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Protocol for Study M21-446

Moderate to Severe Ulcerative Colitis: A Single Arm, Open-Label Study to Evaluate the Efficacy and Safety of ABBV-668

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FULL TITLE: A Single-Arm, Open-Label Study to Evaluate the Efficacy and Safety of ABBV-668 in Subjects with Moderate to Severe Ulcerative Colitis

Incorporating Versions 1.0 and 2.0 and Administrative Change 1.

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1 SYNOPSIS

Title: A Single-Arm, Open-Label Study to Evaluate the Efficacy and Safety of ABBV-668 in Subjects with Moderate to Severe Ulcerative Colitis	
Background and Rationale:	Despite the availability of various ulcerative colitis (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 for patients with moderate to severe UC. Based on pre-clinical and clinical evidence, ABBV-668 could potentially demonstrate efficacy with a favorable safety profile in the treatment of patients with moderately to severely active UC. ABBV-668 has been studied in two phase 1 studies of healthy human subjects, Study M21-442 and Study M21-443. In Phase 1 studies, ABBV-668 single doses CCI mg and multiple doses CCI mg twice a day (BID) were safe and well tolerated with no serious or severe AEs or trends observed in healthy adult subjects (including Japanese and Chinese subjects). Taken together, the data support further development of ABBV-668 in Phase 2 for subjects with moderate to severe UC. For details, please see findings from completed studies, including safety data, in the current ABBV-668 Investigator's Brochure.
Objective and Endpoints:	**Primary Objective** To characterize the safety and efficacy of ABBV-668 CCI mg orally (PO) BID as treatment in adult subjects with moderately to severely active UC. **Hypothesis** The primary hypothesis is that ABBV-668 will be safe, well tolerated and efficacious in subjects with moderate to severe UC. **Primary Endpoint** The primary endpoint is the achievement of endoscopic improvement (Mayo endoscopic subscore [ESS] of 0 or 1) at Week 8. **Secondary Endpoints** • Achievement of clinical remission per Adapted Mayo score at Week 8. • Achievement of clinical response per Adapted Mayo score at Week 8. • Achievement of clinical response per Partial Adapted Mayo score at Week 8. • Achievement of endoscopic remission at Week 8.
Investigators:	Multicenter
Study Sites:	23 sites globally

Study Population and Number of Subjects to be Enrolled:	The study will enroll approximately 40 subjects with moderate to severe UC.
Investigational Plan:	Study M21-446 is a Phase 2a, multicenter, open-label proof of concept study to investigate the efficacy and safety of ABBV-668 in subjects with moderate to severe UC. The study contains a 30-day screening period, 16-week treatment period, and a 30-day follow up period from the last dose of study drug. Approximately 40 subjects will be enrolled in this study. An endoscopy is required at Screening and at Week 8 to evaluate endoscopic improvement. To explore the time course of ABBV-668 efficacy, subjects will continue through Week 16. An endoscopy will be performed at Week 16 for subjects: • Who have an endoscopic subscore of ≥ 1 at the Week 8 endoscopy; or • Who have an endoscopic subscore of 0 at the Week 8 endoscopy AND have subsequent worsening of their disease (as assessed by the investigator) after the Week 8 endoscopy.
Key Eligibility Criteria:	Key eligibility criteria include: 1. Adult **male or female**, at least 18 years old at time of the Baseline visit. 2. Diagnosis of UC for at least 90 days prior to Baseline. Appropriate documentation of biopsy results consistent with the diagnosis of UC in the assessment of the investigator, must be available. 3. 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). 4. Demonstrated inadequate response to, loss of response to, or intolerance to at least one of the following: oral aminosalicylates, corticosteroids, immunosuppressants and/or biologics or targeted immunomodulators.
Study Drug and Duration of Treatment:	Subjects will receive ABBV-668 CCI mg PO BID for 16-weeks.
Date of Protocol Synopsis:	03 March 2023

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted?

Ulcerative colitis (UC) is one of the two primary forms of idiopathic inflammatory bowel disease (IBD). Ulcerative colitis is a chronic, relapsing inflammatory disease of the large intestine characterized by inflammation and ulceration of the mucosal and, occasionally, submucosal intestinal layers. The hallmark clinical symptoms are bloody diarrhea associated with rectal urgency and tenesmus. The clinical course is marked by exacerbation and remission.

UC is a serious disease that, in some cases, may cause life-threatening complications or be fatal.[1,2] The burden of UC on the healthcare system is profound, accounting for nearly 500,000 physician visits and more than 46,000 hospitalizations per year in the United States (US) alone.[3] The most severe intestinal manifestations of UC include toxic megacolon, fulminant colitis, and perforation. Extraintestinal complications include arthritis (peripheral or axial involvement), dermatological conditions (erythema nodosum, aphthous stomatitis, and pyoderma gangrenosum), inflammation of the eye (uveitis), and liver dysfunction (primary sclerosing cholangitis).

Conventional therapies include 5-aminosalicylic acid (5-ASA) derivatives, corticosteroids and thiopurines.[4] The biological agents infliximab, adalimumab, golimumab, vedolizumab, and ustekinumab as well as small molecule Janus kinase (JAK) inhibitor, including tofacitinib and upadacitinib, and sphingosine-1-phosphate (S1P) receptor modulator ozanimod are also indicated for the treatment of moderate to severe UC. Despite increasingly available therapies, current therapies for UC have limited efficacy[5-7] and have a potential for significant safety events.[8-11] Only 17% to 45% of patients who receive biologics are able to achieve clinical remission. In addition, anti-drug antibodies can lead to loss of response and increased hypersensitivity reactions.[12-15] Thus, a large unmet need continues to exist for the treatment of UC.

ABBV-668 is a receptor-interacting protein kinase (RIPK1) inhibitor and is the phosphate prodrug of CCI .

RIPK1 mediates pro-inflammatory necroptosis and toll-like receptor (TLR) dependent inflammatory cytokine production. Inhibition of RIPK1-associated pro-inflammatory necroptosis may provide clinical benefit to patients with IBD. Published and preliminary AbbVie generated data have demonstrated an increase in phosphorylated mixed lineage kinase domain-like protein, which is downstream of RIPK1 in the TNF and TLR4 necroptotic signaling cascades, in human Crohn's disease (CD) and UC patient samples.[16] For details, please see the current ABBV-668 Investigator's Brochure.

2.2 Benefits and Risks to Subjects

Despite the availability of various UC therapies, including biologic and small molecule therapies, many patients do not respond adequately to these treatments, gradually lose response over time, or discontinue treatment due to significant adverse events (AE). Thus, there remains a large unmet medical need for additional therapeutic options for patients with moderate to severe UC. Based on

pre-clinical and clinical evidence, ABBV-668 could potentially demonstrate efficacy with a favorable safety profile in the treatment of patients with moderately to severely active UC.

ABBV-668 has been studied in two phase 1 studies of healthy human subjects, Study M21-442 and Study M21-443. In Phase 1 studies, single doses of ABBV-668 CCI mg and multiple doses CCI mg twice a day (BID) were safe and well tolerated with no serious or severe AEs or trends observed in healthy adult subjects (including Japanese and Chinese subjects).

Taken together, the data support further development of ABBV-668 in Phase 2 for subjects with moderate to severe UC.

For details, please see findings from completed studies, including safety data in the current ABBV-668 Investigator's Brochure.

Considering the coronavirus – 2019 (COVID-19) pandemic and based on the information to date, it is unknown whether study subjects treated with ABBV-668 may be at an increased risk for COVID-19 or experience more serious illness if infected.

3 OBJECTIVE AND ENDPOINTS

3.1 Objective, Hypothesis, and Estimands

Primary

To characterize the safety and efficacy of ABBV-668 CCI mg orally (PO) twice a day (BID) as treatment in adult subjects with moderately to severely active UC.

Hypothesis

The primary hypothesis is that ABBV-668 will be safe, well tolerated and efficacious in subjects with moderate to severe UC.

Estimands

The estimand for the primary endpoint is defined as the difference in the proportion of subjects achieving endoscopic improvement at Week 8 regardless of premature discontinuation of study treatment and without initiation or dose escalation of UC-related corticosteroids between the ABBV-668 treatment group in the Intent-to-Treat (ITT) Population and the historical placebo group. Subjects will be counted as non-responders after the start of rescue medication (initiation or dose escalation of UC-related corticosteroids).

The estimands corresponding to the secondary efficacy objectives are:

For each binary secondary endpoint specified in Section 3.3: The difference in the proportion of subjects achieving a response regardless of premature discontinuation of study treatment and without initiation or dose escalation of UC-related corticosteroids in the ABBV-668 treatment group in the ITT Population versus in the historical placebo group. Subjects will be counted as non-responders after the start of rescue medication (initiation or dose escalation of UC-related corticosteroids).

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

Endoscopic Remission: Mayo ESS = 0

Histologic Remission: Geboes score of < 2.0

Histologic-Endoscopic Mucosal Improvement: Mayo ESS ≤ 1 and Geboes score ≤ 3.1

Mucosal Healing: endoscopic (Mayo ESS = 0) and histologic remission (Geboes score of < 2.0).

3.2 Primary Endpoint

The primary endpoint is the achievement of endoscopic improvement (Mayo ESS of 0 or 1) at Week 8.

3.3 Secondary Endpoints

The secondary endpoints are as follows:

- Achievement of clinical remission per Adapted Mayo score at Week 8.
- Achievement of clinical response per Adapted Mayo score at Week 8.
- Achievement of clinical response per Partial Adapted Mayo score at Week 8.
- Achievement of endoscopic remission at Week 8.

3.4 Additional Efficacy Endpoints

In addition, the primary and secondary efficacy endpoints will be analyzed at all other scheduled visits as noted in the Study Activities Table (Appendix D) during which the assessments are measured.

The following endpoints will also be evaluated at scheduled visits during which the assessments are measured as noted in the Study Activities Table (Appendix D), unless otherwise specified:

- Achievement of clinical response per Full Mayo score over time in subjects with a Full Mayo score of 6 to 12 at Baseline.
- Achievement of 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).
- Achievement of SFS = 0, RBS = 0, and ESS = 0 over time (at visits with endoscopy).
- Achievement of SFS = 0, RBS = 0, and ESS ≤ 1 over time (at visits with endoscopy).
- Time to clinical response per Partial Adapted Mayo.
- Achievement of SFS ≤ 1 over time.
- Achievement of RBS = 0 over time.
- Change from Baseline in RBS over time.
- Change from Baseline in SFS over time
- Achievement of histologic-endoscopic mucosal improvement over time (at visits with endoscopy).
- Achievement of histologic remission over time (at visits with endoscopy).
- Achievement of mucosal healing (endoscopic and histologic remission) over time (at visits with endoscopy).
- Change from Baseline in number of extraintestinal manifestations (EIM) over time (as captured in the EIM electronic case report form [eCRF]).
- Change from Baseline in fecal calprotectin (FCP) over time.
- Achievement of FCP below 150 mg/kg over time.
- Achievement of FCP below 250 mg/kg over time.
- Change from Baseline in high sensitivity C-reactive protein (hs-CRP) over time.
- Achievement of no nocturnal bowel movements at Week 8 as assessed by the UC symptom daily diary.
  Achievement of no nocturnal bowel movements at Week 16 as assessed by the UC symptom daily diary.
- Achievement of no tenesmus at Week 8 as assessed by the UC symptom daily diary.
  Achievement of no tenesmus at Week 16 as assessed by the UC symptom daily diary.
- Change from Baseline in number of fecal incontinence episodes per week at Week 8 as assessed by the UC symptom daily diary.
  Change from Baseline in number of fecal incontinence episodes per week at Week 16 as assessed by the UC symptom daily diary.
- Change from Baseline in number of days over a week with sleep interrupted due to UC symptoms at Week 8 as assessed by the UC symptom daily diary.

Change from Baseline in number of days over a week with sleep interrupted due to UC symptoms at Week 16 as assessed by the UC symptom daily diary.

- Change from Baseline at Week 8 in Inflammatory Bowel Disease Questionnaire (IBDQ) total score.
  Change from Baseline at Week 16 in IBDQ total score.
- Achievement of no abdominal pain at Week 8 as assessed by the UC symptom daily diary.
  Achievement of no abdominal pain at Week 16 as assessed by the UC symptom daily diary.
- Achievement of no bowel urgency at Week 8 as assessed by the UC symptom daily diary.
  Achievement of no bowel urgency at Week 16 as assessed by the UC symptom daily diary.
- Change from Baseline at Week 8 in Functional Assessment of Chronic Illness (FACIT)-Fatigue.
  Change from Baseline at Week 16 in FACIT-Fatigue.

3.5 Safety Endpoints

Safety evaluations include AE monitoring, physical examinations (including neurological examinations), vital sign measurements, electrocardiogram (ECG) variables, C-SSRS evaluations, and clinical laboratory testing (hematology, chemistry, and urinalysis) as measures of safety and tolerability for the entire study duration.

3.6 Pharmacokinetic Endpoints

Plasma concentrations of the active parent of ABBV-668 CCI) will be obtained at each sampling time point as indicated in Appendix D. A nonlinear mixed-effects modeling approach will be used to estimate the population central values and the empirical Bayesian estimates of the individual values of ABBV-668 CCI oral clearance (CL/F) and apparent volume of distribution (V/F). Additional parameters may be estimated if useful in the interpretation of the data.

3.7 Biomarker Research Endpoints

Biospecimens (blood, serum, plasma, peripheral blood mononuclear cell [PBMC], stool, 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 in circulation or at tissue sites. Some of these samples may be optional. Types of biomarkers may include nucleic acids, proteins, lipids, and/or metabolites, either free or in association with particular cell types.

Biopsies for biomarker analysis will be done when performing endoscopies; 8 biopsies will be taken at each visit with an endoscopy as outlined in Appendix D. Biopsies will be taken from one region in areas that represent the average degree of inflammation and from areas that represent the most inflamed intestinal tissue: 4 biopsies for histologic assessment (2 that represent average inflammation and 2 that represent the most inflamed [one of which will be assessed by central review]); 2 biopsies for gene expression (average and most inflamed); and 2 biopsies for IHC/MOA analysis (average and most inflamed).

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 RIPK1 target engagement.

Serum samples will be used to evaluate pathway engagement/PD analysis CCI

Blood, serum, plasma, PBMC, and stool samples may be used for biomarker research to assess and generate prognostic, predictive, pharmacodynamic, or surrogate biomarker signatures. Intestinal biopsy tissue samples may also be used for biomarker 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 ABBV-668 or drugs of similar classes.

The results from these analyses are exploratory in nature and may not be included with the clinical study report. Further details regarding the biomarker research rationale and collection time points are located in the Operations Manual (Appendix D), Section 3.6.

Provision of biospecimens for biomarker research is mandatory, but they will not be collected from sites where local regulations do not allow for the collection, use, and storage of samples as described in the protocol.

Optional whole blood samples will be collected at specific time points (Appendix D) and may be analyzed for genetic factors contributing to UC, related conditions, or the subject's response to ABBV-668 in terms of pharmacokinetics, efficacy, tolerability, and safety. Such genetic factors may include genes associated with drug metabolizing enzymes, drug transport proteins, the target pathway, drug response, or UC or related conditions. The samples may be analyzed as part of a multistudy assessment of genetic factors involved with UC, related conditions or the response to ABBV-668 or drugs of this class. The samples may also be used for the development of diagnostic tests related to UC, related conditions, or ABBV-668 (or drugs of this class).

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

Study M21-446 is a Phase 2a, multicenter, open-label proof of concept study to investigate the efficacy and safety of ABBV-668 in subjects with moderate to severe UC. The study contains a 30-day screening period, 16-week treatment period, and a 30-day follow up period from the last dose of study drug.

Approximately 40 subjects will be enrolled in this study.

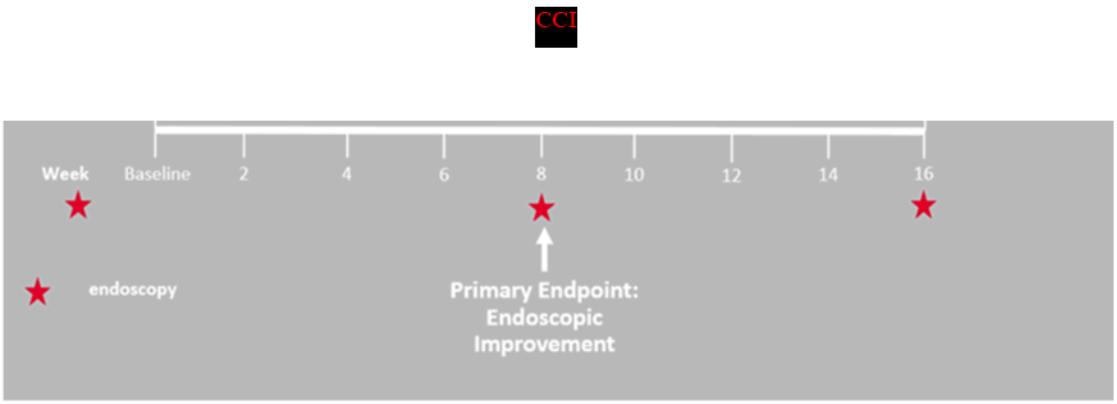
An endoscopy is required at Screening and at Week 8 to evaluate endoscopic improvement. To explore the time course of ABBV-668 efficacy, subjects will continue through Week 16. An endoscopy will be performed at Week 16 for subjects:

- Who have an endoscopic subscore of ≥ 1 at the Week 8 endoscopy; or
- Who have an endoscopic subscore of 0 at the Week 8 endoscopy AND have subsequent worsening of their disease (as assessed by the investigator) after the Week 8 endoscopy.

The schematic of the study is shown in Figure 1. Details regarding study procedures are provided in the Operations Manual (Appendix F).

See Section 5.1 for information regarding eligibility criteria.

Figure 1. Study Schematic



BID = twice a day

4.2 Discussion of Study Design

Choice of Control Group

The efficacy of ABBV-668 will be evaluated through comparison with a 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 definitions and time point of analysis. The objective nature of the centrally read endpoints, as well as the consistently low placebo rate of endoscopic improvement, makes the use of historical placebo control a feasible method to assess the effect of ABBV-668. Subjects will therefore not be enrolled into a concurrent control group within this study.

Appropriateness of Measurements

Standard clinical and laboratory procedures will be used. The efficacy and safety-related measurements used in this study are standard for assessing disease activity in subjects with UC. All clinical and laboratory procedures used 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 study population selected was based on the unmet medical need of those subjects with moderate to severe UC.

Selection of Doses in the Study

The dose selection in this study is based on analysis of pharmacokinetic (PK), pharmacodynamic, safety, and tolerability data from healthy volunteers in Phase 1 Study M21-442 and Phase 1 Study M21-443.

Given the uncertainty in correlation between blood RIPK1 occupancy in healthy subjects and RIPK1 occupancy at the site of action in patients with UC, and the uncertainty in correlation between RIPK1 occupancy and efficacy in patients with UC, the selected dose is intended to approximate exposures at or greater than those needed to achieve maximal RIPK1 occupancy.

In the Phase 1 ABBV-668 multiple ascending dose study (Study M21-443), CCI [redacted] was achieved with CCI mg orally (PO) BID and CCI mg PO BID doses throughout the dosing interval. Following BID dosing of ABBV-668 at CCI mg PO BID and CCI mg PO BID, it is predicted that CCI [redacted] of subjects will be able to achieve CCI [redacted] at trough concentration, respectively. A CCI mg PO BID dose is selected to maximize RIPK1 occupancy in subjects with UC.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria 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. Subject must 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**, at least 18 years old 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:
  - Hemoglobin ≥ 8 g/dL;
  - Serum aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2 × upper limit of normal (ULN).
- 4. Are willing and able to comply with procedures required in this protocol.

- 5. Estimated glomerular filtration rate (eGFR) calculated by Cockcroft-Gault ≥ 90 mL/min at the Screening visit.

Disease/Condition Activity

- 6. Diagnosis of UC for at least 90 days prior to Baseline. Appropriate documentation of biopsy results consistent with the diagnosis of UC in the assessment of the investigator, must be available prior to enrollment.
- 7. Subject meets the following disease activity criteria: Active UC with an Adapted Mayo score of 5 to 9 points and ESS of 2 to 3 (confirmed by central review prior to enrollment).

Subject History

- 8. 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 currently be positive 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 the Operations Manual);
  - Subject must not have evidence of active tuberculosis (TB) or meet TB exclusionary parameters (See specific requirements for TB testing in Section 3.13 of the Operations Manual).
- 9. No known active SARS-CoV-2 infection. If a subject has signs/symptoms suggestive of SARS-CoV-2 infection, the subject must have a negative molecular (e.g., PCR) test or 2 negative antigen test results at least 24 hours apart. Note: SARS CoV-2 diagnostic tests should be applied following local requirements/recommendations.
  - Subjects who do not meet SARS-CoV-2 infection eligibility criteria may only resume screening for the study after they meet the following SARS-CoV-2 infection viral clearance criteria:
    - At least 10 days since the first positive test result has passed in asymptomatic patients or at least 10 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.
- 10. No current diagnosis of CD or inflammatory bowel disease-unclassified (IBD-U).
- 11. No extent of inflammatory disease limited to the rectum as assessed by screening endoscopy.
- 12. 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.

- 13. Subject must not have current suicidal ideation with plan within the prior month, via answering "yes" to questions 4 or 5 to the suicidal ideation portion of the Columbia-Suicide Severity Rating Scale (C-SSRS) completed at Screening and Baseline, or any history of suicide attempt(s) within the last 2 years.
- 14. No history of seizures (excluding history of a single childhood febrile seizure before age 5), epilepsy, convulsions, significant head injury, or other significant neurologic conditions.
- 15. Subjects must not have an ostomy or ileoanal pouch.
- 16. No history of radiation colitis or ischemic colitis.
- 17. 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.
- 18. No history of clinically significant (per investigator's judgment) drug or alcohol abuse within the last 12 months.
- 19. 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.
- 20. No history of an allergic reaction or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class.
- 21. 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).
- 22. No history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly.

Prior and Concomitant Medications

- 23. Subject must have demonstrated an inadequate response to, loss of response to, or intolerance to at least one of the following: oral aminosalicylates, corticosteroids, immunosuppressants, and/or targeted immunomodulators (including biologics and non-biologics) as defined below:

  Note: Intolerance does not require minimum dose or duration of use.

  - Oral aminosalicylates (e.g., mesalamine, sulfasalazine, olsalazine, balsalazide)
    - Signs and symptoms of persistently active disease, in the opinion of the investigator, during a current or prior course of at least 4 weeks of treatment with 2.4 g/day mesalamine (2 g/day if controlled release), 4 g/day sulfasalazine, 1 g/day olsalazine, or 6.75 g/day balsalazide.

- Corticosteroids
  - Signs and symptoms of persistently active disease despite a history of at least one induction regimen that included a dose equivalent to prednisone ≥ 40 mg/day PO for at least 3 weeks or intravenously for 1 week, OR
  - Unable to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily PO without recurrent active disease, OR
  - Signs and symptoms of persistently active disease during or after a course of at least 4 weeks of treatment with 9 mg/day budesonide or 5 mg/day beclomethasone, OR
  - Unable to taper oral budesonide to at or below 6 mg/day without recurrent active disease, OR
  - History of intolerance to corticosteroids (including, but not limited to Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, infection).
- Immunosuppressants
  - Signs and symptoms of persistently active disease despite a history of at least one 90 day regimen of oral azathioprine (AZA) (≥ 1.5 mg/kg/day) rounded to the nearest available tablet or half tablet formulation, 6 mercaptopurine (6MP) (≥ 1 mg/kg/day) rounded to the nearest available tablet or half tablet formulation (or a documented 6-thioguanine nucleotide [6-TGN] level of 230 – 450 pmol/8 × 108 red blood cell [RBC] count or higher on the current dosing regimen), or injectable methotrexate ([MTX] ≥ 15 mg/week subcutaneous [SC] or intramuscular [IM]), OR
  - History of intolerance to at least one immunosuppressant (including, but not limited to nausea/vomiting, abdominal pain, pancreatitis, liver enzyme abnormalities, lymphopenia, infection).

    Note: Oral MTX use is allowed during the study, however prior or current use of oral MTX is not sufficient for inclusion into the study unless these subjects were previously treated with aminosalicylates, corticosteroids, immunosuppressants (azathioprine [AZA] or 6-MP) or biologic and targeted immunomodulatory therapy and have inadequate response to, loss of response to or intolerance to the therapy as defined above.
- Targeted Immunomodulatory Therapy (including biologics and non-biologics) for UC
  - Signs and symptoms of persistently active disease despite a history of any 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 Weeks 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);

- Ustekinumab: At least an induction regimen of a single weight-based infusion dose of ustekinumab (260 mg [≤ 55 kg] or 390 mg [> 55 to ≤ 85 kg] or 520 mg [> 85 kg] IV);
- Tofacitinib: At least one 8-week induction regimen of tofacitinib (10 mg PO BID);
- Ozanimod: At least one 10-week induction regimen of ozanimod (0.92 mg PO once a day beginning with dose titration);
- Upadacitinib: At least one 8-week induction regimen of upadacitinib (45 mg PO once daily);
- Filgotinib (EU only): At least one 10-week induction regimen of filgotinib (200 mg PO once daily);
- Recurrence of symptoms during scheduled, maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify); or
- History of intolerance to at least one biologic agent or targeted immunomodulatory therapy (including, but not limited to infusion-related reaction, demyelination, congestive heart failure, infection).

- 24. Subject must have discontinued all biologic or non-biologic targeted immunomodulatory (TIM) therapies prior to the first dose of study drug. Subject must not have been treated with any of the approved biologic agents infliximab, adalimumab, golimumab, vedolizumab within 8 weeks prior to Baseline, OR with ustekinumab within 12 weeks prior to Baseline. Subjects must not have been treated with tofacitinib, filgotinib, upadacitinib, or ozanimod within 14 days 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.
- 25. Subject must not be on immunomodulators (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 30 days prior to Baseline.
- 26. Subject must not receive cyclosporine, tacrolimus, or mycophenolate mofetil (unless for ocular application) within 30 days prior to Baseline.
- 27. Subject must not receive oral aminosalicylates or oral UC-related antibiotics within 14 days prior to Baseline unless they have been on stable doses for greater than 14 days prior to Baseline.
- 28. Subject 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.
- 29. 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.

- 30. Subject must not receive treatment with rectal aminosalicylates or corticosteroids, other enemas/suppositories (other than required for endoscopy prep), within 14 days prior to the Screening endoscopy and during the remainder of the Screening Period.
- 31. Subject must not receive any parenteral nutrition within 30 days prior to Baseline.
- 32. Subject must not receive fecal microbial transplantation within 30 days prior to Baseline.
- 33. Subject must not receive IV anti-infectives within 30 days prior to Baseline visit or oral/intramuscular (IM) anti-infectives (non-UC-related) within 14 days prior to the Baseline visit.
- 34. Subject must not have been treated with any investigational drug within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug or is currently enrolled in another clinical study.
- 35. Subject must not have received systemic treatment with known cytochrome P450 (CYP)3A inhibitors or CYP3A inducers within 30 days of the Screening Period and through the end of the study.
- 36. Subject must not have received any live vaccine, with the exception of non-replicating live viral vaccines such as the Jynneos vaccine, within 30 days prior to the first dose of study drug, or expected need of live vaccination during study participation including at least 30 days after the last dose of study drug.

Contraception and Pregnancy

- 37. For all females of child-bearing 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.
- 38. Female subjects of childbearing potential must practice at least 1 protocol-specified method of birth control, that is effective from Study Day 1 through at least 30 days after the last dose of study drug. Female subjects of non-childbearing potential do not need to use birth control.
- 39. Female who is not pregnant or breastfeeding and is not considering becoming pregnant or donating eggs during the study or for approximately 30 days after the last dose of study drug.

5.2 Contraception

Contraception Requirements for Females

Subjects must follow 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:

  1. Premenopausal female with permanent sterility or permanent infertility due to one of the following:

- Permanent sterility due to a hysterectomy, bilateral salpingectomy, bilateral oophorectomy
- Non-surgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals.

2. Postmenopausal female
   - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
   - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level ≥ 30 IU/L.

- Females, of Childbearing Potential
  - Females of childbearing potential must avoid pregnancy while taking study drug and for at least 30 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 the sole sexual partner 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 use of concomitant therapies prescribed should be based on the local label.

5.3 Prohibited Medications and Therapy

During the study, the following are prohibited medications:

- 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;
- Oral or systemic cyclosporine, tacrolimus, or mycophenolate mofetil;
- Rectal therapy with any therapeutic enemas or suppositories, with the exception of those required for endoscopy;
- Parenteral nutrition;
- Fecal microbial transplant;
- Live replicating vaccines are not permitted (non-replicating live viral vaccines such as the Jynneos vaccine can be administered) during study participation and including up to 30 days after the last dose of study drug. Examples of live attenuated vaccines include, but are not limited to, the following:
  - Bacille Calmette-Guérin (BCG)
  - Zoster vaccine live (Zostavax®)
  - Measles-mumps-rubella or measles mumps rubella varicella
  - Monovalent live attenuated influenza A (intranasal)
  - Oral polio vaccine
  - Rotavirus
  - Seasonal trivalent live attenuated influenza (intranasal)
  - Smallpox
  - Monkeypox
  - Oral typhoid vaccine
  - Varicella (chicken pox)
  - Yellow fever
  - Dengue (Dengvaxia®)
- Any known CYP3A inhibitors (e.g., amiodarone, clarithromycin, fluconazole, ciprofloxacin, itraconazole, ketoconazole, quinidine, fluoxetine, and paroxetine) or inducers (e.g., carbamazepine, rifampin, phenobarbital, and phenytoin) of drug metabolizing enzymes within 30 days of the first dose of study drug and through the end of the study.
- Any investigational agent.

5.4 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded from the Screening Visit through the 30-Day Follow-Up Visit. Additionally, medications taken for UC since the date of diagnosis (based on subject recollection and available medical records) should be entered into the appropriate eCRF inclusive of the dates of first and last dose, maximum dosage taken, and route of administration.

Any questions regarding concomitant or prior therapy should be raised to the AbbVie emergency contact. Information regarding potential drug interactions with ABBV-668 are provided in the current ABBV-668 Investigator's Brochure.

Subjects must be able to safely discontinue any prohibited medications as specified in the eligibility criteria; where not specified, discontinuation must occur 5 half-lives or 4 weeks prior to initial study drug administration. Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

Subjects taking oral aminosalicylates, immunomodulators, oral corticosteroids, and/or UC-related antibiotics at Baseline must continue their concomitant treatment for the duration of the treatment period (through Week 16). Initiating and/or increasing doses of oral aminosalicylates, immunomodulators, oral corticosteroids, and/or UC-related antibiotics during the study is prohibited through Week 16. Decreasing doses of oral aminosalicylates, immunomodulators, oral corticosteroids, and/or UC-related antibiotics during the treatment period is prohibited, except in the event of moderate-to-severe treatment related toxicities and after discussion with the AbbVie TA MD.

COVID-19 Pandemic-Related Vaccination Guidance

Given the ongoing COVID-19 pandemic, selected non-live vaccines (e.g., messenger ribonucleic acid, non-replicating viral vector, protein subunit) to prevent SARS-CoV-2 infection may be administered during screening, the treatment period, or follow up, as long as components of the vaccine are not contraindicated.

The decision to receive a locally available vaccine should be based on local guidance and an individual discussion between the treating physician and the subject.

The potential impact of ABBV-668 on SARS-CoV-2 vaccination is unknown. Therefore, study drug should be administered as follows:

- The first dose of study drug (ABBV-668), when possible, is preferred to be given at least ± 7 days from the SARS-CoV-2 vaccine administration.

Note: The above guidance applies to all SARS-CoV-2 vaccine doses given as part of the complete vaccination course.

These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines in patients with UC and as more data are collected in real-world scenarios and clinical trials.

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine eCRF. Refer to the Operations Manual (Appendix F) for instructions on reporting any AEs associated with the COVID-19 vaccine.

5.5 Withdrawal of Subjects and Discontinuation of Study

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

- Serious or CTCAE grade 3 or higher clinically significant abnormal laboratory results or AEs considered related to study drug that necessitate discontinuation from the study, as determined by the investigator or the Sponsor.
- Malignancy or high-grade dysplasia of the gastrointestinal tract, except for localized nonmelanoma skin cancer (NMSC) or carcinoma in-situ of the cervix.
- Serious infections (e.g., sepsis) that cannot be adequately controlled within 2 weeks by antiinfective treatment or would put the subject at risk with continuation of the study drug as determined by the investigator in consultation with the AbbVie Therapeutic Area Medical Director.
- The investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- 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 is significantly noncompliant with study procedures, which would put the subject at risk for continued participation in the trial.

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 at any time, 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.

Safety Stopping Criteria

In addition to the individual stopping criteria, AEs, SAEs, laboratory abnormalities, ECG abnormalities, changes in vital signs, changes in physical examination findings (including neurological examinations), or changes in C-SSRS occurring in all enrolled subjects will be regularly reviewed by the sponsor study team to ensure appropriate subject safety.

Should two CTCAE grade 3 or higher treatment emergent adverse events of similar nature (with the exception of those related to the underlying disease) that are considered related to study drug by the investigator occur, the sponsor will convene with the appropriate sponsor safety review team to determine whether discontinuation or modification of the study is indicated.

Any changes to the study due to safety reasons will be promptly communicated to the investigators, subjects, and regulatory authorities.

In the event the study is terminated, all subjects will be asked to return for a PD visit and all subjects will receive a 30-day follow-up phone call after the last dose of study dose.

COVID-19 Pandemic-Related Acceptable Protocol Modification

During the COVID-19 pandemic, it has been 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 described in the protocol to ensure all acceptable mitigation steps have been explored.

Interruption/Discontinuation of Study Drug Due to COVID-19 Infection

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

- At least 10 days since first positive test result have passed in asymptomatic patients or at least 10 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.

Delays in study drug dosing due to the above COVID-19 testing guidance for subjects must be discussed with the AbbVie medical contact, along with the possibility of premature discontinuation from the study drug dosing period. Follow subsequent protocol Section 5.6 for subjects who discontinued study drug.

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

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

If a subject prematurely discontinues study participation (withdrawal of informed consent), 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, a 30-day follow-up phone call after

the last dose of study drug may be completed to ensure all treatment-emergent AEs/serious adverse events (SAE) 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.

All subjects should be referred to their treating physician for appropriate management for UC following completion of the study.

5.7 Study Drug

ABBV-668 will be taken PO BID beginning on Day 1 (Baseline) and should be taken at approximately the same time each day. Study drug can be taken with or without food. If subjects should forget to take their ABBV-668 dose at their regularly scheduled dosing time, they should take the forgotten dose as soon as they remember as long as it is at least 6 hours before their next scheduled dose. Otherwise, they should take the next dose at the next scheduled dosing time.

The subject will be instructed to return all drug containers (even if empty) to the study site personnel at each study visit. The study site personnel will document compliance.

AbbVie will provide study drug for ABBV-668. AbbVie-provided study drug should not be substituted or alternately sourced unless otherwise directed by AbbVie.

ABBV-668 will be packaged in bottles with quantities sufficient to accommodate the study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Site staff will complete all blank spaces on the label before dispensing to subjects. Study drug will only be used for the conduct of this study.

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

Information about ABBV-668 is presented in Table 1.

Table 1. Description of Study Drug

	Investigational Product
Investigational product name	ABBV-668
Active ingredient	ABBV-668
Mode/route of administration	Oral
Formulation	CCI [redacted]
Dosage Form	Capsule
Dose and units	CCI mg twice a day (BID)
Drug Preparation/packaging	65 count bottles
Frequency of administration	Open label
Storage conditions	Store between 2°C to 25°C (36°F to 77°F)

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 this single arm, open-label study.

5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic), the investigator is responsible for notifying IECs/IRBs, regulatory authorities (as applicable), and AbbVie.

5.10 Data Monitoring Committee

Study M21-446 is an open-label study and therefore no data monitoring committee is required.

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 damage or not working properly, or packaging issues.

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

Reporting will be done via electronic data capture (EDC). The date the product complaint details are entered into EDC and the form is saved represents the date reported to AbbVie. A back-up paper form will be provided for reporting complaints related to unassigned product or in the event of an EDC system issue. If a back-up paper form is used, the date the form is emailed to RD_PQC_QA@abbvie.com represents the date reported to AbbVie.

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

Medical Complaints/Adverse Events and Serious Adverse Events: ABBV-668

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

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations" such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an AE or not. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meets protocol-specific criteria (see Section 6.2 regarding toxicity management), and/or if the investigator considers them to be AEs.

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

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

been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If any of the following events are reported, then the following supplemental report must be completed.

Event	Supplemental Report
Cardiac events **Myocardial infarction or unstable angina** **Heart failure** **Cerebral vascular accident and transient ischemic attack** **Cardiovascular procedures (SAE Supplemental Procedure eCRF)**	Cardiovascular (Cardiac) Adverse Event eCRF MI and Unstable Angina Adverse Event eCRF Heart Failure Adverse Event eCRF Cerebral Vascular Accident and Transient Ischemic Attack AE eCRF Combination Thrombotic Event AE eCRF Arrhythmia 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**	Hepatic AE eCRF
Renal impairment **Renal dysfunction** **Renal failure** **Serum creatinine > 2.0 mg/dL**	Renal AE Renal Supplemental Local Labs Renal Supplemental Procedures Renal Abnormal Lab Value Supplemental
Herpes zoster infection	Herpes zoster eCRF
Any malignancy	Malignancy eCRF
Suspected anaphylactic/systemic hypersensitivity reactions	Hypersensitivity Reaction Signs and Symptoms eCRF
Confirmed COVID-19 infection	COVID-19 eCRF
TB infections	TB Supplemental eCRF
Any death	Death eCRF

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance as a serious adverse event (SAE) within 24 hours of the site being made aware of the SAE (refer to Section 4.2 of the Operations Manual 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.

All adverse events reported from the time of study drug administration until 30 days after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, study procedure-related serious and nonserious adverse events will be collected from the time the subject signs the study-specific informed consent.

The following definitions will be used for Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Reaction (SUSAR):

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

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

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

Safety Topics of Interest

The following safety topics of interest will be monitored during the study:

- Serious infections, opportunistic infections, fungal infection, and tuberculosis (TB);
- Malignancies;
- Hypersensitivity reactions;
- Psychiatric adverse reactions such as suicidal ideations or attempt, abnormal/vivid dreams, or nightmares; and
- Neurological events.

Adverse Event Severity and Relationship to Study Drug

The investigator will rate the severity of each AE according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 5.0).

The investigator will use the following definitions to assess the relationship of the AE 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 AE, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 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 30 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 toxicity management of the AEs including safety topics of interest, consists of safety monitoring (review of AEs on an ongoing basis), and, if applicable, interruption of study drug dosing with appropriate clinical management and/or discontinuation of the subjects from study drug. 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 a serious opportunistic infection. A subject who develops a new serious 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.

Malignancy: Subjects who develop malignancy other than nonmelanoma skin cancer (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.

Psychiatric Symptoms: Subjects who develop new onset suicidal ideations or attempt should be discontinued from study drug. For subjects who develop other clinically significant psychiatric symptoms considered related to study drug by the investigator (for example, abnormal/vivid dreams and nightmares), study drug interruption or discontinuation should be considered if the symptoms are severe (CTCAE psychiatric disorders Grade 3 or higher), persistent or worsening.

Neurologic Symptoms: Subjects with new onset related seizure(s) should be discontinued from study drug and should undergo appropriate prompt diagnostic evaluation and intervention. For subjects who develop clinically significant new onset tremor or other neurological condition considered related to study drug by the investigator, study drug interruption or discontinuation should be considered if the symptoms are severe (CTCAE Grade 3 or higher), persistent or worsening.

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.

Laboratory parameter toxicity guidelines are presented in Table 2.

Table 2. Laboratory Parameter Toxicity Guidelines

Laboratory Parameters Toxicity Guidelines		
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.
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 immediately 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 immediately 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 along with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).	Interrupt study drug immediately and redraw lab with a new sample. If confirmed ALT or AST > 3 × ULN by repeat testing with new sample along with 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.
	ALT or AST > 3 × ULN and either a total bilirubin > 2 × ULN or an international normalized ratio (INR) > 1.5	Interrupt study drug immediately and redraw lab with a new sample. If ALT or AST > 3 × ULN is confirmed and total bilirubin > 2 × ULN or international normalized ratio (INR) > 1.5, discontinue study drug and complete supplemental hepatic eCRF.
	Subjects who are HBc Ab+ and HBV DNA negative at Screening who develop: ALT or AST > 5 × ULN OR ALT or AST > 3 × ULN, if an alternative cause is not readily identified	Interrupt study drug immediately 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.

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 Primary Analysis will be conducted after all subjects have either completed the Week 8 assessment or withdrawn from the study. The final analysis will be conducted after all subjects have either withdrawn from the study or completed the Week 16 assessment and the safety Follow-up Visit.

7.2 Definition for Analysis Populations

The ITT Population consists of all subjects who received at least 1 dose of study drug. The ITT Population will be used for all efficacy and baseline analyses.

The Safety Population consists of all subjects who received at least 1 dose of study drug. The Safety Population will be used for all safety analyses.

7.3 Handling Potential Intercurrent Events for the Primary and Secondary Endpoints

For both the primary and secondary endpoints, data collected will be used regardless of premature discontinuation of study drug. Subjects will be considered as non-responders after the start of rescue medication (initiation or dose escalation of UC-related corticosteroids).

7.4 Statistical Analyses for Efficacy

Summary and Analysis of the Primary Endpoint

The Primary Analysis will be performed after all subjects have either completed the Week 8 assessment or withdrawn from the study. The final analysis will be conducted after all subjects have either withdrawn from the study or completed the Week 16 assessment and the safety Follow-up Visit.

The primary efficacy endpoint is achievement of endoscopic improvement at Week 8.

Analysis of the primary efficacy endpoint will be conducted on the ITT Population. Comparison of the primary efficacy endpoint will be performed between the ABBV-668 treatment group and historical placebo group using the Bayesian approach with prior distribution obtained from meta-analysis for the historical placebo data, and non-informative prior for the ABBV-668 treatment group. The placebo prior will be determined based on placebo data from similar trials available before the Primary Analysis database lock. The posterior probability of rate difference > 0 given data will be calculated. The mean difference and the corresponding 95% credible interval will be provided.

For the analyses of the primary and secondary endpoints, the primary approach for handling missing data will be Non-Responder Imputation incorporating multiple imputation (NRI-MI). Subjects with missing data will be counted as non-responders, except when missing at random can be reasonably assumed, which will be handled by multiple imputation. For example, missing due to COVID-19 logistical restriction or due to political conflict will be handled by multiple imputation.

Summary and Analysis of Secondary Endpoints

Similar analysis described above comparing ABBV-668 treatment group and historical placebo group will be performed for the secondary endpoints.

7.5 Statistical Analyses for Safety

Safety analyses will be performed using the Safety Population, as defined in Section 7.2. Safety will be assessed by AEs, physical examination (including neurological exams), C-SSRS evaluation, laboratory assessments, and vital signs. Missing safety data will not be imputed. Details for each safety endpoint analysis will be provided in the SAP.

Treatment-emergent adverse events (TEAEs) will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and by preferred term (PT) for the treatment group. Summaries of SAEs, deaths, AEs leading to discontinuation and AESIs will be provided as well. For selected laboratory and vital signs parameters, mean change from Baseline and percentage of subjects with evaluations meeting the criteria for pre-defined potentially clinically significant (PCS) values will be summarized.

7.6 Interim Analysis

Interim analyses may be performed to provide information for future study decisions.

7.7 Overall Type I Error Control

Overall Type I error control is not planned in this Phase 2a study.

7.8 Sample Size Determination

The planned sample size is approximately 40 subjects.

A meta-analysis for historical placebo data from UC studies for tofacitinib (OCTAVE1/2), upadacitinib (Phase 2b and Phase 3; data on file), and ustekinumab (UNIFI) gives CCI [redacted] improvement rate at Week 8. A prior placebo distribution that matches this overall rate and has a variance close to the variance of the rate estimate from CCI [redacted] The prior distribution for the ABBV-668 treatment group is set to Jeffreys non-informative prior *Beta* (0.5, 0.5). Assuming a response rate increase of 30% in the ABBV-668 group compared to historical placebo, a sample size of 40 subjects will provide more than 90% probability to demonstrate that the posterior probability of rate difference (ABBV-668 vs. external placebo) > 0 is larger than 90%. The external

placebo response may be updated if new placebo data from similar trials become available before the Primary Analysis database lock.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board

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, 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). During the COVID-19 pandemic and geo-political conflict in Ukraine and surrounding impacted regions, remote data review/verification 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 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 START AND COMPLETION OF THE STUDY

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

The end-of-study is defined as the date of end of study participation by the last subject in the last country where the study was conducted.

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APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
6-TGN	6-thioguanine nucleotide
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
Ag	antigen
ALT	alanine transaminase
AST	aspartate transaminase
AZA	azathioprine
BID	twice a day
BM	biomarker
BP	blood pressure
CD	Crohn's disease
CFR	Code of Federal Regulations
CL/F	apparent clearance or apparent oral clearance
CRP	C-reactive protein
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
CYP3A	cytochrome P450 3A isoform subfamily
DNA	deoxyribonucleic acid
DTP	direct-to-patient
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EIM	extraintestinal manifestation
ESS	Endoscopic Subscore
EU	European Union

Abbreviation	Definition
FACIT	Functional Assessment of Chronic Illness Therapy
FCP	fecal calprotectin
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GR	glucocorticoid receptor
HAQ-DI	Health Assessment Questionnaire Disability Index
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
hs-CRP	high sensitivity C-reactive protein
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IBD-U	inflammatory bowel disease-unclassified
ICH	International Council for Harmonisation
IEC	independent ethics committee
IEC/IRB	Independent Ethics Committee/Institutional Review Board
IHC	immunohistochemistry
IM	intramuscular
IMP	Investigational Medicinal Product
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
ITT	Intent-to-Treat
IU	international unit
IUD	intrauterine device
IUS	Intrauterine hormone-releasing system
IV	intravenous
JAK	Janus kinase
LDA	low disease activity
MA	marketing authorization
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid

Abbreviation	Definition
MTX	methotrexate
NAb	neutralizing antibody
NCI	National Cancer Institute
NCS	not clinically significant
NMSC	nonmelanoma skin cancer
NRI	Non-Responder Imputation
NRI-MI	Non-Responder Imputation incorporating multiple imputation
OR	odds ratio
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PCS	potentially clinically significant
PD visit	Premature Discontinuation visit
PGA	Physicians' Global Assessment
PK	Pharmacokinetics
PO	orally
PRO	patient-reported outcome
PT	preferred term
QOL	quality of life
QTcF	QT interval corrected for heart rate using Fridericia's formula
RA	regulatory affairs
RBC	red blood cell
RBS	Rectal Bleeding Subscore
RIPK1	Receptor interacting serine/threonine-protein kinase 1
RNA	ribonucleic acid
RSI	Reference Safety Information
S1P	sphingosine-1-phosphate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAR	serious adverse reaction
SC	subcutaneous
SFS	Stool Frequency Subscore
SOC	system organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction

Abbreviation	Definition
TB	tuberculosis
TEAE	treatment-emergent adverse event
TLR	toll-like receptor
TNF	tumor necrosis factor
UC	ulcerative colitis
ULN	upper limit of normal
V/F	apparent volume of distribution

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M21-446: A Single-Arm, Open-Label Study to Evaluate the Efficacy and Safety of ABBV-668 in Subjects with Moderate to Severe Ulcerative Colitis

Protocol Date: 03 March 2023

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and local laws and 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 (within one (1) calendar day to AbbVie, the ethics committees/institutional review boards (as required) and other appropriate individuals (e.g., coordinating investigator, institution director):
    - All changes in the research activity and all unanticipated problems involving risks to human subjects or others
    - Any departure from relevant clinical trial law or regulation, GCP, or the trial protocol that has the potential to affect the following:
        - Rights, safety, physical or mental integrity of the subjects in the clinical trial
        - Scientific value of the clinical trial, reliability or robustness of data generated
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
PPD		Clinical Study Leadership Clinical Development Immunology Statistics

APPENDIX D. ACTIVITIES SCHEDULE

The following table shows the required activities for each visit. The individual activities are described in detail in the **Operations Manual** (Appendix F). Allowed modifications due to COVID-19 and/or the geo-political conflict in Ukraine and surrounding impacted regions are detailed in the Operations Manual.

Activity	Screening	16 Week Open Label Treatment Period (± 3 days)									PD Visit (± 3 days)	Unscheduled Visit	30- Day Follow-Up (± 7 days)
		Baseline	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16			
INTERVIEWS & QUESTIONNAIRES													
Informed consent	✓												
Eligibility criteria	✓	✓											
Medical/surgical history	✓	✓											
Prior and concomitant medication	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
IBDQ		✓				✓				✓			
FACIT-F		✓				✓				✓			
C-SSRS	✓	✓				✓				✓	✓		
PGIS		✓	✓	✓	✓	✓	✓	✓	✓	✓			
PGIC			✓	✓	✓	✓	✓	✓	✓	✓			
Monitor Adverse Events	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Latent TB risk assessment form	✓												
Review and document continued compliance with pregnancy avoidance recommendations in the source records as appropriate	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Provide stool kit	✓	✓			✓		✓		✓				
Dispense Daily Subject Diary	✓												
Daily Subject Diary review		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
LOCAL LABS & EXAMS													
Endoscopy	✓					✓				✓			
Chest X-Ray	✓												

Activity	Screening	16 Week Open Label Treatment Period (± 3 days)									PD Visit (± 3 days)	Unscheduled Visit	30- Day Follow-Up (± 7 days)
		Baseline	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16			
12-lead ECG	✓			✓						✓	✓		
Height	✓												
Weight	✓	✓				✓				✓	✓		
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Physical examination	✓	✓				✓				✓	✓		
Neurological examination	✓	✓	✓	✓	✓	✓		✓		✓	✓		
Urine pregnancy test (females of childbearing potential)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
CENTRAL LABS													
Estimated glomerular filtration rate (eGFR)	✓												
Optional biologic drug level	✓												
Serum pregnancy test (females of childbearing potential)	✓												
FSH (if needed to confirm postmenopausal status)	✓												
QuantiFERON-TB Gold test (and/or local PPD skin test)	✓												
hs-CRP, clinical chemistry, hematology (CBC)	✓	✓	✓	✓		✓		✓		✓	✓		
Urinalysis	✓									✓	✓		
Lipid test	✓									✓	✓		
HBV, HCV, and HIV Screening	✓												
Intestinal biopsies: histology	✓					✓				✓			
Stool sample (C. difficile toxin)	✓												

Activity	Screening	16 Week Open Label Treatment Period (± 3 days)									PD Visit (± 3 days)	Unscheduled Visit	30- Day Follow-Up (± 7 days)
		Baseline	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16			
Stool sample (Fecal calprotectin)		✓	✓			✓		✓		✓	✓		
Blood samples for CCI and ABBV-668 PK assays		✓	✓		✓	✓				✓	✓		
BIOMARKER RESEARCH SAMPLES													
RIPK1 Target Engagement (Two baseline samples needed)		✓	✓	✓		✓				✓			
Pathway Engagement/PD: CCI (Two baseline samples needed)		✓	✓	✓		✓				✓			
PBMC		✓				✓				✓			
Serum		✓	✓	✓		✓				✓	✓		
Plasma		✓	✓	✓		✓				✓	✓		
Stool		✓	✓			✓		✓		✓	✓		
Whole blood PaxGene RNA		✓	✓	✓		✓				✓	✓		
Optional biomarker sample: Whole blood DNA (Baseline or anytime during study)		✓											
Intestinal biopsies: RNAlater	✓					✓				✓			
Intestinal biopsies: FFPE for MOA (e.g., CCI	✓					✓				✓			
TREATMENT													
Adapted Mayo/Full Mayo Score		✓				✓				✓			
Partial Mayo/Adapted Partial Mayo Score		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Study drug dispensing/administration		✓		✓		✓		✓					

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	25 August 2022
Administrative Change 1	13 October 2022

The purpose of Version 2.0 is to amend subject safety and enrollment criteria and to clarify the statistical estimand, as well as to correct minor clerical errors:

1. Restated the withdrawal criteria related to clinically significant laboratory results or adverse events (AEs) to specify serious or CTCAE grade 3 or higher clinically significant results or AEs that are considered related to study drug and necessitate discontinuation from the study (Protocol Section 5.5).
2. Added safety stopping criteria to convene with the appropriate sponsor safety review team to determine whether discontinuation or modification of the study is indicated (Protocol Section 5.5).
3. Changed the neurological adverse event of special interest from "Neurologic: New onset of seizure and/or tremor adverse reactions" to "Neurological Events" (Protocol Section 6.1).
4. Added neurological examinations at the Screening, Baseline, Week 2, Week 4, Week 6, Week 8, Week 12, Week 16, and premature discontinuation visits (Protocol Appendix D and Operations Manual Section 2.1 and Section 3.11).
5. Added that all subjects should be referred to their treating physician for appropriate management for ulcerative colitis following completion of the study (Protocol Section 5.6).
6. Added that normal renal function (i.e., estimated glomerular filtration rate of ≥ 90 mL/min calculated by the Cockcroft-Gault equation) is required at the Screening visit (Protocol Section 5.1).
7. Revised the estimand definition and intercurrent events handling for the primary and secondary endpoints (Protocol Section 3.1 and Section 7.3).
8. Added how to score the rectal bleeding subscore of the Mayo Score (Operations Manual Section 7.2).
9. Added that at unscheduled visit a physical examination (including neurological examination) may be performed at the investigator's discretion (Operations Manual Section 2.1).

APPENDIX F. OPERATIONS MANUAL

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Operations Manual for Clinical Study Protocol M21-446

Moderate to Severe Ulcerative Colitis: A Single-Arm, Open-Label Study to Evaluate the Efficacy and Safety of ABBV-668

SPONSOR:	AbbVie	ABBVIE INVESTIGATIONAL PRODUCT:	ABBV-668

FULL TITLE: A Single-Arm, Open-Label Study to Evaluate the Efficacy and Safety of ABBV-668 in Subjects with Moderate to Severe Ulcerative Colitis

1 CONTACTS

Sponsor/ Emergency Medical Contact	PPD MD, MSc AbbVie 1 North Waukegan Road North Chicago, Illinois 60064 EMERGENCY 24-hour Number: +1 (973) 784-6402	Office: Mobile: Email: PPD
Safety Concerns	Immunology Safety Team 1 North Waukegan Road North Chicago, IL 60064	Toll Free: +1 (833) 942-2226 Email: SafetyManagement_immunology@abbvie.com
SAE Reporting outside of EDC	Email: PPDINDPharmacovigilance@abbvie.com	Fax: +1 (847) 938-0660
Protocol Deviations and Product complaints	PPD AbbVie PPD 1 North Waukegan Road North Chicago, IL 60064	Phone: Email: PPD
Certified Clinical Lab	LabCorp Laboratory Services Limited Partnership 8211 SciCor Drive Indianapolis, IN 46214 United States	Phone: +1 (317) 271-1200
Central Imaging	Alimentiv, Inc. 100 Dundas Street, Suite 200 London, Ontario, Canada N6A 5B6	Phone: +1 (226) 270-7868
PK Sample Lab	AbbVie Sample Receiving 150 S. Northpoint Blvd. Waukegan, IL 60085 United States	Phone: +1 (847) 937-0889 Fax: +1 (847)938-9898 Email: sample.receiving@abbvie.com

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2 PROTOCOL ACTIVITIES BY VISIT

State of Emergency or Pandemic-Related Acceptable Protocol Modifications

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. 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.

The Screening and Baseline visits should be completed onsite.

Out of Window Visits Due to Cases of State of Emergency or Pandemic Situations:

If a visit can be performed onsite but out-of-window, consult the sponsor to determine if the out-of-window visit is permitted.

2.1 Individual Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit.

Activities are grouped by category (Interview, Exam, etc.). Further information about each activity is provided in Section 3.

SCREENING:

INTERVIEW	• Informed consent • Medical/surgical history • Evaluation of eligibility criteria • Review compliance with pregnancy avoidance recommendations as appropriate • Provide stool kits	• Serious adverse events (SAEs) and protocol-related nonserious adverse events (AEs) • Prior and concomitant medications • Latent tuberculosis (TB) assessment form
PRO	• Dispense subject diary	• Columbia-Suicide Severity Rating Scale (C-SSRS)
EXAM	• Height • Weight • 12-lead electrocardiogram (ECG) • Chest X-Ray, if applicable	• Vital signs • Physical examination • Endoscopy • Neurological examination
LAB	• TB screen (Purified Protein Derivative [PPD] skin test)	
CENTRAL LAB	• Hepatitis B, Hepatitis C screening and Human immunodeficiency virus (HIV) test • Stool sample (C. difficile toxin) • TB screen (QuantiFERON-TB Gold Test) • SARS-CoV-2 molecular test, if applicable • Urinalysis • Lipid test • Estimated glomerular filtration rate (eGFR)	• Optional biologic drug level • Serum pregnancy test[a] • Follicle stimulating hormone (FSH), if needed to confirm postmenopausal status • Chemistry and hematology • High sensitivity C-reactive protein (hs-CRP) • Intestinal biopsies- histology • Intestinal biopsies- RNAlater for biomarker (BM) analysis • Intestinal biopsies- FFPE for MOA (e.g., CCI [redacted])

Note: Refer to Section 8.2 for the minimum numbers of days necessary for stool frequency subscore (SFS) and rectal bleeding subscore (RBS) calculation. The Screening period (30 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).

Baseline (DAY 1):

INTERVIEW	• Medical/surgical history • Evaluation of eligibility criteria • Review compliance with pregnancy avoidance recommendations as appropriate • Provide stool kits	• AE assessment • Prior and concomitant medications assessment • Review subject diary
PRO	• Inflammatory Bowel Disease Questionnaire (IBDQ) • Functional Assessment of Chronic Illness (FACIT-F)	• C-SSRS • Patient Global Impression Scale (PGIS)
EXAM	• Weight • Vital signs	• Physical examination • Neurological examination
LAB	• Urine pregnancy test[b]	
CENTRAL LAB[c]	• Chemistry and hematology • hs-CRP • Blood samples for CCI and ABBV-668 PK assays • RIPK1 Target Engagement (2 baseline samples needed) • Pathway Engagement/PD: CCI (2 baseline samples needed) • PBMC for BM analysis	• Serum for BM analysis • Plasma for BM analysis • Stool sample for BM analysis[d] • Stool sample for Fecal calprotectin (FCP)[d] • Whole blood PaxGene RNA for BM analysis • Optional Whole blood DNA for BM analysis (Baseline or anytime during study)
TREATMENT	• Partial Mayo/Adapted Partial Mayo Score • Adapted Mayo/Full Mayo Score	• Study drug dispensing/administration

WEEK 2:

INTERVIEW	• Prior and concomitant medications assessment • AE assessment	• Review compliance with pregnancy avoidance recommendations as appropriate • Review subject diary
PRO	• PGIS	• PGIC
EXAM	• Vital signs	• Neurological examination
LAB	• Urine pregnancy test[b]	
CENTRAL LAB	• Chemistry and hematology • hs-CRP • Stool sample for FCP[d] • Blood samples for CCI and ABBV-668 PK assays • RIPK1 Target Engagement	• Pathway Engagement/PD: CCI • Serum for BM analysis • Plasma for BM analysis • Stool sample for BM analysis[d] • Whole blood PaxGene RNA for BM analysis
TREATMENT	• Partial Mayo/Adapted Partial Mayo Score	

WEEK 4:

INTERVIEW	• Prior and concomitant medications assessment • AE assessment	• Review compliance with pregnancy avoidance recommendations as appropriate • Review subject diary
PRO	• PGIS	• PGIC
EXAM	• Vital signs • Neurological examination	• ECG
LAB	• Urine pregnancy test[b]	
CENTRAL LAB	• Chemistry and hematology • hs-CRP • RIPK1 Target Engagement	• Pathway Engagement/PD: CCI • Serum for BM analysis • Plasma for BM analysis • Whole blood PaxGene RNA for BM analysis
TREATMENT	• Partial Mayo/Adapted Partial Mayo Score	• Study drug dispensing/administration

WEEK 6:

INTERVIEW	• Prior and concomitant medications assessment • AE assessment • Provide stool kits	• Review compliance with pregnancy avoidance recommendations as appropriate • Review subject diary
PRO	• PGIS	• PGIC
EXAM	• Vital signs	• Neurological examination
LAB	• Urine pregnancy test[b]	
CENTRAL LAB	• Blood samples for CCI and ABBV-668 PK assays	
TREATMENT	• Partial Mayo/Adapted Partial Mayo Score	

WEEK 8:

INTERVIEW	• Prior and concomitant medications assessment • AE assessment	• Review compliance with pregnancy avoidance recommendations as appropriate • Review subject diary
PRO	• IBDQ • FACIT-F • C-SSRS	• PGIS • PGIC
EXAM	• Endoscopy • Weight • Vital signs	• Physical examination • Neurological examination
LAB	• Urine pregnancy test[b]	
CENTRAL LAB	• Chemistry and hematology • hs-CRP • Blood sample for CCI and ABBV-668 PK assays • RIPK1 Target Engagement • Pathway Engagement/PD: CCI PBMC • PBMC for BM analysis • Serum for BM analysis • Plasma for BM analysis	• Stool sample for BM analysis[d] • Stool sample for FCP[d] • Whole blood PaxGene RNA for BM analysis • Intestinal biopsies- histology • Intestinal biopsies- RNAlater for BM analysis • Intestinal biopsies- FFPE for MOA (e.g., CCI
TREATMENT	• Partial Mayo/Adapted Partial Mayo Score • Adapted Mayo/Full Mayo Score	• Study drug dispensing/administration

WEEK 10:

INTERVIEW	• Prior and concomitant medications assessment • AE assessment • Provide stool kits	• Review compliance with pregnancy avoidance recommendations as appropriate • Review subject diary
PRO	• PGIS	• PGIC
EXAM	• Vital signs	
LAB	• Urine pregnancy test[b]	
TREATMENT	• Partial Mayo/Adapted Partial Mayo Score	

WEEK 12:

INTERVIEW	• Prior and concomitant medications assessment • AE assessment	• Review compliance with pregnancy avoidance recommendations as appropriate • Review subject diary
PRO	• PGIS • PGIC	
EXAM	• Vital signs	• Neurological examination
LAB	• Urine pregnancy test[b]	
CENTRAL LAB	• Chemistry and hematology • hs-CRP •	• Stool sample for BM analysis[d] • Stool sample for Fecal calprotectin (FCP)[d]
TREATMENT	• Partial Mayo/Adapted Partial Mayo Score	• Study drug dispensing/administration

WEEK 14:

INTERVIEW	• Prior and concomitant medications assessment • AE assessment • Provide stool kits	• Review compliance with pregnancy avoidance recommendations as appropriate • Review subject diary
PRO	• PGIS	• PGIC
EXAM	• Vital signs	
LAB	• Urine pregnancy test[b]	
TREATMENT	• Partial Mayo/Adapted Partial Mayo Score	

WEEK 16:

INTERVIEW	• Prior and concomitant medications assessment • AE assessment	• Review compliance with pregnancy avoidance recommendations as appropriate • Review subject diary
PRO	• IBDQ • FACIT-F • C-SSRS	• PGIS • PGIC
EXAM	• Endoscopy • Weight • Vital signs	• Physical examination • ECG • Neurological examination
LAB	• Urine pregnancy test[b]	
CENTRAL LAB	• Chemistry and hematology • hs-CRP • Blood sample for CCI and ABBV-668 PK assays • RIPK1 Target Engagement • Pathway Engagement/PD: CCI • PBMC for BM analysis • Urinalysis • Lipid test	• Serum for BM analysis • Plasma for BM analysis • Stool sample for BM analysis[d] • Stool sample for FCP[d] • Whole blood PaxGene RNA for BM analysis • Intestinal biopsies: histology • Intestinal biopsies- RNAlater for BM analysis • Intestinal biopsies- FFPE for MOA (e.g., CCI
TREATMENT	• Partial Mayo/Adapted Partial Mayo Score	• Adapted Mayo/Full Mayo Score

PD Visit:

INTERVIEW	• Prior and concomitant medications assessment • AE assessment	• Review compliance with pregnancy avoidance recommendations as appropriate • Review subject diary
PRO	• C-SSRS	
EXAM	• Weight • Vital signs	• Physical Examination • ECG • Neurological examination
LAB	• Urine pregnancy test[b]	
CENTRAL LAB	• Chemistry and hematology • hs-CRP • Urinalysis • Lipid test • Stool sample for FCP[d] • Blood samples for CCI and ABBV-668 PK assays	• Serum for BM analysis • Plasma for BM analysis • Stool sample for BM analysis[d] • Whole blood PaxGene RNA for BM analysis
TREATMENT	• Partial Mayo/Adapted Partial Mayo Score	

Unscheduled Visit:

INTERVIEW	• Prior and concomitant medications assessment • AE assessment	• Review compliance with pregnancy avoidance recommendations as appropriate • Review subject diary
EXAM	• Vital signs	
TREATMENT	• Partial Mayo/Adapted Partial Mayo Score	

Note: During Unscheduled Visits, blood and urine samples may be obtained for the laboratory tests listed in Section 3.13 or for other tests at the investigator's discretion; physical examination (including neurological examination) may be performed at the investigator's discretion.

30-Day Follow-Up:

INTERVIEW	• Prior and concomitant medications assessment • AE assessment	• Review compliance with pregnancy avoidance recommendations as appropriate
LAB	• Urine pregnancy test[b]	

Footnotes for protocol activities:

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

b. Urine pregnancy test will be performed locally as indicated in the table for all females of childbearing potential.

c. Laboratory 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.

d. For the visit when endoscopy will be conducted, stool sample should be collected prior to bowel preparation and should be brought 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.

Note: Urinalysis, chemistry, hematology, hs-CRP, and FCP may be collected at any scheduled and unscheduled visits than indicated in the table if they are warranted by the investigator.

3 STUDY PROCEDURES

3.1 Study Subject Information and Informed Consent

The investigator or his/her representative will explain the nature of the study to the subject, the benefits and risks anticipated from participation in the study and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject or any medications being discontinued by the subject in order to participate in this study, the informed consent statement will be reviewed, signed, and dated by the subject or their legally authorized representative, 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 because of participation in the study can be found in the informed consent form.

Optional biomarker research samples will only be collected if the subject has voluntarily signed and dated a written consent form for this testing that has been approved by an IRB/IEC, after the nature of

the testing has been explained and the subject has had an opportunity to ask questions. The written consent may be part of the main consent form, or it may be a separate form. If the subject does not consent to the optional biomarker sample collection, it will not impact the subject's participation in the study.

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

3.2 Medical History/Concomitant Medications

A complete medical history including demographics, history of tobacco, alcohol, and drug use will be taken at screening. The subject's medical history will be updated at the 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.

State of Emergency or Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, subject visits may be conducted via phone or video conference. In these situations, concomitant medications may be obtained by the subject or caregiver as needed.

3.3 Adverse Event Assessment

Please refer to Section 4.1.

3.4 Patient-Reported Outcomes

Subjects will complete the self-administered patient-reported outcome (PRO) instrument (when allowed per local regulatory guidelines). Subjects should be instructed to follow the instructions provided with the instrument and to provide the best possible response to each item. Site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Subjects who are functionally unable to read any of the instruments may have site personnel read the questionnaire to them. Site personnel will encourage completion of the instrument at all specified visits and will ensure that a response is entered for all items.

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 provided by the technology vendor Medidata. 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, Medidata, 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 Medidata.

Internet access to the ePRO data will be provided by Medidata 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.

All PRO assessments should be completed at the specified study visit prior to clinical assessments, dosing, drug administration, or any other procedure. The only exception should be the patient daily diary which is collected daily, not at the study visit.

The subject should complete the questionnaire before site personnel perform any clinical assessments and before any interaction with site personnel has occurred to avoid biasing the subject's response.

Diary Based

The ePRO data (bowel urgency, abdominal pain, interrupted sleep due to UC, nocturnal bowel movement, tenesmus, fecal incontinence, use of medications used for endoscopy preparation, and anti-diarrheal medication) 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 vendor 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 Medidata. 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 rectal bleeding subscore (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 = stool has streaks of blood, 2 = stool has more than just streaks of blood 3 = blood alone passed). 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 the following categories: none, mild, moderate or severe.

Bowel Urgency

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

Tablet Based

Information 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 Medidata. 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.

Inflammatory Bowel Disease Questionnaire

The Inflammatory Bowel Disease Questionnaire (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 categorized 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.

Functional Assessment of Chronic Illness Therapy – Fatigue

The Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) is a 13-item instrument designed to assess fatigue-related symptoms and impacts on daily functioning and activities. The instrument includes items such as tiredness, weakness, listlessness, lack of energy, and the impact of these feelings on daily functioning (e.g., sleeping, and social activities); the recall period for each item is 7 days. Item scores range from 0 ("not at all") to 4 ("very much"), and the total score ranges from 0 to 52; lower scores indicate greater fatigue.

Patient Global Impression of Change

The Patient Global Impression of Change (PGIC) is a self-administered 1-item instrument that assesses patient-perceived change in overall symptoms due to UC. The PGIC asks subjects to rate overall improvement in their UC symptoms since start of the treatment. Subjects rate their change utilizing the following 5-point Likert scale: "Much better," "A little better," "No change," "A little worse," "Much worse." The recall period is "since you started taking the study medication."

Patient Global Impression of Severity

The Patient Global Impression of Severity (PGIS) is a self-administered 1-item instrument that assesses patient-perceived severity of overall symptoms due to UC. Subjects rate their change in overall severity of UC symptoms over the past week utilizing the following 5-point Likert scale: "None," "Mild," "Moderate," "Severe," "Very severe."

Columbia – Suicide Severity Rating Scale

The Columbia – Suicide Severity Rating Scale (C-SSRS) is a systematically administered instrument developed to track suicidal adverse events across a treatment study. The instrument is designed to assess suicidal behavior and ideation, track and assess all suicidal events, as well as the lethality of attempts. Additional features assessed include frequency, duration, controllability, reason for ideation, and deterrents. The C-SSRS is considered a low burden instrument as it takes less than 5 minutes to administer. The C-SSRS evaluation prior to initial dosing will serve as the baseline for clinical assessment. Subject must not have current suicidal ideation with plan within the prior month, via answering "yes" to questions 4 or 5 (after administration of the entire questionnaire) to the suicidal ideation portion of the C-SSRS completed at Screening and Baseline, or any history of suicide attempt(s) within the last 2 years.

The study physician will be immediately informed of any current active suicidal ideations and evaluate the subject. The AbbVie Therapeutic Area Medical Director will also be informed. Appropriate steps should be taken by the study physician to protect the subject anytime throughout the study including the screening period, refer to toxicity management instructions (see Section 6.2 of the protocol), including referral for appropriate psychiatric care. Any such subject at Screening or at Baseline will also be excluded from the study.

COVID-19 Pandemic-Related Protocol Modifications

Due to the COVID-19 pandemic, if an event occurs leading to difficulties in performing protocol-specified administration of PRO assessments, AbbVie may engage with site personnel to deploy alternate methods for assessments (e.g., phone contacts or virtual site visits). In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC.

3.5 Pharmacokinetic Sampling

Blood samples for pharmacokinetic analysis will be collected at visits specified in Section 2.1.

Starting 3 days prior to each clinical site visit, subjects are advised to take the study drug dose at the time that matches their scheduled visit time at the clinical site. Following the clinical visit, subjects may continue taking study drug dose according to their regular schedule.

On the day of the study visit, subjects will take their ABBV-668 dose at the clinical site and blood samples for pharmacokinetic assessments should be collected within specified time intervals at each visit as follows:

- At Baseline, between 0.5 and 8 hours post dosing;
- At Week 2, pre-dose, and between 0.5 and 8 hours post dosing;
- At Week 6, pre-dose, between 0.5 and 2 hours, between 2 and 4 hours, and between 4 and 8 hours post dosing;
- At Week 8, pre-dose, and between 0.5 and 8 hours post dosing;
- At Week 16, pre-dose; and
- Premature discontinuation (PD), at any time during the visit.

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

3.6 Biomarker Sampling

Biospecimen (blood, serum, plasma, PBMC, stool and tissue biopsy) samples will be collected for biomarker research at the visits specified in Section 2.1. Assessments may include, but are not limited to, biomarkers related to the pathway(s) targeted by the study drug, or those believed to be related to the disease(s) being studied. The information learned from analyzing these samples may be used to investigate factors influencing response to treatment, scientific questions related to UC and/or in the development of new therapies and diagnostic tests. For RIPK1 target engagement analysis, 2 blood samples will be collected at BL and 1 sample will be taken at all other visits. For pathway engagement/PD analysis CCI , 2 serum samples will be collected at BL and 1 sample will be taken at all other visits. Biopsies for biomarker analysis will be collected when performing endoscopies. Eight biopsies will be taken at each visit with endoscopy for biomarker research. Four biopsies will be for histologic assessment: 2 biopsies that represent areas of average degree of inflammation and 2 biopsies that represent areas of the most inflamed intestinal tissue (one of which will be assessed by central review). Two biopsies will be utilized for gene expression analysis: 1 that represents average inflammation and 1 that represents most inflamed. Two biopsies will be for IHC to confirm the MOA: 1 that represents average inflammation and 1 that represents most inflamed.

Collection of biomarker samples should occur prior to administration of drug on treatment days when applicable. All biomarker samples should be 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 ABBV-668 (or drugs of this class) or ulcerative colitis and related conditions continues, but for no longer than 20 years after study completion, or per local requirement.

3.7 12-Lead Electrocardiogram

12-Lead Electrocardiogram

Resting 12-lead ECGs will be obtained at the visits specified in Section 2.1. The investigator's real-life evaluations of ECGs at the study site will be used for subject safety assessments, including AE determination and management and determining whether a subject will be discontinued from the study. Any subject administered study drug having confirmed ECG changes that are considered clinically significant and considered related to study drug, or a confirmed absolute QTcF value > 500 msec, or a confirmed absolute QTcF value change from Baseline > 60 msec, will discontinue study drug. 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.

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

ECG Safety Review

Each ECG will be evaluated by an appropriately trained physician (preferably a cardiologist) at the study site (the "local reader"). The local reading of the ECG will be used by the investigator for subject safety assessments, including adverse event determination and management, and decision on whether a subject will be discontinued from the study.

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

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

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

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

State of Emergency or Pandemic Situations Acceptable Protocol Modifications

In the event this may not be performed due to study modifications related to cases of a state of emergency or pandemic situations, perform the 12-lead ECG at the next earliest feasible visit or arrange to have an alternative acceptable local facility perform the ECG for the subject.

3.8 Height and Weight

Height will be measured at screening only. Body weight will be measured at the visits specified in Section 2.1. The subject will wear lightweight clothing and no shoes during weighing.

State of Emergency or Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, subject visits may be conducted via phone or video conference. In these situations, height, weight, and body circumference measurements may be performed by the subject or caregiver as needed.

3.9 Vital Signs

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

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

State of Emergency or Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, subject visits may be conducted via phone or video conference. In these situations, vital signs may be obtained by the subject or caregiver as needed.

3.10 Physical Examination

A complete physical examination, including height (at Screening only) and weight, will be performed at the visits specified in Section 2.1. The physical examination performed on Study Day 1 will serve as the baseline physical examination for the entire study. Physical examination abnormalities noted at the Baseline Visit prior to the first dose of study drug should be recorded in the subject's medical history. 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 Neurological Examination

A neurological examination, consisting of the following, will be performed at the visits specified in Section 2.1:

- Mental status – assessment of orientation, speech, and memory.
- Cranial nerves – assessment of cranial nerves II-XII
- Motor system – assessment of tone and strength, including assessment for tremor
- Sensory system – brief survey for light touch and temperature
- Reflexes – assessment of deep tendon reflexes and plantar responses (Babinski sign)
- Gait – assessment of tandem gait

The neurological examination on Day 1 will serve as the baseline neurological examination for the entire study. Neurological examination findings noted at the Baseline visit prior to the first dose of study drug should be recorded in the subject's medical history. Any significant neurological 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 neurological examination can be performed as deemed necessary by the investigator.

3.12 Dispense Study Drug

Study drug will be dispensed to subjects beginning at Baseline (Day 1) and as specified in Section 2.1. The first dose of study drug will be administered after all other baseline (Day 1) procedures are completed. At the visits specified in Section 2.1, the site personnel will review returned study drug kits and empty study drug packaging to verify compliance.

Study drug (ABBV-668) capsules should be dosed together and taken with or without food.

State of Emergency or Pandemic-Related Acceptable Protocol Modifications

Study drug may be shipped from the study site directly to the study subject's home if all the following criteria are met:

- Direct-to-patient (DTP) shipment of study drug is allowed by local regulations and the relevant ethics committee.
- Subject agrees to have the study drug shipped directly to their home.
- Instructions will be provided by AbbVie as to how a study site can initiate a DTP shipment using Marken, a global vendor selected by AbbVie to provide this service when necessary. Shipments of study drugs from the study site to a subject's home will be appropriately temperature controlled (qualified shipper or temperature monitoring) within the labeled storage conditions. Signature is required upon delivery; due to COVID-19- related social distancing, this may be provided by the courier after delivery. Documentation of the shipment is to be retained by the clinical site.
- AbbVie will not receive subject identifying information related to these shipments, as the site will work directly with the courier.

The study site is responsible for meeting IRB/IEC reporting requirements related to DTP shipments of study drug, and for obtaining consent to provide delivery information to the courier and documenting this consent in source documents.

3.13 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.

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

- repeat the test to verify the out-of-range value;

- follow the out-of-range value to a satisfactory clinical resolution; or
- discontinue the subject from the study or require the subject to receive treatment; in this case, the laboratory result will be recorded as an adverse event.

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.

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).

Laboratory tests are listed in Table 1.

Table 1. Laboratory Tests

Hematology	Clinical Chemistry	Other Tests
Hematocrit Hemoglobin Red blood cell count White blood cell count Neutrophils, including absolute neutrophil count (ANC) Bands Lymphocytes, including absolute lymphocyte count Monocytes Basophils Eosinophils Platelet count	Blood urea nitrogen Creatinine Total bilirubin Direct and indirect bilirubin Gamma-glutamyl transferase Lactate dehydrogenase Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Total protein Glucose Albumin Chloride Bicarbonate/CO_2 Creatine phosphokinase	High sensitivity C-reactive protein Urine and serum pregnancy test as applicable Follicle stimulating hormone Human immunodeficiency virus Hepatitis B surface antigen Hepatitis B core antibody Hepatitis B surface antibody Hepatitis B virus polymerase chain reaction (PCR) (if needed) Hepatitis C virus antibody Hepatitis C virus RNA (reflex only) QuantiFERON-TB (or interferon gamma release assay [IGRA] equivalent) and/or purified protein derivative (PPD) Covid-19 testing as applicable
		Lipid Panel
		Cholesterol LDL HDL Triglycerides
Coagulation		**Urinalysis**
International normalized ratio (INR)[a]		Specific gravity Ketones pH Protein Blood Glucose Urobilinogen Bilirubin Nitrate Leukocytes Erythrocytes Microscopic examination (if needed)
		Stool Samples
		C. difficile test Fecal calprotectin

a. INR will only be measured if ALT and/or AST > 3 × upper limit of normal (ULN) and total bilirubin < 2 × ULN.

Estimated Glomerular Filtration Rate

The eGFR will be calculated by Cockcroft-Gault at Screening as specified in Section 2.1.

Pregnancy Tests (Serum and Urine)

Pregnancy testing should not be performed for postmenopausal women.

A qualitative serum pregnancy test will be performed at Screening and a urine pregnancy test will be performed at the visits specified in Section 2.1.

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, this will be considered documentation of continued lack of a positive result and 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

A minimum 8-hour fast will be necessary for blood samples to be drawn for chemistry. If a subject is not able to fast when necessary due to unforeseen circumstances, the nonfasting status will be recorded in study source documentation.

Urinalysis

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

Tuberculosis Testing/TB Prophylaxis

All subjects must be evaluated for tuberculosis (TB) at Screening. Subjects with negative QuantiFERON-TB Gold test and/or purified protein derivative (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. 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 (Section 8.1) and tested for TB infection by QuantiFERON-TB Gold test or PPD test. The site staff will complete the TB risk assessment form and enter the data into the appropriate eCRF.

If a subject had a negative 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 chest x-ray. Subjects with a positive TB test (due to a history of TB) may only be enrolled if documented completion of a full course of anti-TB therapy per local guidelines is available, the subject has no evidence of current active TB, and 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. Otherwise, all other subjects with a positive TB test, including subjects with evidence of active TB, must not be enrolled.

During the study, subjects with new evidence of latent TB should initiate prophylactic treatment immediately per local guidelines and study drug should be discontinued. Newly initiated prophylactic treatment and prior therapy should be captured in the eCRF.

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 (refer to Chest X-Ray guidance).
- 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.

- 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.

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 chest x-ray 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 chest x-ray. The investigator will indicate the clinical significance of any findings and will sign and date the report.

In the assessment of the chest x-ray, 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 chest x-ray demonstrates changes suggestive of previous TB (e.g., calcified nodule, fibrotic scar, or 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)

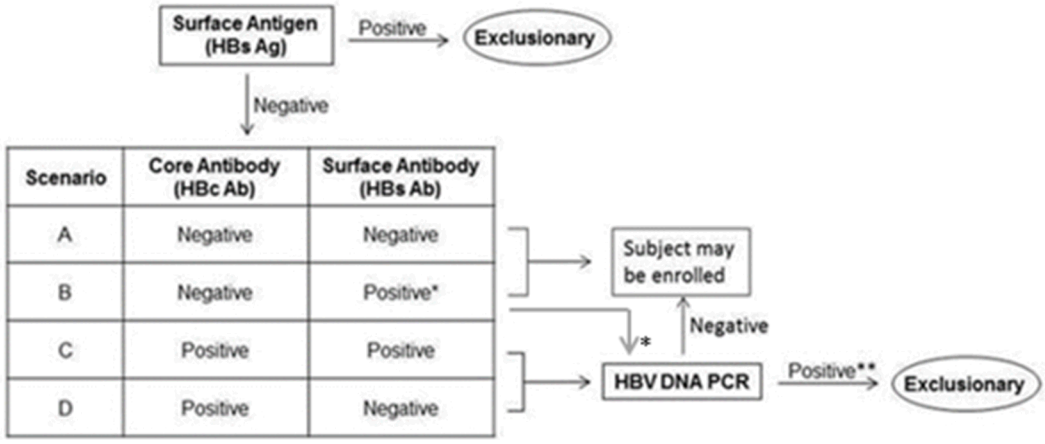
A positive result for HBs Ag will be exclusionary.

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 polymerase chain reaction (PCR) testing and the subject is eligible to enroll in the study (Figure 1, Scenarios A and B).
- For a subject who had an 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, Scenarios B).

- 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 (automatic reflex testing; 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 for HBV DNA that exceeds detection sensitivity will be considered positive and will be exclusionary. A subject with a negative result for HBV DNA may be enrolled.

Figure 1. Interpretation and Management of HBV Serologic Test Results



* Subjects who have had an 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. This testing is to be done at the central lab. AbbVie will not receive results from the testing and will not be made aware of any positive result.

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.

Fecal Calprotectin

Fecal calprotectin (FCP) will be performed at the study visits indicated in Section 2.1. 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.

State of Emergency or Pandemic-Related Acceptable Protocol Modifications

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

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

3.14 Subject Withdrawal

All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate eCRF page. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the

investigator's best clinical judgment, irrespective of whether the subject decides to continue participation in the study.

In the event a subject withdraws consent from the clinical study, biomarker research will continue unless the subject explicitly requests analysis to be stopped. When AbbVie is informed the subject has withdrawn and no longer wishes biomarker research to continue, 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. A subject may withdraw consent for optional biomarker research at any time and remain in the clinical study. Data generated from clinical study and/or optional biomarker research, before subject withdrawal of consent, will remain part of the study results.

3.15 Unscheduled Visits

An Unscheduled Visit should be performed when the subject comes in for a medical visit for evaluation and assessment. During Unscheduled Visits, blood and urine samples may be obtained for the laboratory tests listed in Section 3.13 or for other tests at the investigator's discretion; physical examination (including neurological examination) may be performed at the investigator's discretion.

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

3.16 Additional Assessments as Required

Endoscopy

Endoscopy at/during Screening 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 and Week 16.

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 endoscopy.

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

All endoscopies will be performed and recorded at the site in a video format. Videos from subjects with eligible Mayo endoscopic subscores during Screening and all videos from subjects at Week 8 and Week 16 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.

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 during endoscopies occurring during Screening, Week 8, and Week 16 as described below:

- 8 biopsies will be collected at each time point from the region of most severe involvement as determined by endoscopic assessment. Biopsies will be used for histologic, gene expression and IHC/MOA analyses. For all biopsies, the segment from which the biopsy was collected should be documented during endoscopy. For biopsies collected for histologic analysis, the distance from anal verge should also be documented.
    - 4 biopsies will be collected for histologic analysis:
        - 2 biopsies representative of the average degree of inflammation
        - 2 biopsies representative of the most inflamed intestinal tissue (if the area is ulcerated, the sample should be obtained from the edge of the ulcer)
    - 2 biopsies will be collected for gene expression analysis:
        - 1 biopsy representative of the average degree of inflammation
        - 1 biopsy representative of the most inflamed intestinal tissue (if the area is ulcerated, the sample should be obtained from the edge of the ulcer)
    - 2 biopsies will be collected for IHC/MOA analysis:
        - 1 biopsy representative of the average degree of inflammation
        - 1 biopsy representative of the most inflamed intestinal tissue (if the area is ulcerated, the sample should be obtained from the edge of the ulcer)
- The biopsies for histopathological, gene expression, and IHC/MOA analysis collected for the main study may also be used for biomarker 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 SMA and kept with the subject's source documents onsite.

Biopsy sampling should be recorded on the endoscopy video.

Unless endoscopic findings indicate otherwise, biopsies will be taken from the rectosigmoid segment of the colon at each visit with endoscopy.

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 to calculate Full Mayo Score, Adapted Mayo Score (also referred to the modified Mayo Score), and Partial Adapted Mayo Score at the time points indicated in Section 2.1.

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, RBS, and PGA subscores of the Full Mayo Score, Adapted Mayo Score, and Partial Adapted Mayo Score are described in Section 8.2.

3.17 Rescreening

Subjects who initially screen fail for the study 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 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), electrocardiogram (ECG), and chest x-ray 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. If a subject is being rescreened more than 14 days (> 14 days have passed) from the collection date of the previous screening laboratory testing then chemistry/hematology, urinalysis, serum pregnancy, and C. difficile should be repeated during rescreening.

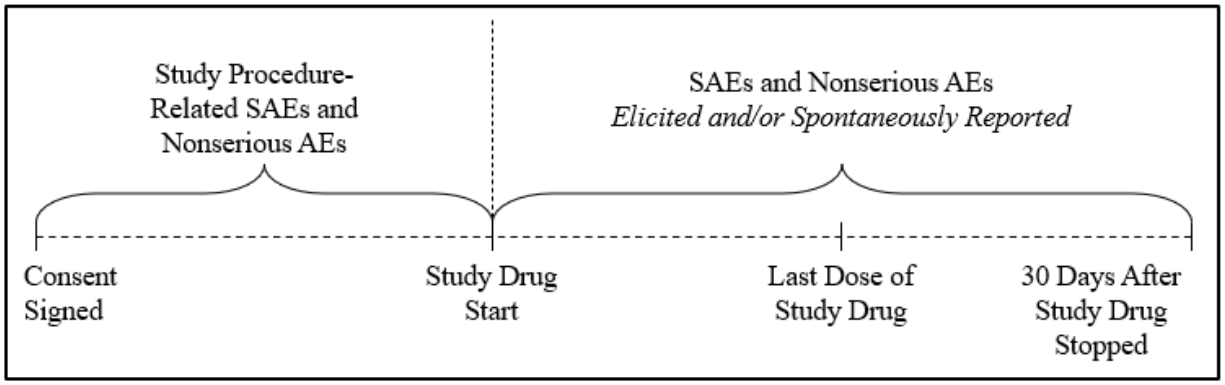
An endoscopy with biopsy will not be required to be repeated for re-screening provided the conditions noted in Section 3.16 are met and the endoscopy is within 45 days of the Baseline visit. All other screening procedures will be repeated unless otherwise stated above. Sites may contact the AbbVie TA MD if there are questions on if subjects should or should not be re-screened.

All subjects need to have their average daily Stool Frequency subscore, average daily RBS, and Adapted Mayo score calculated to verify eligibility criteria before randomization at Baseline.

4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

All serious and nonserious adverse events that could be related to study procedures 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 30 days after the last dose of study drug or study treatment, all nonserious and serious adverse events will be collected whether solicited or spontaneously reported by the subject. After 30 days following the last dose of study drug or completion of study treatment only spontaneously reported SAEs will be collected (nonserious AEs will not be collected).



4.2 Reporting Adverse Events and Intercurrent Illnesses

In the event of an 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: SafetyManagement_immunology@abbvie.com

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

PPD

EMERGENCY MEDICAL CONTACT:

PPD **MD, MSc**

AbbVie
1 North Waukegan Road
North Chicago, Illinois 60064

Contact Information:

Office: PPD
Mobile:
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.

State of Emergency or Pandemic-Related Acceptable Protocol Modifications

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

SARS-CoV-2 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 nonserious events):

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

If a subject has a confirmed or suspected SARS-CoV-2 infection and study drug was interrupted, the investigator should contact the sponsor emergency medical contact listed above before reintroducing study drug.

Reactions known to be associated with the SARS-CoV-2 vaccine should be reported as adverse events. If the event meets the criteria for an SAE, then follow the SAE reporting directions. All adverse events associated with the SARS-CoV-2 vaccine will be linked to the vaccine on the COVID-19 Vaccine eCRF.

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 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 (ABBV-668) will be dispensed in the form of capsules at the visits listed in Section 2.1. Subjects will be instructed to take study drug at the same time every day with or without food.

ABBV-668 will be provided by AbbVie as CCI to be taken as CCI mg PO BID CCI

Study drug administration instructions will be provided separately.

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

6.2 Packaging and Labeling

All study drugs will be supplied in bottles.

Each bottle will be labeled as required per country requirements.

The labels must remain affixed to the bottles. All blank spaces should be completed by site staff prior to dispensing to subject.

6.3 Storage and Disposition of Study Drug

Study drug must be stored between 2°C to 25°C (36°F to 77°F).

The investigational product is 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 dispensed for subject use or destroyed on site as appropriate.

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

6.4 Method of Assigning Subjects to Treatment Groups

This is a non-randomized, open-label, single arm study. All eligible subjects will receive the same dosage of ABBV-668 for 16 weeks.

At the screening visit, all subjects will be assigned a unique subject number using 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.

6.5 Selection and Timing of Dose for Each Subject

CCI of ABBV-668 will be dosed together BID. All subjects should take all doses of study drug with or without food around the same time each day.

7 References

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

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

3. 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.

8 Appendices

8.1 SCREENING/ANNUAL TB RISK ASSESSMENT QUESTIONNAIRE EXAMPLE

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

Part I

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?

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

Have you ever been diagnosed or treated for active or latent tuberculosis?

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)

Have you lived or worked in a prison, refugee camp, homeless shelter, immigration center, or nursing home?

8.2 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: Stool Frequency subscore, Rectal Bleeding subscore, Endoscopy subscore, and Physician's Global Assessment subscore.

The adapted Mayo Score is a composite of the following subscores: Stool Frequency subscore, Rectal Bleeding subscore and Endoscopy subscore.

The Partial Adapted Mayo Score is a composite of the following subscores: Stool Frequency sbuscore and Rectal Bleeding subscore.

Adapted Mayo Score (also known as Modified Mayo Score):[1-3]

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

Stool Frequency Subscore

- The subject should be asked to identify at the screening visit how many bowel movements (when a subject passed stool, blood alone, blood and mucus, or mucus only) he or she had in a

24-hour period when their ulcerative colitis is **not** active. This value will serve as the reference Stool Frequency and must be a full number of at least 1.

- The Stool Frequency subscore is calculated by comparing the stool frequency to the reference Stool Frequency.
- Subjects will record the daily number of bowel movements throughout the trial. Using these numbers, the 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 subscore during days which the subject received anti-diarrheal medication will be scored as a 3.
- The Stool Frequency subscores based on 7 days prior to each study visit will be averaged and used for the Stool Frequency subscore for each study visit
- A minimum of 3 consecutive days of completed diary entries or 4 nonconsecutive days are necessary. Otherwise, the Stool Frequency subscore should be considered missing.
- For visits that have endoscopies, the calculation of the 7-day average should exclude the subscores from non-applicable days which are defined as: 1) the day of bowel preparation; 2) day of endoscopy; and 3) 2 days after endoscopy. Earlier diary entries will be used accordingly to provide the most recent data for 7 applicable 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.
  - Stool with streaks of blood during the respective day should be scored as 1.
  - Stool with more than streaks of blood during the respective day should be scored as 2.
  - Blood alone passed during the respective day should be scored as a 3.
- The Rectal Bleeding subscores based on 7 days prior to each study visit will be averaged and used for the Rectal Bleeding subscore for each study visit.
- A minimum of 3 consecutive days of completed diary entries or 4 nonconsecutive days are necessary. Otherwise, the Rectal Bleeding subscore should be considered missing.
- For visits that have endoscopies, the calculation of the 7-day average should exclude the subscores from non-applicable days, which are defined as: 1) the day of bowel preparation,

2) day of endoscopy, and 3) 2 days after endoscopy. Earlier diary entries will be used accordingly to provide the most recent data for 7 applicable days prior to the respective study visit.

Endoscopy Subscore

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

Physician's Global Assessment Subscore

The physician's global assessment acknowledges the 2 subject-reported subscores, the endoscopy subscore as applicable, and the subject's daily record of abdominal pain based on the 7 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

Document Approval

Study Protocol - m21446-protocol-v2-0-ops-manual-text - 03-Mar-2023

Version: 1.0 **Date:** 03-Mar-2023 **Company ID:** 20230303-0900f9f6860b00d2-1.0-en

Signed by:	Date:	Meaning of Signature:
PPD	03-Mar-2023 17:11 UTC	Approver
	03-Mar-2023 15:58 UTC	Approver
	03-Mar-2023 15:54 UTC	Approver - Statistics

Document Approval

Study Protocol - m21446-protocol-v2-0-text - 03-Mar-2023

Version: 1.0 **Date:** 03-Mar-2023 **Company ID:** 20230303-0900f9f6860b00d0-1.0-en

Signed by:	Date:	Meaning of Signature:
PPD	03-Mar-2023 17:12 UTC	Approver
	03-Mar-2023 15:58 UTC	Approver
	03-Mar-2023 15:54 UTC	Approver - Statistics