Moise-Marcinhes 1217 Geneva Meyrin Switzerland	Phone: +41 (58) 822-7901 +41 (58) 822-7000 (Collect call) Fax: +41 (58) 822-7521
	For sites in Asia: Covance (Asia) Pte. Limited 1 International Business Park #01-01 The Synergy Singapore 609917	Phone: +65 6560-8793 Fax: +65 6565-5901 For country specific toll free numbers please refer to the Covance Lab Manual.

Pharmacokinetic Lab	AbbVie Deutschland GmbH and Co KG Bioanalysis Large Molecules Knollstrasse Building 11, Room 311 67061 Ludwigshafen, Germany	Phone: +49 (621) 589-2022 Fax: +49 (621) 589-3184
Exploratory Sample Lab	Refer to the laboratory manuals for lab contact details.	

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2 PROTOCOL ACTIVITIES BY VISIT

Study visits may be impacted due to cases of state of emergency or pandemic situations. This may include changes such as phone or virtual visits, visits at alternative locations, home visits, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided in the subsequent section. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. If visits cannot be conducted onsite due to travel restrictions or other state of emergency or pandemic-related reasons, follow the updates below on how to proceed. Supplemental study case report forms should be completed in the event of missed/virtual visits, or study drug interruptions or discontinuations related to COVID-19.

2.1 Individual Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Treatment Period Activity Schedule.

Activities are grouped by category (Interview, Exam, etc.). Further information about each activity is provided in Section 2.1, which contains the definitions of superscript text.

Hospitalization and UC-related surgery will be captured as a part of supplemental Health Care Resource Utilization (HCRU) form of adverse event (AE) collection in electronic data capture (EDC) for the entire study.

Visit windows for the study

The Screening period may be extended as necessary after consultation with the TA MD in case of external, but not subject-related (e.g., scheduling conflict), circumstances.

Baseline visit date will serve as the reference for all subsequent visits. A ± 7 day window is permitted around all study visits after Baseline. All visit windows may be extended as necessary after consultation with the TA MD in case of external, but not subject-related (e.g., scheduling conflict), circumstances. Consecutive doses should not be administered less than a week (7 days) apart.

If a visit occurs on a day of overlapping visit windows, the subject visit will account for the preceding visit, and the subject will attend the next visit as close to the scheduled day based on the Baseline visit.

State of Emergency or Pandemic-Related Acceptable Protocol Modifications

Study Visits and/or activities should be performed as scheduled whenever possible. Screening and Baseline Day 1 visits and all study drug administration must be conducted at the study site. During a state of emergency or pandemic situation, if it is not possible for all study procedures to be performed as specified due to travel restrictions or other reasons, the following modifications are allowed:

- An endoscopy may be performed at a local center other than the study site if the PI can confirm study requirements with the local center. The local center must be able to provide the PI with a recording/video of the required specifications and quality.

- Laboratory work may be done at a local lab, hospital, or other facility. Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. Local lab results should be reviewed by the investigator as soon as possible.
- If laboratory samples cannot be obtained, study drug administration may be continued up to 4 weeks in the induction period, and up to 12 weeks in the maintenance period, after the last laboratory testing provided a post-baseline laboratory analysis is available and the investigator has reviewed all prior laboratory results and confirms and discusses with the subject that there is no safety concern for the subject to continue use of the study drug in the absence of current labs. The subject should be scheduled for laboratory draws as soon as feasible.
- If subjects are not able to enter PRO data, sites will read the PRO questions and response options to the subject and record the subject's responses. The subject's ability to view the PRO to understand the questions and response options should be preserved. Sites may share the questionnaire by videoconference or send the questionnaires (email or hard copy) to the subjects to allow them to read/understand the questions and responses when the subject is providing responses over the phone. The date and time of PRO data collection should be recorded along with who collected the information.
- Height, body weight measurements or vital signs may be performed by the subject or caregiver as needed, or at home visits.
- Physical examination may be performed at a local center, other than the study site, or at home visits.
- All procedures performed at local facilities outside of the study site must also be performed by appropriately qualified personnel.

Induction Period

SCREENING:

INTERVIEW	• Informed consent • Medical History • Evaluation of eligibility criteria	• Serious AEs (SAEs) and protocol-related nonserious adverse events[a] • Prior and concomitant medications assessment • Tuberculosis (TB) risk factor questionnaire[b]
PRO/ASSESSMENT	• Dispense subject diary[c]	
EXAM	• Height • Weight[d] • 12-lead electrocardiogram (ECG)	• Vital signs[d] • Physical examination[e] • Chest X-ray (CXR) • Endoscopy[f]
LOCAL LAB	• TB screen (Purified Protein Derivative [PPD] Skin Test)	
CENTRAL LAB	• Hepatitis B[u], Hepatitis C Screening[g] and Human immunodeficiency virus (HIV) Test[h] • *C. difficile* toxin • TB screen (QuantiFERON-TB Gold Test) • SARS-CoV-2 molecular test, if applicable	• Serum pregnancy test[i] • FSH, if needed to confirm postmenopausal status • Urinalysis[j,k] • Chemistry and hematology[k] • Intestinal Biopsies[l]

NOTES:

- The Screening period should be a minimum of 3 days for stool frequency subscore (SFS) and rectal bleeding subscore (RBS) calculation.
- The Screening period (35 days) may be extended as necessary after consultation with the AbbVie TA MD for subjects in case of external, not subject-related circumstances (e.g., due to the delay of availability of screening test results).
- Subjects who initially screen fail for the study or who received placebo only in the study prior to version 4.0 may be permitted to re-screen following re-consent. The subject must meet all eligibility criteria at the time of re-screening in order to qualify for the study. There is no minimum period of time a subject must wait to re-screen for the study.
- ECG will be performed on all subjects at Screening. Repeat ECG will be performed as needed at the discretion of the investigator throughout the study.
- Either a QuantiFERON-TB Gold test or purified protein derivative (PPD) test will be performed on all subjects at Screening.
- Chest X-ray will be performed only on those subjects with positive QuantiFERON and/or PPD test.
- If the subject had a complete initial screening evaluation including the TB test, Hepatitis B virus (HBV), Hepatitis C virus (HCV), HIV and ECG, these tests will not be required to be repeated for

re-screening provided the conditions noted in Section 3 are met and no more than 90 days have passed.

- FSH is only for women ≤ age 55, no menses for > 12 months, and no history of permanent surgical sterilization to confirm postmenopausal status.

DAY 1:

INTERVIEW	• Medical History • Evaluation of eligibility criteria[m]	• AE assessment • Prior and concomitant medications assessment
PRO/ ASSESSMENT	• Inflammatory Bowel Disease Questionnaire (IBDQ)	• Review subject diary • Partial Adapted Mayo • Adapted Mayo/Full Mayo
EXAM	• Weight[d] • Vital signs[d]	• Physical examination[e]
LOCAL LAB	• Urine pregnancy test[n]	
CENTRAL LAB	• Urinalysis[j,k,o] • Chemistry and hematology[k,o] • hsCRP[k] • Fecal calprotectin (FCP)[k,p] • Serum ravagalimab • Serum anti-drug antibodies (ADAs) and neutralizing anti-drug antibodies (nAbs)[q] • Biomarker: CD40 receptor occupancy (RO) and T cells, NK cells and B cell subsets (including plasmablasts)[s]	• Biomarker Sample: Whole Blood Epigenetic (DNA) • Biomarker Sample: Whole Blood Transcriptomic (RNA) • Biomarker: Whole Blood Immunoassays (Plasma) • Biomarker: Whole blood Immunoassays (Serum)
TREATMENT	• Drug assignment	• Administer study drug[r]

NOTES:

- The Screening period should be a minimum of 3 days for stool frequency subscore (SFS) and rectal bleeding subscore (RBS) calculation. The Screening period may be extended as necessary after consultation with the TA MD in case of external, but not subject-related (e.g., scheduling conflict), circumstances. The Baseline Adapted Mayo score will be calculated using the data collected during the Screening period.

WEEK 2:

INTERVIEW	• AE assessment	• Concomitant medications assessment
PRO/ ASSESSMENT	• Review subject diary	• Partial Adapted Mayo
EXAM	• Vital signs[d]	
LOCAL LAB	• Urine pregnancy test[n]	
CENTRAL LAB	• Chemistry and hematology[k] • hsCRP[k]	• Serum ravagalimab
TREATMENT	• Administer study drug[s]	

WEEK 4:

INTERVIEW	• AE assessment	• Concomitant medications assessment
PRO/ ASSESSMENT	• Review subject diary	• Partial Adapted Mayo
EXAM	• Vital signs[d]	
LOCAL LAB	• Urine pregnancy test[n]	
CENTRAL LAB	• Urinalysis[j,k] • Chemistry and hematology[k] • hsCRP[k] • Serum ravagalimab	• Serum ADAs and nAbs[q] • Biomarker: T cells, NK cells and B cell subsets (including plasmablasts)
TREATMENT	• Administer study drug[r]	

WEEK 6:

INTERVIEW	• AE assessment	
LOCAL LAB	• Urine pregnancy test[n]	
TREATMENT	• Administer study drug[r]	

WEEK 8:

INTERVIEW	• AE assessment	• Concomitant medications assessment
PRO/ ASSESSMENT	• IBDQ • Review subject diary	• Partial Adapted Mayo • Adapted Mayo/Full Mayo
EXAM	• Weight[d] • Vital signs[d]	• Physical examination[e] • Endoscopy
LOCAL LAB	• Urine pregnancy test[n]	
CENTRAL LAB	• Urinalysis[j,k] • Chemistry and hematology[k] • hsCRP[k] • FCP[k,p] • Serum ravagalimab • Biomarker: CD40 RO and T cells, NK cells and B cell subsets (including plasmablasts)[s] • Intestinal biopsies[l]	• Biomarker Sample: Whole Blood Epigenetic (DNA) • Biomarker Sample: Whole Blood Transcriptomic (RNA) • Biomarker: Whole Blood Immunoassays (Plasma) • Biomarker: Whole blood Immunoassays (Serum)
TREATMENT	• Administer study drug[r]	

WEEK 10:

INTERVIEW	• AE assessment	
LOCAL LAB	• Urine pregnancy test[n]	
TREATMENT	• Administer study drug[r]	

WEEK 12 (Induction Period):

INTERVIEW	• AE assessment	• Concomitant medications assessment
PRO/ ASSESSMENT	• IBDQ	• Review subject diary • Partial Adapted Mayo
EXAM	• Weight[d]	• Vital signs[d] • Physical examination[e]
LOCAL LAB	• Urine pregnancy test[n]	
CENTRAL LAB	• Urinalysis[j,k] • Chemistry and hematology[k] • hsCRP[k] • FCP[k,p] • Serum ADAs and nAbs[q] • Serum ravagalimab • Biomarker: T cells, NK cells and B cell subsets (including plasmablasts)[s]	• Biomarker Sample: Whole Blood Epigenetic (DNA) • Biomarker Sample: Whole Blood Transcriptomic (RNA) • Biomarker: Whole Blood Immunoassays (Plasma) • Biomarker: Whole blood Immunoassays (Serum)

Premature discontinuation (PD, Induction Period):

INTERVIEW	• AE assessment	• Concomitant medications assessment
PRO/ ASSESSMENT	• IBDQ	• Review subject diary • Partial Adapted Mayo • Adapted Mayo/Full Mayo
EXAM	• Weight[d] • Vital signs[d]	• Physical examination[e] • Endoscopy[f]
LOCAL LAB	• Urine pregnancy test[n]	
CENTRAL LAB	• Urinalysis[j,k] • Chemistry and hematology[k] • hsCRP[k] • FCP[k,p] • Intestinal Biopsies[l] • Serum ADAs and nAbs[q] • Serum ravagalimab	• Biomarker: CD40 RO and T cells, NK cells and B cell subsets (including plasmablasts)[s] • Biomarker Sample: Whole Blood Epigenetic (DNA) • Biomarker Sample: Whole Blood Transcriptomic (RNA) • Biomarker: Whole Blood Immunoassays (Plasma) • Biomarker: Whole blood Immunoassays (Serum)

NOTES:

- If the subject discontinues between Week 4 and 8, endoscopy will be performed at the PD visit. If the subject discontinues after Week 8, endoscopy will not be performed at the PD visit.

Unscheduled (Induction Period):

INTERVIEW	• AE assessment	• Concomitant medications assessment
PRO/ ASSESSMENT	• Review subject diary	• Partial Adapted Mayo
EXAM	• Vital signs[d]	

NOTES:

- Visits to retest a lab will not be considered an Unscheduled visit. Unscheduled visits are for purposes when the subject is coming in a visit for evaluation and assessment.
- Urinalysis, chemistry and hematology, high sensitivity C-reactive protein (hs-CRP), and FCP may be collected at other scheduled and unscheduled visits than indicated in the table if they are warranted by the Investigator.

Maintenance Period

WEEK 12 (Maintenance Period):

TREATMENT	• Administer study drug[s]	

NOTES: Study drug dispensation, the only study activity indicated for the maintenance period Week 12 visit, is only for subjects who continue onto the maintenance period.

WEEK 14 (Study drug administration visit):

INTERVIEW	• AE assessment	
LOCAL LAB	• Urine pregnancy test[n]	
TREATMENT	• Administer study drug[r]	

WEEK 16:

INTERVIEW	• AE assessment	• Concomitant medications assessment
PRO/ ASSESSMENT	• Review subject diary	• Partial Adapted Mayo
EXAM	• Vital signs[d]	
LOCAL LAB	• Urine pregnancy test[n]	
CENTRAL LAB	• Urinalysis[j,k]	• Chemistry and hematology[k]
TREATMENT	• Administer study drug[r]	

WEEK 18 (Study drug administration visit):

INTERVIEW	• AE assessment	
LOCAL LAB	• Urine pregnancy test[n]	
TREATMENT	• Administer study drug[r]	

WEEK 20:

INTERVIEW	• AE assessment	• Concomitant medications assessment
PRO/ ASSESSMENT	• Review subject diary	• Partial Adapted Mayo
EXAM	• Vital signs[d]	
LOCAL LAB	• Urine pregnancy test[n]	
CENTRAL LAB	• Urinalysis[j,k] • Chemistry and hematology[k]	• Biomarker Sample: Whole Blood Epigenetic (DNA) • Biomarker Sample: Whole Blood Transcriptomic (RNA) • Biomarker: Whole Blood Immunoassays (Plasma) • Biomarker: Whole blood Immunoassays (Serum)
TREATMENT	• Administer study drug[r]	

WEEKS 22, 24, 26 (Study drug administration visits):

INTERVIEW	• AE assessment
LOCAL LAB	• Urine pregnancy test[n]
TREATMENT	• Administer study drug[r]

WEEK 28:

INTERVIEW	• AE assessment	• Concomitant medications assessment
PRO/ ASSESSMENT	• Review subject diary	• Partial Adapted Mayo
EXAM	• Vital signs[d]	• Physical examination[e]
LOCAL LAB	• Urine pregnancy test[n]	
CENTRAL LAB	• Urinalysis[j,k] • hsCRP[k]	• Chemistry and hematology[k]
TREATMENT	• Administer study drug[r]	

WEEKS 30, 32, 34 (Study drug administration visits):

INTERVIEW	• AE assessment	
LOCAL LAB	• Urine pregnancy test[n]	
TREATMENT	• Administer study drug[r]	

WEEK 36:

INTERVIEW	• AE assessment	• Concomitant medications assessment
PRO/ ASSESSMENT	• Review subject diary	• Partial Adapted Mayo
EXAM	• Vital signs[d]	
LOCAL LAB	• Urine pregnancy test[n]	
CENTRAL LAB	• Urinalysis[j,k]	• Chemistry and hematology[k]
TREATMENT	• Administer study drug[r]	

WEEKS 38, 40, 42 (Study drug administration visits):

INTERVIEW	• AE assessment	
LOCAL LAB	• Urine pregnancy test[n]	
TREATMENT	• Administer study drug[r]	

WEEK 44:

INTERVIEW	• AE assessment	• Concomitant medications assessment
PRO/ ASSESSMENT	• Review subject diary	• Partial Adapted Mayo
EXAM	• Vital signs[d]	
LOCAL LAB	• Urine pregnancy test[n]	
CENTRAL LAB	• Urinalysis[j,k]	• Chemistry and hematology[k]
TREATMENT	• Administer study drug[r]	

WEEKS 46, 48, 50 (Study drug administration visits):

INTERVIEW	• AE assessment
LOCAL LAB	• Urine pregnancy test[n]
TREATMENT	• Administer study drug[r]

WEEK 52:

INTERVIEW	• AE assessment	• Concomitant medications assessment • TB risk factor questionnaire
PRO/ ASSESSMENT	• IBDQ • Review subject diary	• Partial Adapted Mayo • Adapted Mayo/Full Mayo
EXAM	• Weight[d] • Endoscopy	• Vital signs[d] • Physical examination[e]
LOCAL LAB	• Urine pregnancy test[n] • TB screen (Purified Protein Derivative [PPD] Skin Test)	
CENTRAL LAB	• Urinalysis[j,k] • Chemistry and hematology[k] • hsCRP[k] • Serum ravagalimab • Serum ADA and nAb[q] • Biomarker: CD40 RO and T cells, NK cells and B cell subsets (including plasmablasts)[s] • FCP[k,p] • Intestinal biopsies[l] • TB screen (QuantiFERON-TB Gold Test)[b]	• Biomarker Sample: Whole Blood Epigenetic (DNA) • Biomarker Sample: Whole Blood Transcriptomic (RNA) • Biomarker: Whole Blood Immunoassays (Plasma) • Biomarker: Whole blood Immunoassays (Serum)
TREATMENT	• Administer study drug[r]	

NOTE: Either a QuantiFERON-TB Gold test or purified protein derivative (PPD) test will be performed on all subjects if tested negative at Screening.

WEEKS 54, 56, 58, 60, 62 (Study drug administration visits):

INTERVIEW	• AE assessment
LOCAL LAB	• Urine pregnancy test[n]
TREATMENT	• Administer study drug[r]

WEEK 64:

INTERVIEW	• AE assessment	• Concomitant medications assessment
PRO/ ASSESSMENT	• Review subject diary	• Partial Adapted Mayo
EXAM	• Vital signs[d]	
LOCAL LAB	• Urine pregnancy test[n]	
CENTRAL LAB	• Urinalysis[j,k]	• Chemistry and hematology[k]
TREATMENT	• Administer study drug[r]	

WEEKS 66, 68, 70, 72, 74 (Study drug administration visits):

INTERVIEW	• AE assessment	
LOCAL LAB	• Urine pregnancy test[n]	
TREATMENT	• Administer study drug[r]	

WEEK 76:

INTERVIEW	• AE assessment	• Concomitant medications assessment
PRO/ ASSESSMENT	• Review subject diary	• Partial Adapted Mayo
EXAM	• Vital signs[d]	• Physical examination[e]
LOCAL LAB	• Urine pregnancy test[n]	
CENTRAL LAB	• Urinalysis[j,k] • hsCRP[k]	• Chemistry and hematology[k]
TREATMENT	• Administer study drug[r]	

WEEKS 78, 80, 82, 84, 86 (Study drug administration visits):

INTERVIEW	• AE assessment	
LOCAL LAB	• Urine pregnancy test[n]	
TREATMENT	• Administer study drug[r]	

WEEK 88:

INTERVIEW	• AE assessment	• Concomitant medications assessment
PRO/ ASSESSMENT	• Review subject diary	• Partial Adapted Mayo
EXAM	• Vital signs[d]	
LOCAL LAB	• Urine pregnancy test[n]	
CENTRAL LAB	• Urinalysis[j,k]	• Chemistry and hematology[k]
TREATMENT	• Administer study drug[r]	

WEEKS 90, 92, 94, 96, 98, 100, 102 (Study drug administration visits):

INTERVIEW	• AE assessment	
LOCAL LAB	• Urine pregnancy test[n]	
TREATMENT	• Administer study drug[r]	

NOTES: Week 102 is the last visit in which study drug will be administered.

WEEK 104:

INTERVIEW	• AE assessment	• Concomitant medications assessment • TB risk factor questionnaire
PRO/ ASSESSMENT	• IBDQ • Review subject diary	• Partial Adapted Mayo • Adapted Mayo/Full Mayo
EXAM	• Weight[d] • Endoscopy	• Vital signs[d] • Physical examination[e]
LOCAL LAB	• Urine pregnancy test[n] • TB screen (Purified Protein Derivative [PPD] Skin Test)	
CENTRAL LAB	• Urinalysis[j,k] • Chemistry and hematology[k] • hsCRP[k] • Serum ravagalimab • Serum ADA and nAb[q]	• Intestinal biopsies[l] • TB screen (QuantiFERON-TB Gold Test)[b]

NOTE: Either a QuantiFERON-TB Gold test or purified protein derivative (PPD) test will be performed on all subjects if tested negative at Screening or Week 52.

PD (Maintenance Period):

INTERVIEW	• AE assessment • TB risk factor questionnaire	• Concomitant medications assessment
PRO/ ASSESSMENT	• Review subject diary • IBDQ	• Partial Adapted Mayo • Adapted Mayo/Full Mayo
EXAM	• Weight[d] • Vital signs[d] • Endoscopy	• Physical examination[e]
LOCAL LAB	• Urine pregnancy test[n]	
CENTRAL LAB	• Urinalysis[j,k] • Chemistry and hematology[k] • hsCRP [k] • FCP[k,p] • Serum ravagalimab • Intestinal Biopsies[l]	• Serum ADA and nAb[q] • Biomarker: CD40 RO and T cells, NK cells and B cell subsets (including plasmablasts)[s,t] • Biomarker Sample: Whole Blood Epigenetic (DNA)[t] • Biomarker Sample: Whole Blood Transcriptomic (RNA)[t] • Biomarker: Whole Blood Immunoassays (Plasma)[t] • Biomarker: Whole blood Immunoassays (Serum)[t]

Unscheduled (Maintenance Period):

INTERVIEW	• AE assessment	• Concomitant medications assessment
PRO/ ASSESSMENT	• Review subject diary	• Partial Adapted Mayo
EXAM	• Vital signs[d]	

NOTES:

- Visits to retest a lab will not be considered an Unscheduled visit. Unscheduled visits are for purposes when the subject is coming in a visit for evaluation and assessment.
- Urinalysis, chemistry and hematology, hs-CRP, and FCP may be collected at other scheduled and unscheduled visits than indicated in the table if they are warranted by the Investigator.

84-Day Follow-Up Visit:

INTERVIEW	• AE assessment • Chemistry and hematology[k]

NOTE: 84-Day Follow-up may be performed as a call if a visit is not possible.

Footnotes for protocol activities:

a. Collection of SAEs and protocol-related nonserious adverse events begins the day the subject signs the informed consent.

b. Subjects with negative QuantiFERON-TB Gold test and/or PPD test within 90 days of Screening will not require a repeat test (documentation must be available), provided nothing has changed in the subject's medical history to warrant a repeat test. PPD skin test is to be read 48 to 72 hours after placement. In case of positive PPD/positive or repeat indeterminate IGRA testing, subjects may participate in the study if further work up (according to local practice/guidelines) is negative for active TB. Only subjects with positive QuantiFERON-TB Gold test and/or PPD test will be required to have a CXR. The subject will be required to initiate and have taken at least 2 weeks (or per local guidelines, whichever is longer) of an ongoing course of Centers for Disease Control and Prevention (CDC) recommended prophylaxis or prophylaxis per local guidelines prior to starting study therapy. The Screening period may be extended as necessary for subjects who require initiation of prophylactic anti-TB therapy. For subjects with a negative TB test, an annual TB test will be required at Weeks 52 and 104. If the annual TB screen is positive, a CXR will be required for evaluation of active TB. Annual TB screening will not be required for subjects who have been treated for latent TB.

c. Subjects should also be dispensed the patient information card if applicable per local regulations.

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

e. A complete physical examination, including an assessment of extra-intestinal manifestations (EIMs), will be performed at the designated study visits. At any time, a symptom-directed physical examination can be performed as deemed necessary by the investigator.

f. Endoscopy at/during the screening period or within 45 days of the Baseline visit will be required to calculate the Mayo endoscopy subscore at Baseline. Endoscopic evaluations using Mayo endoscopic score confirmed by central reader will be done at Screening.

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

h. HIV testing will be performed at the central laboratory, which will report the results directly to the sites. AbbVie will not receive results from the testing and not be made aware of any positive result.

i. Serum pregnancy test will be performed on all females of childbearing potential at Screening.

j. Dipstick urinalysis will be provided by the central laboratory and completed locally at the site at required visits. If the dipstick urinalysis is abnormal, then a microscopic analysis will be sent to the central laboratory, in the event the dipstick results show protein, ketones or blood greater than negative or glucose other than normal.

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

l. Mandatory intestinal biopsies will be collected for histopathology, gene expression, and tissue RO (sites in the United States). Four biopsies will be collected in the United States and two biopsies will be collected outside of the United States. Mandatory intestinal biopsies may also be used for exploratory biomarker research. Additional biopsies may also be collected at the Investigator's discretion to confirm disease diagnosis and/or to rule out dysplasia, colon cancer and infection.

m. Update eligibility criteria, prior and concomitant therapy, and medical/surgical history information at Baseline to assure subject eligibility.

n. Urine pregnancy test will be performed locally as indicated in the table for all females of childbearing potential. The urine pregnancy test must be negative to receive study drug. If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory.

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

p. For the visit when endoscopy will be conducted, stool sample should be collected prior to bowel prep and should be returned to the site within 3 days of collection. If a sample cannot be obtained during the site visit, the site will give instructions and a stool sample supply kit.

q. Day 1 serum ravagalimab concentrations will be collected at the end of the ravagalimab IV infusion and Day 1 ADA/nAb will be determined from samples collected at any time during the visit. All subsequent samples will be collected just prior to dosing on the study visit. At Week 104 or if a patient prematurely discontinues, serum ravagalimab and/or ADA/nAb will be collected at any time during the visit. The date and time of sample collection will be captured on the electronic case report form (eCRF).

r. Administration of drug will be performed after all assessments and examinations scheduled for that day have been completed.

s. CD40 receptor occupancy (RO) and T cells, NK cells and B cell subsets (including plasmablasts) should be collected prior to dose at each visit when applicable.

t. Only to be collected at PD visit if subject discontinues prior to Week 52.

u. 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.

3 STUDY PROCEDURES

3.1 Subject Information and Informed Consent

The investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject 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. A copy

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

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

In cases of state of emergency or pandemic situations, it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations.

3.2 Medical History and Prior/Concomitant Medications

A complete list of prior/concomitant medications and medical history including demographics, history of tobacco, alcohol, and drug use will be taken at screening. The subject's prior/concomitant medications and medical history will be updated at the Study Day 1 visit. This updated medical history will serve as the baseline for clinical assessment. Concomitant medications will be reviewed at each study visit listed in Section 2.1.

3.3 Adverse Event Assessment

Please refer to Section 4.2.

3.4 Patient-Reported Outcomes and Subject Diary

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

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

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

The ePRO data will be collected by diary based and tablet-based methods. Subject must be able and willing to give written informed consent and to comply with the requirements of this study protocol.

Diary Based

The ePRO data (stool information, use of medications used for endoscopy preparation, abdominal pain, anti-diarrheal medication, and general well-being) will be collected electronically via a handheld device into which the subject will record the required pieces of information on a daily basis. The electronic device will be programmed to allow data entry once per day. All data entered on the device will be immediately stored to the device itself and manually/automatically uploaded to a central server administrated by CRF Health. The investigational site staff will be able to access all uploaded subject entered data via a password protected website, up until the generation, receipt and confirmation of the study archive. Completion will be reinforced during study visits as necessary.

Stool frequency for SFS

The stool frequency is captured by subjects recording the number of stools over the last 24 hours throughout the trial (range 0 - 99). The SFS is calculated by comparing the stool frequency to a reference number. The reference number is the number of stools per day (24 hours) that is typical for the subject when his/her UC is not active and needs to be designated once prior to enrollment. The reference number should represent a full number of at least 1. A higher score indicates higher stool frequency.

Rectal bleeding for RBS

The RBS is based on diary entries of subjects recording the most severe category that describes the amount of blood they had in their stools for a given day (0 = No blood seen, 1 = blood seen in fewer than half of the stools, 2 = blood seen in half or more of the stools, 3 = only blood without any stool). A higher score indicates a higher degree of rectal bleeding.

Abdominal Pain

The abdominal pain score is captured from diary entries of subjects recording the level of worst abdominal pain experienced over 24 hours using a numeric rating scale (range 0 to 10; 0 = No pain and 10 = worst possible abdominal pain). A higher score indicates a higher level of abdominal pain.

Bowel Urgency

Bowel urgency is captured from diary entries of subjects recording the presence (yes/no) of bowel urgency over 24 hours.

Tablet Based

The IBDQ will be collected electronically via a Tablet device into which the subject will directly enter the required pieces of information while at the site. The electronic device will be programmed to allow data entry for only the visits specified in the protocol and will not allow for subjects to complete more than one of the same assessment at any one visit. All data entered on the device will be immediately stored to the device itself and (manually/automatically) uploaded to a central server administrated by CRF

Health. The investigational site staff will be able to access all uploaded subject entered data via a password protected website, up until the generation, receipt and confirmation of the study archive.

IBDQ

The IBDQ is a widely used questionnaire for health-related quality of life (QoL) assessment in patients with inflammatory bowel diseases (IBD). It consists of 32 items categories into 4 dimensions: "bowel symptoms," "systemic symptoms," "social function," and "emotional function." Item responses are graded on a 7-point Likert scale, with 1 being most severe and 7 being no problem at all. A higher score indicates a better health status.

3.5 Pharmacokinetic Sampling

On the day of the study visit, subjects will be administered the ravagalimab intravenous (IV) or subcutaneous (SC) dose and blood samples for pharmacokinetic (PK) and ADA assessments should be collected at the specified time points at each visit as follows:

For PK samples:

- At Baseline (Week 0) at the end of the ravagalimab IV infusion
- At Weeks 2, 4, 8, 12, and 52 prior to administration of ravagalimab SC dose
- At Week 104 or in the event of PD at any time during the visit.

For ADA and nAb samples:

- At Baseline (Week 0) at any time during the visit
- At Weeks 4, 12, and 52 prior to administration of ravagalimab SC dose
- At Week 104 or in the event of PD at any time during the visit.

The date and time of sample collection will be captured on the electronic case report form (eCRF).

3.6 Biomarker Sampling

Blood samples will be collected for biomarker research at the designated study visits as specified in Section 2.1. Biopsies for biomarker analysis will be done when performing endoscopies. Up to 4 biopsies will be taken at each visit with endoscopy for biomarker research; 1 biopsy for histologic assessment by central review, 1 biopsy for gene expression analysis (including CD40 signature), 2 biopsies for tissue RO (where applicable). Collection of biomarker samples should occur prior to administration of drug on treatment days when applicable. Whole blood for CD40 RO and/or analysis of T cells, NK cells and B cell subsets (including plasmablasts) will be collected prior to drug administration at Baseline, Week 4, Week 8, and Week 12; and at any time during the visit at Week 52 or in the event of PD prior to Week 52. All biomarker samples should be collected, labeled, and shipped as outlined in the study-specific laboratory manual. AbbVie (or people or companies working with AbbVie) will store

the samples and data in a secure storage space with adequate measures to protect confidentiality. The samples may be retained while research on ravagalimab (or drugs of this class) or UC and related conditions continues, but for no longer than 20 years after study completion, or per local requirement.

3.7 12-Lead Electrocardiogram

A 12-lead ECG will be performed at the designated study visits as specified in Section 2.1. For subjects with a normal ECG taken within 90 days of Screening, a repeat ECG at Screening will not be required, provided source documentation is available. Subjects can have a repeat ECG at any time during the study as warranted based on the opinion of the Investigator. The ECG should be performed prior to blood collection.

The ECGs will be evaluated by an appropriately trained physician at the site ("local reader"). The local reader from the site will sign and date all ECG tracings and will provide his/her global interpretation as a written comment on the tracing using the following categories:

- Normal ECG
- Abnormal ECG – not clinically significant
- Abnormal ECG – clinically significant

Only the local reader's evaluation of the ECG will be collected and documented in the subject's source folder. The automatic machine reading (i.e., machine-generated measurements and interpretation that are automatically printed on the ECG tracing) will not be collected.

ECGs with QT interval corrected for heart rate using Fridericia's correction formula (QTcF) should be reported (or calculated) and documented in the source documents and later transcribed on to the appropriate eCRF if QTcF prolongation is observed.

A valid QTcF cannot be calculated in subjects who have a pacemaker or supraventricular or ventricular conduction abnormalities. In cases of QTcF prolongation, the baseline QTcF will need to be entered into the appropriate eCRF for comparison as well. In addition, any clinically significant findings will be documented in the source documents and later transcribed on to the appropriate eCRF. Each signed original ECG will be monitored by the responsible site monitor and kept with subject's source documents onsite.

3.8 Height and Weight

Height will be measured at screening only. Body weight will be measured at scheduled visits as specified in Section 2.1 and before blood draws are performed. The subject will wear lightweight clothing and no shoes during weighing.

3.9 Vital Signs

Vital sign determinations of systolic and diastolic blood pressure, pulse rate, and body temperature will be obtained at visits as specified in Section 2.1. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes. Blood pressure, pulse rate, temperature, and respiratory rate should be performed before blood draws are performed.

3.10 Physical Examination

A complete physical examination, including an assessment of EIMs, will be performed at the designated study visits as specified in Section 2.1. The physical examination performed on Study Day 1 will serve as the baseline physical examination for the entire study. Any significant physical examination findings after the first dose will be recorded as adverse events. 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.

3.11 Administer Study Drug

Intravenous study drug will be administered to all subjects on-site. For female subjects of childbearing potential, the urine pregnancy test needs to be negative prior to receiving study drug. The site will be provided administration instructions. Study drug will be administered to subjects beginning at baseline (Day 1) and as specified in Section 2.1. Administration of drug will be performed after all assessments and examinations scheduled for that day have been completed. At the visits specified in Section 2.1, the site personnel will review and retain a copy of the subject diary, review returned study drug kits, and empty study drug packaging to verify compliance. A separate study drug administration guideline will be provided as well.

3.12 Clinical Laboratory Tests

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 drug.

A certified laboratory will be utilized 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 and sent to the following certified laboratory addresses:

For sites in North America:

Covance
8211 SciCor Drive
Indianapolis, IN 46214 USA

For sites in Europe:

Covance
7 rue Moise-Marcinhes
1217 Geneva
Meyrin Switzerland

Blood samples will be obtained for the laboratory tests listed in the Clinical Laboratory Tests table below. Blood draws should be performed, as much as possible, after efficacy assessments and questionnaires (IBDQ, etc.) and vital sign determinations are obtained during a visit. Blood draws should be performed before study drug administration.

All abnormal laboratory tests that are considered clinically significant by the Investigator will: 1) be followed to a satisfactory resolution, 2) follow the toxicity management instructions for Select Laboratory Abnormalities as applicable (see Section 6.2 of the protocol).

Clinical Laboratory Tests		
Hematology	**Clinical Chemistry**	**Urinalysis**
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Platelet count **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	**Enzymes** Aspartate transaminase (AST, GOT) Alanine transaminase (ALT, GPT) Alkaline Phosphatase Creatine Kinase **Electrolytes** Calcium Sodium Potassium Chloride Bicarbonate **Substrates** Blood urea nitrogen Creatinine Bilirubin Total Bilirubin Direct (if total is elevated) Bilirubin Indirect (if total is elevated) Albumin Cholesterol, total Low-density lipoprotein (LDL)-Cholesterol High-density lipoprotein (HDL)-Cholesterol Triglycerides Glucose	**Dipstick Urinalysis (local)** Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Urine RBC/Erythrocytes Urine WBC/Leukocytes Urine pH Urine creatinine **Urine-Sediment** (microscopic examination, **only if** urine analysis abnormal) Urine Sediment Bacteria Urine Cast in Sediment Urine Squamous Epithelial Cells Urine Sediment Crystals, Unspecified Urine Sediment RBC/Erythrocytes Urine Sediment WBC/Leucocytes **Urine** Urine Albumin-to-Creatinine Ratio
Stool Samples	**Coagulation**	**Other Tests**
C. difficile toxin Fecal calprotectin (FCP)	INR[a]	Urine Pregnancy test[b] (local) Serum Pregnancy test[b] Tryptase[c] Histamine[c] Hepatitis B screening Hepatitis C screening HIV test SARS-CoV-2 molecular test, if applicable
PK/Immunogenicity	**Biomarkers**	**Biopsy**
Serum ravagalimab concentration[c] Serum ADA[c] and nAb[c]	high-sensitivity C-reactive protein (hs-CRP) CD40 receptor occupancy (RO) Plamablast frequency Exploratory biomarker research	Histopathology scoring Tissue RO (If applicable) Gene expression

a. INR test only drawn if ALT or AST > 3 × ULN (upper limit of normal) and Total Bilirubin < 2 × ULN. Refer to Section 6.2 in the protocol for more information.

b. Pregnancy testing is not required for women of nonchildbearing potential.

c. To be done with the occurrence of a suspected anaphylaxis.

Pregnancy Tests (Serum and Urine)

A serum pregnancy test will be performed for all female subjects of childbearing potential during Screening. Pregnancy testing should not be performed for postmenopausal women. Determination of postmenopausal status will be made during the Screening period based on the subject's history or FSH testing.

A quantitative serum pregnancy test will be performed at Screening and a urine pregnancy test will be performed at baseline for all female subjects of childbearing potential. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is positive the subject is considered a screen failure. If the serum pregnancy test is borderline, it should be repeated ≥ 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 (considered documentation of continued lack of a positive result), the subject can be enrolled into the study (unless prohibited per local requirements) in the absence of clinical suspicion of pregnancy and other pathological causes of borderline results.

Additional urine pregnancy tests will be performed at visits indicated in Section 2.1.

More frequent pregnancy tests can be performed throughout the study at the investigator's discretion or if required per local/country requirements.

- If the baseline urine pregnancy test is negative, then dosing with study drug may begin.
- If the baseline or post-baseline urine pregnancy test is positive, dosing with study drug must be withheld and a serum pregnancy test is required (as stated above).

Clinical Chemistry

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

Urinalysis

Dipstick urinalysis will be provided by the central laboratory and completed locally at the site at all required visits. If the dipstick urinalysis is abnormal, then a microscopic analysis will be sent to the central laboratory in the event the dipstick results show protein, ketones or blood other than negative or glucose greater than normal.

Tuberculosis (TB) Testing/TB Prophylaxis

All subjects must be evaluated for TB at Screening and annually. The TB screening tests provide diagnostic test results to be interpreted in the context of the subject's epidemiology, history, exam findings, etc., and it is the responsibility of the Investigator to determine if a subject has previous, active, or latent TB. Expert consultation for the evaluation and/or management of TB may be considered per Investigator discretion.

At screening, all subjects will be assessed for evidence of increased risk for TB by a risk assessment form (Appendix C) and tested for TB infection by QuantiFERON-TB Gold test or purified protein derivative (PPD) test. The site staff will complete the TB risk assessment form and enter the data into the appropriate eCRF. The TB risk assessment questionnaire will be completed annually (Part I only) for all subjects, regardless of TB test results.

If a subject had a negative purified protein derivative (PPD) test within 90 days prior to Screening and a QuantiFERON-TB Gold test cannot be performed by Central Lab at Screening and source documentation is available, TB testing by PPD Skin Test does not need to be repeated, provided nothing has changed in the subject's medical history to warrant a repeat test. These cases may be discussed with the AbbVie TA MD. The results of the TB test(s) will be retained at the site as the original source documentation.

Subjects with a negative TB test may be enrolled. Subjects with a positive TB test must be assessed for evidence of active TB versus latent TB, including signs and symptoms and CXR. Subjects with no signs or symptoms and a CXR not suggestive of active TB may be enrolled after initiation of TB prophylaxis. Subjects with evidence of active TB must not be enrolled.

Any positive TB test after a subject with a negative test at Baseline has started the study should be reported as an AE of latent TB or active TB (as applicable).

If the subject is experiencing signs or symptoms suspicious for TB or something has changed in the subject's medical history to warrant a repeat test, the case (including the TB test results) must be discussed with the AbbVie TA MD.

TB Test

- Subjects with documentation of prior positive result of QuantiFERON-TB Gold Test (or equivalent) and/or PPD test are not required to repeat either test at Screening or during the study and should be considered positive.
- For regions that require both PPD and QuantiFERON-TB Gold testing, both will be performed. If either PPD or QuantiFERON-TB Gold are positive, the TB test is considered positive.
- The PPD Skin Test (also known as a TB Skin Test or Mantoux Test) should be utilized only when a QuantiFERON-TB Gold Test is not possible for any reason (unless both tests are required per local guidelines).
- If subjects require repeat TB testing during the trial, the TB test used for repeat testing should be the same as the test used during Screening.

- Subjects without a history of active or latent TB and who have a negative TB test result at Screening or the most recent evaluation will undergo annual TB testing by QuantiFERON-TBGold Test and/or PPD skin test.
- If a subject enters the study with a QuantiFERON-TB Gold test alone, then the subject should have their annual TB test performed with a QuantiFERON-TB Gold test. Similarly, if only a PPD is placed at Screening, then the TB test to be used for the remainder of the study for that subject is the PPD.
- If the QuantiFERON-TB Gold Test is NOT possible (or if both the QuantiFERON-TB Gold Test and the PPD are required per local guidelines) the PPD will be performed. The PPD should be read by a licensed healthcare professional between 48 and 72 hours after administration. A subject who does not return within 72 hours will need to be rescheduled for another skin test. The reaction will be measured in millimeters (mm) of induration and induration ≥ 5 mm is considered a positive reaction. The absence of induration will be recorded as "0 mm" not "negative." Subjects who have an ulcerating reaction to the PPD in the past should not be re-exposed and the PPD should be considered positive.
- If the QuantiFERON-TB Gold test is indeterminate, then the investigator should perform a local QuantiFERON-TB Gold test (or through the central laboratory if not locally available) to rule out a positive test result. If testing remains indeterminate or is positive, then the subject is considered to be positive for the purpose of this study. If the testing result is negative, then the subject is considered to be negative.
- If the subject is experiencing signs or symptoms suspicious for TB or something has changed in the subject's medical history to warrant investigation and a repeat test before the next scheduled annual TB retest, the case (including the TB test results) should be discussed with the AbbVie TA MD.
- If TB testing is done for subjects with a prior positive TB test at the annual evaluation, repeated TB prophylaxis is not required for a positive result unless indicated by the subject's medical history.

TB Prophylaxis

At screening, if the subject has evidence of latent TB infection, prophylactic treatment must be initiated at least 2 weeks prior to administration of study drug (or per local guidelines, whichever is longer). At least 6 months of prophylaxis need to be completed. However, the full course of prophylaxis does not need to be completed prior to the first dose of study drug.

Of note, Rifampicin or Rifapentine is not allowed for TB prophylaxis.

Subjects with a prior history of latent TB that have documented completion of a full course of anti-TB therapy will be allowed to enter the study provided nothing has changed in the subject's medical history

to warrant repeat treatment. For subjects with completion of a full course of anti-TB therapy, but insufficient documentation, the investigator should consult with the AbbVie TA MD.

During the study, subjects with new evidence of latent TB should initiate prophylactic treatment immediately per local guidelines and complete at least 6 months of prophylaxis. TB prophylaxis should be initiated and study drug(s) should not be withheld. The subject should be re-evaluated (unscheduled visit) for signs and symptoms as well as laboratory assessment of toxicity to TB prophylaxis 2 to 4 weeks later. Newly initiated prophylactic treatment and prior therapy should be captured in the eCRF.

Chest X-Ray

Chest X-ray (posterior-anterior and lateral views) is required for all subjects at Screening who have a positive QuantiFERON-Gold TB and/or PPD test. Subjects can have a CXR at any time during the study as warranted based on the opinion of the Investigator. A radiologist or pulmonologist must perform and document an assessment of the CXR. The Investigator will indicate the clinical significance of any findings and will sign and date the report.

A CXR is required annually for subjects with a newly positive PPD and/or QuantiFERON-TB Gold test after Baseline or a positive response to the TB risk questionnaire Part I questions.

In the assessment of the CXR, if possible per local / site guidelines, the Investigator or their delegate must indicate the presence or absence of calcified granulomas, pleural scarring/thickening, and signs of active TB. If the CXR demonstrates changes suggestive of previous TB (e.g., calcified nodule, fibrotic scar, apical or basilar pleural thickening) or other findings that are clinically significant, the Investigator should contact the AbbVie TA MD before enrolling the subject.

Hepatitis B Testing

All subjects will be tested for the presence of HBV at screening using the following tests:

- HBs Ag (Hepatitis B surface antigen)
- HBc Ab/anti-HBc (Hepatitis B core antibody)
- HBs Ab/anti-HBs (Hepatitis B surface antibody)

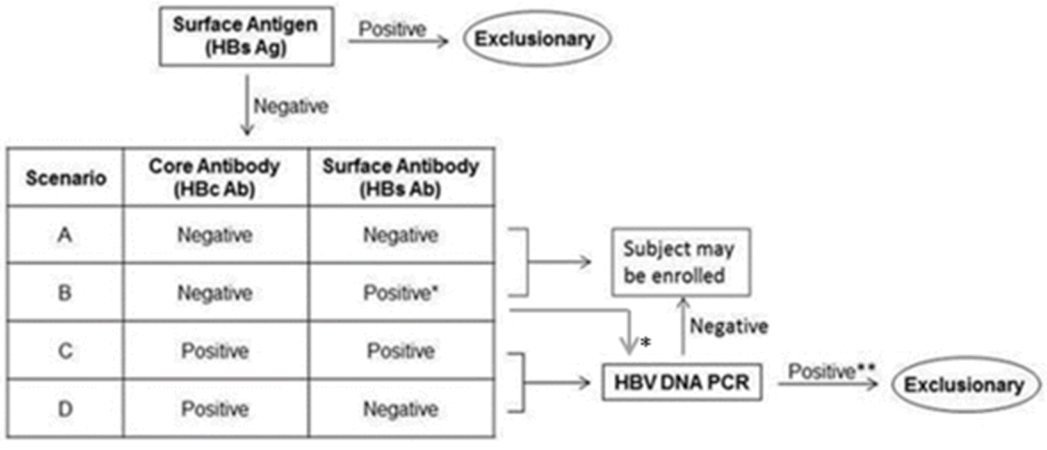
A positive result for HBs Ag will be exclusionary.

A negative result for HBs Ag will trigger automatic reflex testing for core antibodies (HBc Ab) and surface antibodies (HBs Ab).

- A negative test result for HBc Ab does not require HBV DNA PCR qualitative testing and the subject may be enrolled (Figure 1, Scenarios A and B).
- For a subject who has had a HBV vaccination (should document in the medical history), a positive test result for HBs Ab is expected, the HBV DNA PCR qualitative testing is not required and the subject may be enrolled (Figure 1, Scenario B*).

- A positive test result for HBc Ab requires HBV DNA PCR testing (automatic reflex testing) (Figure 1, Scenarios C and D).
  - A result that exceeds detection sensitivity by central laboratory will be considered a positive result for HBV DNA and will be exclusionary.
  - A subject with a negative result for HBV DNA may be enrolled.
- Where mandated by local requirements: A positive result for HBs Ab requires HBV DNA PCR testing.
  - A result that exceeds detection sensitivity by central laboratory will be considered a positive result for HBV DNA and will be exclusionary.
  - A subject with a negative result for HBV DNA may be enrolled.
  - For subjects with HBs Ab+ and/or HBc Ab+ and negative HBV DNA at screening, HBV DNA PCR test should be performed every 12 weeks. HBV DNA PCR testing every 12 weeks is not necessary when the subject has a history of HBV vaccine and HBs Ab+, HBc Ab-.
- At any time during the study for subjects with HBc Ab+ (irrespective of HBs Ab status) and negative HBV DNA at screening, a positive result for HBV DNA PCR testing accompanied by the following will require immediate interruption of study drug:
  - an ALT > 5 × ULN OR
  - ALT/AST > 3 × ULN and either a total bilirubin > 2 × ULN or INR > 1.5 OR
  - ALT/AST > 3 × ULN along with clinical signs of possible hepatitis.

Figure 1. Interpretation and Management of HBV Serologic Test Results



* Subjects who have had a HBV vaccination are expected to have a positive test result for HBs Ab and do not require HBV DNA PCR testing. 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.

Hepatitis C Testing

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

HIV Testing

Subjects with a known history of HIV infection are excluded from study participation. HIV testing will be conducted as part of the infection screening at the Screening visit. The Investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report these results to their health agency per local regulations, if necessary. If a subject has a confirmed positive result, the Investigator must discuss with the subject the potential implications to the subject's health and subjects should be referred for clinical care promptly. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing and will not be made aware of any positive result. This testing is to be done at the central lab.

Stool Sample Testing

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

FCP

Fecal calprotectin will be performed at the study visits indicated in Section 2.1. If subjects are unable to provide a sample at the site visit, subjects will be sent home with a stool sample supply kit and the site will give instructions to assist with collection procedures. If the FCP sample is collected during the Screening period, it may be used as the Baseline. All stool samples should be collected before any bowel preparation for endoscopy is started and returned to the site within 3 days of collection.

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

The sample must be shipped to the central laboratory using dry ice.

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

Blood samples for hs-CRP will be obtained at the study visits indicated in Section 2.1.

Anaphylaxis Testing

In the event of a suspected anaphylaxis, a PK, ADA, and nAb sample should be collected once within 24 hours of the reaction. In addition to PK, ADA, and nAb assays, blood tests to be conducted in the event of a suspected anaphylaxis are:

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

Refer to Appendix E (Clinical Criteria for Diagnosing Anaphylaxis) for more information.

3.13 Subject Withdrawal from Study

All attempts must be made to determine the primary reason for discontinuation of study drug or study participation. The information along with the date of the last study drug dose 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 study drug, the subject will be treated in accordance with the investigator's best clinical judgment, irrespective of whether or not the subject decides to continue participation in the study.

If a subject withdraws from the main study, biomarker research samples will continue to be stored and analyzed. A subject must contact the Investigator if they no longer want their samples to be stored and analyzed. Once AbbVie is notified, no new information will be collected, no new analysis will be started, and the samples will be destroyed unless a regulatory authority requires AbbVie to keep them. However, if AbbVie (or people or companies working with AbbVie) collected any information or did any testing before withdrawal, AbbVie (or people or companies working with AbbVie) will still use and disclose such information, use the test results, and keep the data generated from the samples.

3.14 Rescreening

Subjects who initially screen fail for the study or who received placebo only in the study prior to version 4.0 may be permitted to re-screen following re-consent. The subject must meet all the eligibility criteria as assessable at the time of re-screening in order to qualify for the study. There is no minimum period of time a subject must wait to re-screen for the study.

If the subject had a complete initial screening evaluation including the TB test, Hepatitis B virus (HBV), Hepatitis C virus (HCV), human immunodeficiency virus (HIV) and electrocardiogram (ECG), these tests

will not be required to be repeated for re-screening provided the conditions noted in Section 3 are met and no more than 90 days have passed.

If a subject is being rescreened ≤ 14 days from the date of the previous screening testing, it is not required to repeat testing for chemistry/hematology, urinalysis, serum pregnancy, and *C. difficile* provided that the subject's health status has not changed to warrant a repeat test. However, if > 14 days have passed from the date of testing and Baseline, then Baseline samples should be collected (with the exception of *C. difficile*).

All subjects who rescreen need to have their RBS, SFS, and Adapted Mayo score calculated and meet the eligibility criteria before enrollment at Baseline.

An endoscopy with biopsy will not be required to be repeated for re-screening provided the conditions noted in Section 3.15 are met and the endoscopy is within 45 days of the Baseline visit. All other screening procedures will be repeated (with the possible exceptions noted above). Sites may contact the AbbVie TA MD if there are questions on if subjects should or should not be re-screened.

3.15 Additional Assessments

Endoscopy

Endoscopy at/during Screening or within 45 days of the Baseline visit will be required to calculate the Mayo endoscopy subscore (confirmed by a central reader) at Baseline. Endoscopic evaluations using Mayo endoscopic score confirmed by central reader will be done at Screening, Week 8, Week 52, and Week 104/PD.

The same endoscopist, where possible, should perform all endoscopies. In addition, where possible, the Investigator or sub-Investigator should be the endoscopist for the study. It is expected that all subjects who remain in the study through at least Week 6 will have a Week 8/PD endoscopy.

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

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

A full colonoscopy will be performed at Screening unless the subject underwent a full colonoscopy within 24 months prior to Screening. There must be appropriate documentation available to confirm the diagnosis, extent of disease, and to exclude dysplasia and colon cancer. If this is available, the screening endoscopy may be either a full colonoscopy or a flexible sigmoidoscopy. All other endoscopies may be flexible sigmoidoscopies or colonoscopies at the discretion of the Investigator.

All endoscopies will be performed and recorded at the site in a video format. Videos from subjects with eligible Mayo endoscopic sub-scores during Screening and all videos from subjects at Week 8, Week 52, and Week 104/PD will be sent to a central review vendor and scored as described in the central review charter. Endoscopies will be evaluated using the Mayo endoscopic subscore. The Mayo endoscopic subscore, including the presence or absence of friability will be documented by the endoscopist at the site and maintained in the subject's source documents. If, in the assessment of the site endoscopist, the Screening endoscopy does not indicate an endoscopy subscore of 2 or 3 or the extent of inflammation is limited to the rectum, per eligibility requirements, the subject should be screen-failed and the video should not be sent for central reading. In addition to the Mayo endoscopy subscore, the central reader will assess the endoscopy findings using the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) and UC-100 scoring system for additional exploratory analyses.

There will be a window of ± 7 days to conduct the endoscopy. This window may be extended as necessary after consultation with the AbbVie TA MD in case of external, not subject-related circumstances (e.g., scheduling conflict).

Intestinal Biopsy

Mandatory biopsies will be collected from the site of general inflammation during endoscopies occurring during Screening, Week 8, Week 52, Week 104, and/or PD visits as described below:

- US sites: collect 4 biopsies at each time point for histology (centrally read), tissue RO (if applicable), and gene expression analysis
- Ex-US sites: collect 2 biopsies at each time point for histology (centrally read) and gene expression analysis

  The biopsies for histopathological and gene expression analysis collected for the main study may also be used for exploratory research to assess and generate prognostic, predictive, pharmacodynamic, or surrogate biomarker signatures.
- Additional biopsies as indicated:
  - Appropriate documentation of biopsy results consistent with the diagnosis of UC, in the assessment of the Investigator, must be available in order to confirm the subject's eligibility for the study. If this documentation is not available a diagnostic biopsy from the most affected observed area of the colon must be performed during the Screening endoscopy and read by a qualified local pathologist and the results reviewed by the Investigator.
  - Biopsies to rule out dysplasia, colon cancer and infection may be taken per the Investigator's discretion during any endoscopy performed during this study and evaluated by the local pathologist. The signed pathology report will be monitored by the responsible Clinical Research Associate (CRA) and kept with the subject's source documents onsite.
- Biopsy sampling should be recorded on the endoscopy video.
- Unless indicated otherwise, biopsies will be taken from the rectosigmoid segment of the colon at each visit with endoscopy from an area which represents the general degree of mucosal inflammation of the segment.

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 may continue in the study if the lesion has been completely removed after discussion with the AbbVie TA MD.

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

Data from the subject diaries will be collected in order to calculate Full Mayo Score, Adapted Mayo Score, and Partial Adapted Mayo Score at the time points indicated in Section 2.1.

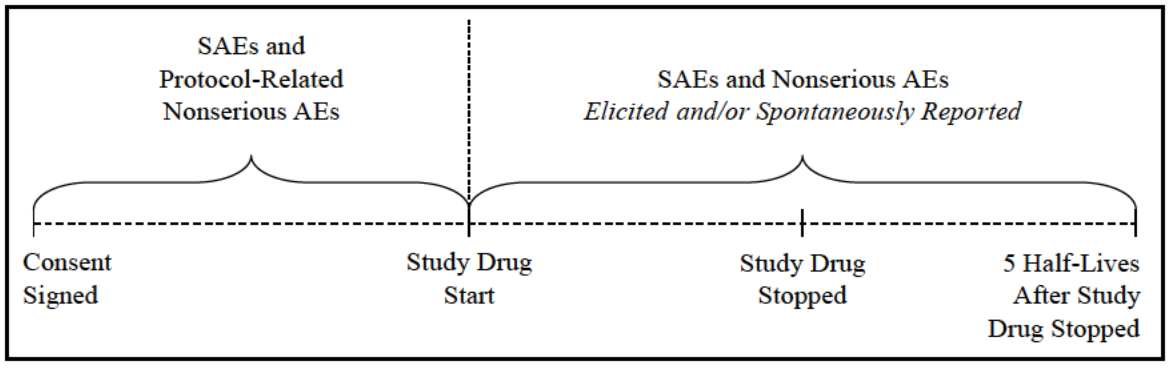
Detailed information about Full Mayo Score, Adapted Mayo Score, and Partial Adapted Mayo Score can be found in Appendix D.

Whenever possible, the same physician (Investigator or Sub-Investigator) should determine the Physician's Global Assessment (PGA) subscore for an individual subject through the duration of the study. The directions for capturing the stool frequency subscore, rectal bleeding subscore, and PGA subscores of the Full Mayo Score, Adapted Mayo Score, and Partial Adapted Mayo Score are described in Appendix D.

4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

All serious adverse events as well as protocol-related nonserious adverse events (e.g., infection at biopsy site, done during screening) will be collected from the time the subject signed the study-specific informed consent until study drug administration. From the time of study drug administration until 5 half-lives (84 days) after discontinuation of study treatment, all adverse events and serious adverse events will be collected whether solicited or spontaneously reported by the subject. After 5 half-lives following completion of study treatment and throughout the Post-Treatment Period, all spontaneously reported SAEs will be collected (nonserious AEs will not be collected).



4.2 Recording Data and Analyses of Safety Findings

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug through 5 half-lives post-study drug dosing) will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term (PT) and compared between arms using Fisher's exact test. The tabulation of the number of subjects with treatment-emergent adverse events by severity grade and relationship to study drug also will be provided. Subjects reporting more than 1 adverse event for a given MedDRA preferred term will be counted only once for that term using the most severe grade according to the severity grade table and the most related according to the relationship to study drug tables. Subjects reporting more than 1 type of event within an SOC will be counted only once for that SOC.

4.3 Reporting Adverse Events and Intercurrent Illnesses

In the event of a serious adverse event (SAE), whether associated with study drug 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 electronic data capture (EDC) system. SAEs that occur prior to the site having access to the RAVE® system, or if RAVE 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) 938-0660

For safety concerns, contact the Immunology Safety Team at:

Immunology Safety Team
1 North Waukegan Road
North Chicago, Illinois 60064
Toll Free: +1 (833) 942-2226
Email: GPRD_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 (AbbVie)
Knollstrasse
67061 Ludwigshafen
Germany

Contact Information:

Office: [redacted]
Mobile
Fax:
Email:

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director 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 Therapeutic Area Medical Director:

HOTLINE: +1 (973) 784-6402

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC.

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

COVID-19 infections should be captured as adverse events. If the event meets the criteria for a serious adverse event (SAE), then follow the SAE reporting directions per the protocol and above. The following COVID-19 related supplemental eCRFs should be completed (for both serious and non-serious events):

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

5 COUNTRY-SPECIFIC REQUIREMENTS

5.1 SUSAR Reporting

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

6 STUDY DRUG

6.1 Treatments Administered

The study drug (ravagalimab) will be administered in the form of IV infusions or SC injections at the visits listed in Section 2.1.

Ravagalimab and placebo will be provided by AbbVie as lyophilized powder for solution for injection/infusion in vials to be reconstituted by a pharmacist or qualified designee.

Ravagalimab will be administered IV once (induction) then SC every other week (eow).

Study drug must not be administered without contacting the interactive response technology (IRT) system. Study drug may only be administered to subjects enrolled in the study through the IRT system. At the end of the Treatment Period or at the PD visit, the site will contact the IRT system to provide visit date information and study drug return information for each kit.

6.2 Packaging and Labeling

All study drugs will be supplied in cartons containing one vial with quantities sufficient to accommodate study design. Each vial will contain 100 mg ravagalimab lyophilized powder for solution for injection/infusion or placebo. Each carton and vial label will contain a unique kit number. This kit number is assigned to a subject via IRT and encodes the appropriate study drug to be administered at the subject's corresponding study visit. Each carton and vial will be labeled as required per country requirements. The labels must remain affixed to the cartons and vials. All blank spaces should be completed by site staff prior to dispensing to subject.

Storage and Disposition of Study Drug

Ravagalimab and placebo must be refrigerated (2° to 8°C/36° to 46°F), protected from light, and must not be frozen. The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until administered for subject use or destroyed on site as appropriate.

6.3 Method of Assigning Subjects to Treatment Groups

This is a Phase 2a, multicenter, single arm, open-label study. All eligible subjects will receive ravagalimab 600 mg IV at Baseline (Week 0), and ravagalimab 300 mg SC eow from Week 2 during the induction period. Subjects who enter the maintenance period will receive open-label ravagalimab 300 mg SC eow.

At the screening visit, all subjects will be assigned a unique subject number through the use of the IRT. 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 drug, the site will acknowledge receipt in the IRT system.

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

6.4 Selection and Timing of Dose for Each Subject

The dose selection in this study is based on analysis of PK, pharmacodynamics, and safety data from Phase 1 studies in healthy volunteers as well as safety data from preclinical animal studies. Ravagalimab dose of 600 mg IV at Week 0, 300 mg SC for Weeks 2, 4, 6, 8, and 10, and 300 mg SC eow from Week 12 to Week 102 is selected for this study.

APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
CXR	Chest X-ray
COVID	Coronavirus Disease-2019
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eow	Every other week
FCP	Fecal calprotectin
FSH	Follicle-stimulating hormone
HBc Ab	Hepatitis B core antibodies
HBs Ag	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCRU	Health Care Resource Utilization
HCV	Hepatitis C Virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
hs-CRP	High sensitivity C-reactive protein
IBDQ	Inflammatory Bowel Disease Questionnaire
IMP	Investigational Medicinal Product
IRT	Interactive response technology
IV	Intravenous(ly)
LDL	Low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
nAb	Neutralizing anti-drug antibody
PK	Pharmacokinetic(s)
PPD	Purified protein derivative
PRO	Patient-reported outcome
PT	Preferred term

QoL	Quality of life
RBC	Red blood cell
RBS	Rectal bleeding subscore
RO	Receptor occupancy
SAE	Serious adverse event
SC	Subcutaneous(ly)
SFS	Stool frequency subscore
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reactions
TA MD	Therapeutic Area Medical Director
TB	Tuberculosis
WBC	White blood cell

APPENDIX B. ADDITIONAL ENDPOINT DEFINITIONS

UCEIS

The UCEIS is a tool for the overall assessment of endoscopic severity of UC. It is calculated based on the following 3 descriptors: vascular pattern (scored 0-2), bleeding (scored 0-3), and erosions and ulcers (scored 0-3). The final score is a sum of these 3 items and ranges from 0 (remission) to 8 (severe).

UC-100

A composite index of disease activity in UC that combines clinical, endoscopic, and histological data that ranges from 1 to 100, with higher values indicating more severe disease activity.

Reference:

Travis SP, Schnell D, Feagan BG, et al. The Impact of Clinical Information on the Assessment of Endoscopic Activity: Characteristics of the Ulcerative Colitis Endoscopic Index Of Severity [UCEIS]. J Crohns Colitis. 2015;9(8):607-16.

Jairath V, Jeyarajah J, Guangyong Z, et al. A composite disease activity index for early drug development in ulcerative colitis: development and validation of the UC-100 score. Lancet Gastroenterol Hepatol. 2019 Jan;4(1):63-70. doi: 10.1016/S2468-1253(18)30306-6. Epub 2018 Oct 18.

APPENDIX C. SCREENING/ANNUAL TB RISK ASSESSMENT QUESTIONNAIRE EXAMPLE

For Screening TB risk assessment, ask Part I and Part II questions.

Part I

1. Has an immediate family member or other close contact been newly diagnosed with or treated for active or latent tuberculosis during the last 3 months?
2. Within the past year, have you, or an immediate family member, had any of the following problems lasting for 3 weeks or longer which remained unexplained:
    - Chronic Cough
    - Production of Sputum
    - Blood-Streaked Sputum
    - Weight Loss
    - Fever
    - Fatigue/Tiredness
    - Night Sweats
    - Shortness of Breath

(reference: https://www.cdc.gov/tb/topic/testing/diagnosingltbi.htm)

Part II

3. Have you ever been diagnosed or treated for active or latent tuberculosis?
4. Have you lived in or had prolonged travels to a TB endemic region?

    (reference: http://gamapserver.who.int/gho/interactive_charts/tb/cases/atlas.html)
5. Have you lived or worked in a prison, refugee camp, homeless shelter, immigration center, or nursing home?

APPENDIX D. SCRIPT FOR COLLECTION OF MAYO SCORES FOR USE IN STUDY M15-722

Mayo Score

Three different Mayo Score are evaluated in this protocol:

- Full Mayo Score
- Adapted Mayo Score
- Partial Adapted Mayo Score

The Full Mayo Score is a composite of the following subscores: SFS, RBS, Endoscopy subscore, and PGA subscore.

The adapted Mayo Score is a composite of the following subscores: SFS, RBS and Endoscopy subscore.

The Partial Adapted Mayo Score is a composite of the following subscores: SFS and RBS.

Subscores

Stool frequency Subscore* 0 = Normal number of stools for this subject 1 = 1 – 2 stools more than normal 2 = 3 – 4 stools more than normal 3 = 5 or more stools more than normal * Each patient serves as his or her own control to establish normal stool frequency and the degree of abnormal stool frequency.
Rectal bleeding Subscore** 0 = No blood seen 1 = Streaks of blood with stool less than half the time 2 = Obvious blood with stool most of the time 3 = Blood alone passed ** The daily bleeding score represents the most severe bleeding of the day.
Endoscopy Subscore: Findings of flexible sigmoidoscopy 0 = Normal or inactive disease 1 = Mild disease (erythema, decreased vascular pattern, mild friability) 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions) 3 = Severe disease (spontaneous bleeding, ulceration)

Physician's Global Assessment Subscore***

0 = Normal (Subscores are 0)

1 = Mild disease (Subscores are mostly 1's)

2 = Moderate disease (Subscores are 1 to 2)

3 = Severe disease (Subscores are 2 to 3)

***The physician's global assessment acknowledges the three other subscores, the subject's daily record of abdominal discomfort and functional assessment, and other observations such as physical findings, and the subject's performance status.

References:

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

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

Stool Frequency Subscore

- The stool frequency subscore is calculated by comparing the stool frequency to a reference number. The reference number is the number of stools per day (24 hours) that is typical for the subject when having active UC but not experiencing a flare and needs to be designated once prior to enrollment. The reference number should represent a full number of at least 1.
- Subjects will record the daily number of stools throughout the trial. Using these numbers, the Stool Frequency subscore will be assessed for each study day as follows:
  - A number of bowel movements lower than or equal to the reference number of bowel movements should be scored as 0 = Normal.
  - One or 2 bowel movements more than the reference number of bowel movements should be scored as 1.
  - Three or 4 bowel movements more than the reference number of bowel movements should be scored as 2.
  - Five or more bowel movements more than the reference number of bowel movements should be scored as 3.
- The Stool Frequency subscores based on 3 days prior to each study visit will be averaged and used for the Stool Frequency subscore for each study visit.
- The Stool Frequency subscore during days which the subject received anti-diarrheal medication will be scored as a 3.
- Diary entries for stool frequency should not be included in the 3 days prior to the visit that are evaluated for the Stool Frequency subscore for the following days: (1) the day the subject received medication for bowel preparation prior to endoscopy, (2) the day the subject underwent an endoscopy, and (3) 2 days following the endoscopy. Earlier diary entries will be

used accordingly in order to provide the most recent data for 3 days prior to the respective study visit.

Rectal Bleeding Subscore

- Subjects will be assigned a daily rectal bleeding subscore value as follows:
  - No visible blood with stool during the respective day should be scored as 0.
  - Visible blood with stool less than half the time during the respective day should be scored as 1.
  - Visible blood with stool at least half the time during the respective day should be scored as 2.
  - A score of 3 for bleeding requires subjects to have at least 50% of bowel movements accompanied by visible blood and at least one bowel movement with blood alone.
- The score entries into subject's diary based on 3 days prior to each study visit will be averaged and used for the Rectal Bleeding subscore for each study visit.
- Diary entries for rectal bleeding should not be included in the 3 days prior to the visit that are evaluated for the Rectal Bleeding subscore for the following days: (1) the day the subject received medication for bowel preparation prior to endoscopy, (2) the day the subject underwent an endoscopy, and (3) 2 days following the endoscopy. Earlier diary entries will be used accordingly in order to provide the most recent data for 3 days prior to the respective study visit.

Physician's Global Assessment Subscore

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

- 0 = Normal
- 1 = Mild disease
- 2 = Moderate disease
- 3 = Severe disease

Endoscopy Subscore

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

APPENDIX E. CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS

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

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING
    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips tongue-uvula)
    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
    c. Reduced blood pressure (BP) or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
    a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
    b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

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

References:

Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-7.