# Protocol

## A Randomised, Double-blind, Placebo-controlled Study of Orally Administered BBT-401-1S in Subjects with Moderate to Severe Ulcerative Colitis, Incorporating a Response-Adaptive, Double-blind Extension Phase

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**STUDY IDENTIFICATION**

| | |
|---|---|
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# SYNOPSIS

## Study Title

A randomised, double-blind, placebo-controlled study of orally administered BBT-401-1S in subjects with moderate to severe ulcerative colitis, incorporating a response-adaptive, double-blind extension phase.

## Objectives

The primary objective of this study is to explore the efficacy of orally administered BBT-401-1S in inducing a clinical response in subjects with active ulcerative colitis (UC).

The secondary objectives of the study are:

- to assess the safety and tolerability of orally administered BBT-401-1S
- to explore additional measurements of the efficacy of orally administered BBT-401-1S in inducing endoscopic and clinical remission.

The exploratory objectives of this study are to evaluate the effects of BBT-401-1S on endoscopic response, subject-reported outcomes, histological improvement, biomarkers, and long-term clinical remission.

## Endpoints

Primary Efficacy:

- clinical response rate at Day 57, as measured by a reduction of ≥3 points and ≥30% improvement from baseline of total Mayo score, which includes a decrease in rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore ≤1.

Secondary Efficacy:

- clinical remission at Day 57, as measured by a total Mayo score of ≤2 points, with no individual subscore exceeding 1 point
- achievement of endoscopic remission at Day 57, as measured by a Mayo endoscopic subscore of 0 or 1.

Exploratory Efficacy:

- endoscopic response rate at Day 57, as defined by a ≥2-point reduction from baseline in Ulcerative Colitis Endoscopic Index of Severity (UCEIS) score
- endoscopic response rate at Day 57, as defined by a reduction of ≥1 grade in the Mayo endoscopic subscore
- Inflammatory Bowel Disease Questionnaire (IBDQ) total score, as measured by change from baseline
- histological improvement, as guided by change from baseline in Geboes score

- biomarkers, including C-reactive protein and faecal calprotectin, as measured by change from baseline
- clinical remission at Day 112, as measured by a total Mayo score of ≤2 points, with no individual subscore exceeding 1 point
- percentage of subjects with sustained remission at Day 112
- clinical response rate at Day 112.

Primary Safety:

- adverse events and serious adverse events.

**Study Design**

This study will comprise 2 periods: a randomised, double-blind, placebo-controlled induction phase; and a response-adaptive, double-blind extension phase.

**Induction Phase**

Subjects will be screened for inclusion in the study within 28 days of Day 1. Eligible subjects will be randomised in a 1:1:1 ratio; 12 subjects will receive 800 mg BBT-401-1S once daily (QD) and placebo QD, 12 subjects will receive 800 mg BBT-401-1S twice daily (BID), and 12 subjects will receive placebo BID. Subjects will receive the first dose of study drug at the study site on Day 1 and will administer study drug away from the study site for 56 days, during which they will attend 2 study site visits on Days 29 and 57. Additionally, subjects will be contacted by telephone on Day 8 for safety and compliance monitoring; however, at the discretion of the investigator, subjects may be requested to attend a study site visit on this day.

Subjects who do not agree to participate in the extension phase will attend the study site for a follow-up visit on Day 71.

**Extension Phase**

Subjects who complete the induction phase will be offered the opportunity to enter the extension phase after the Day 57 visit. Subjects who agree to participate in the extension phase will continue study drug administration while awaiting their clinical remission status from the local reader. Subjects will be assigned to the treatment for the extension phase treatment upon receipt of their clinical remission status.

- Subjects who achieved clinical remission in the induction phase will continue the same treatment.
- Subjects who did not achieve clinical remission in the induction phase and:
    - who received placebo BID will receive 800 mg BBT-401-1S QD and placebo QD
    - who received 800 mg BBT-401-1S QD and placebo QD will receive 800 mg BBT-401-1S BID
    - who received 800 mg BBT-401-1S BID will continue the same treatment.

Subjects will attend the study site on Days 85 and 112 (follow-up visit). Additionally, subjects will be contacted by telephone on Day 71 for safety and compliance monitoring; however, at the discretion of the investigator, subjects may be requested to attend a study site visit on this day.

**Number of Subjects**

Approximately 36 subjects will be randomised.

**Diagnosis and Main Criteria for Inclusion**

Male and female subjects aged ≥18 and ≤60 years who have been diagnosed with active UC for ≥3 months prior to Day 1, and have a total Mayo score ≥6, an endoscopic subscore ≥2, a rectal bleeding subscore ≥1, and a stool frequency subscore ≥1.

**Investigational Medicinal Products, Dose, and Mode of Administration**

200 mg BBT-401-1S capsules for oral administration. Dose levels of 800 mg QD and BID will be studied.

**Reference Product and Mode of Administration**

Reference product: placebo capsules for oral administration.

**Duration of Subject Participation in the Study**

Planned Screening duration: up to 4 weeks.

Induction phase: approximately 10 weeks.

Extension phase: approximately 8 weeks.

Total planned study duration (screening to follow-up): approximately 20 weeks for subjects who are enrolled into the extension phase and approximately 14 weeks for subjects who are not enrolled into the extension phase.

**Study Populations**

The **intent-to-treat population** will include all subjects who received at least 1 dose of study drug, have a partial Mayo score recorded on Day 1, and at least 1 post-baseline Mayo score recorded.

The **safety population** will include all subjects who received at least 1 dose of study drug.

**Statistical Methods**

*Primary and Secondary Efficacy Analyses*

Descriptive summaries will be presented for clinical response, clinical remission, and endoscopic remission rates. The estimate and 95% confidence interval (CI) of clinical response, clinical remission, and endoscopic remission rates at Day 57 will be calculated

using the exact binomial method for each treatment. The Fisher's exact test will be used to evaluate any differences between treatments.

*Exploratory Efficacy Analysis*

The estimate and 95% CI of endoscopic response rate and histological improvement at Day 57, and clinical response rate and the percentage of subjects with clinical remission at Day 112 will be calculated using the exact binomial method for each treatment. Actual values and change from baseline in Mayo scores, UCEIS scores, IBDQ total score, C-reactive protein, and faecal calprotectin over time will be summarised descriptively. No formal hypothesis will be tested on the exploratory efficacy endpoints.

*Safety Analysis*

Adverse events will be presented using descriptive statistics.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| BID | twice daily |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| COVID-19 | coronavirus disease-19 |
| CRO | contract research organisation |
| DSS | Drug Safety Services |
| EC | ethics committee |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| GCP | Good Clinical Practice |
| HRQoL | health-related quality of life |
| IB | investigator's brochure |
| IBDQ | Inflammatory Bowel Disease Questionnaire |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation |
| JAK | Janus kinase |
| IL | interleukin |
| PGA | physician's global assessment |
| QD | once daily |
| QTcF | QT interval corrected for heart rate using Fridericia's method |
| SAE | serious adverse events |
| TNF | tumour necrosis factor |
| UC | ulcerative colitis |
| UCEIS | Ulcerative Colitis Endoscopic Index of Severity |
| ULN | upper limit of normal |

# 1. INTRODUCTION

Refer to the investigator's brochure (IB) for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of the investigational medicinal product (study drug).

## 1.1. Overview

Ulcerative colitis (UC) is a chronic disorder characterised by inflammation of intestinal mucosa, primarily the colon, as well as the rectum in approximately 95% of cases. The goals of treatment of UC are to induce and maintain remission of symptoms. Oral aminosalicylate (eg, sulfasalazine) therapy comprises the conventional standard of care in the pharmacological treatment of mild to moderate active UC. Corticosteroids or immunosuppressants may also be used to treat symptoms. Subjects unable to be treated with conventional therapies or those with moderate to severe disease might receive biological therapy (ie, an anti-tumour necrosis factor [TNF]-α agent).[1]

Conventional therapies are broadly limited by safety and tolerability issues, such as thinning of the skin, effects on bone contributing to osteoporosis, increased risks of infection, and psychological effects with corticosteroid therapy, and headache, nausea, hypersensitivity reactions, and potential for nephrotoxicity with sulfasalazine therapy.[2,3] Biologic therapy is known to have immunocompromising effects that increase patient risks to other diseases and a range of infections (mycobacterial, fungal, viral).[4] Reported treatment failures further limit the utility of biologic therapies.[5] New therapies with novel mechanisms may help address the unmet needs in the treatment of UC.

BBT-401 was derived from Smad6 and developed to modulate inflammatory disorders. BBT-401 directly interacts with Pellino-1 protein, competitively binding in a dose-dependent manner, thus inhibiting the proinflammatory activity of Pellino-1. Given the inflammatory pathophysiology of UC and the effects of BBT-401 on inhibiting inflammatory processes, there is a pharmacological rationale to evaluate BBT-401 in the treatment of UC.

[redacted]. A Phase 1 clinical study of orally administered BBT-401-1S [redacted] showed no systemic exposure and an excellent safety and tolerability profile, with no serious adverse events (SAEs). Mild diarrhoea (usually transient in nature and generally not interfering with normal activities) was the most observed AE in the 1600-mg single- and multiple-ascending-dose cohorts. Additionally, orally administered BBT-401-1S was generally well tolerated at doses of 400 mg/day in an exploratory study of efficacy in subjects with UC. Conclusions on efficacy have not yet been made.

This clinical study of BBT-401-1S is designed to explore the safety and efficacy of BBT-401-1S administered orally in subjects with active UC.[redacted]

## 1.2. Benefit-risk Assessment

Subjects participating in this study may experience therapeutic benefit to symptoms of UC.

Given the excellent safety and tolerability profile in the Phase 1 study and the overall favourable safety profile seen in the nonclinical toxicology studies, BBT-401-1S is expected to demonstrate safety and tolerability with minimal systemic absorption in subjects with active UC. However, as there may be unknown and potential risks with administration of BBT-401-1S because of its pharmacological action and based on clinical experience with compounds that have inhibitory effects on proinflammatory pathways, all subjects will be closely monitored for safety and tolerability.

There is low risk of drug-drug interactions between BBT-401-1S and common comedications, based on the low systemic exposure and benign safety profiles demonstrated in the nonclinical and clinical studies.

More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with BBT-401-1S may be found in the IB.

## 2. OBJECTIVES AND ENDPOINTS

### 2.1. Objectives

The primary objective of this study is to explore the efficacy of orally administered BBT-401-1S in inducing a clinical response in subjects with active UC.

The secondary objectives of the study are:

- to assess the safety and tolerability of orally administered BBT-401-1S
- to explore additional measurements of the efficacy of orally administered BBT-401-1S in inducing endoscopic and clinical remission.

The exploratory objectives of this study are to evaluate the effects of BBT-401-1S on endoscopic response, subject-reported outcomes, histological improvement, biomarkers, and long-term clinical remission.

### 2.2. Endpoints

#### 2.2.1. Primary Endpoints

The primary efficacy endpoint is the clinical response rate at Day 57, as measured by a reduction of ≥3 points and ≥30% improvement from baseline of total Mayo score, which includes a decrease in rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore ≤1.

The primary safety endpoints are AEs and SAEs.

#### 2.2.2. Secondary Endpoints

The secondary efficacy endpoints are:

- clinical remission at Day 57, as measured by a total Mayo score of ≤2 points, with no individual subscore exceeding 1 point

- achievement of endoscopic remission at Day 57, as measured by a Mayo endoscopic subscore of 0 or 1.

### 2.2.3. Exploratory Endpoints

The exploratory efficacy endpoints are:

- endoscopic response rate at Day 57, as defined by a ≥2-point reduction from baseline in Ulcerative Colitis Endoscopic Index of Severity (UCEIS) score
- endoscopic response rate at Day 57, as defined by a reduction of ≥1 grade in the Mayo endoscopic subscore
- Inflammatory Bowel Disease Questionnaire (IBDQ) total score, as measured by change from baseline
- histological improvement, as guided by change from baseline in Geboes score
- biomarkers, including C-reactive protein and faecal calprotectin, as measured by change from baseline
- clinical remission at Day 112, as measured by a total Mayo score of ≤2 points, with no individual subscore exceeding 1 point
- percentage of subjects with sustained remission at Day 112
- clinical response rate at Day 112.

## 3. INVESTIGATIONAL PLAN

### 3.1. Overall Study Design and Plan

This study will comprise 2 periods: a randomised, double-blind, placebo-controlled induction phase; and a response-adaptive, double-blind extension phase.

**Induction Phase**

Subjects will be screened for inclusion in the study within 28 days of Day 1.

Eligible subjects will be randomised in a 1:1:1 ratio; 12 subjects will receive 800 mg BBT-401-1S once daily (QD) and placebo QD, 12 subjects will receive 800 mg BBT-401-1S twice daily (BID), and 12 subjects will receive placebo BID. Subjects will receive the first dose of study drug at the study site on Day 1 and will administer study drug away from the study site for 56 days, during which they will attend 2 study site visits on Days 29 and 57. Additionally, subjects will be contacted by telephone on Day 8 for safety and compliance monitoring; however, at the discretion of the investigator, subjects may be requested to attend a study site visit on this day.

Subjects who do not agree to participate in the extension phase will attend the study site for a follow-up visit on Day 71.

**Extension Phase**

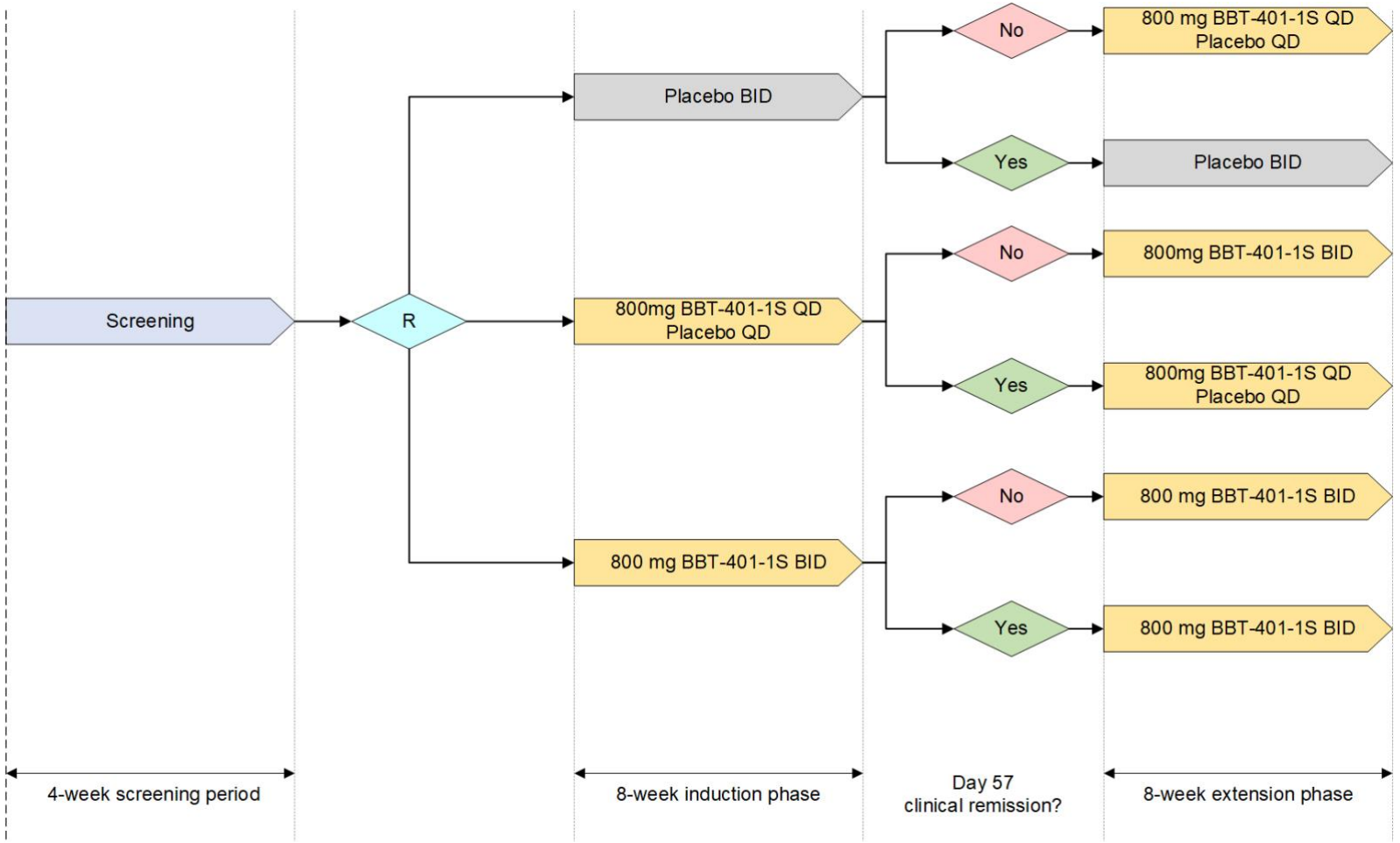
Subjects who complete the induction phase will be offered the opportunity to enter the extension phase after the Day 57 visit. Subjects who agree to participate in the extension phase will continue study drug administration while awaiting their clinical remission status from the local reader. Subjects will be assigned to the treatment for the extension phase treatment upon receipt of their clinical remission status.

- Subjects who achieved clinical remission in the induction phase will continue the same treatment.
- Subjects who did not achieve clinical remission in the induction phase and:
    - who received placebo BID will receive 800 mg BBT-401-1S QD and placebo QD
    - who received 800 mg BBT-401-1S QD and placebo QD will receive 800 mg BBT-401-1S BID
    - who received 800 mg BBT-401-1S BID will continue the same treatment.

Subjects will attend the study site on Days 85 and 112 (follow-up visit). Additionally, subjects will be contacted by telephone on Day 71 for safety and compliance monitoring; however, at the discretion of the investigator, subjects may be requested to attend a study site visit on this day.

The study design is presented in Figure 1 and a schedule of assessments is presented in Appendix 11. The total planned study duration (screening to follow-up) is approximately 20 weeks for subjects who are enrolled into the extension phase and approximately 14 weeks for subjects who are not enrolled into the extension phase.

**Figure 1: Study Design**




Abbreviations: BID = twice daily; QD = once daily; R = randomisation.

### 3.2. Discussion of Study Design

This study will be double-blind and placebo-controlled to avoid bias in the collection and evaluation of data during its conduct. Placebo has been chosen as the control treatment to assess whether any observed effects are treatment related or simply reflect the study conditions.

The study will exclude confounding effects, as is practically possible, by selecting a limited study population and concomitant medications. Additionally, subjects with only mild UC, as determined by the Mayo score, are excluded to provide scope for improvement in symptoms.

### 3.3. Selection of Doses in the Study

Once and twice daily doses of 800 mg have been selected for this study.

Nonclinical pharmacological assays showed a less than dose-proportional increase in efficacy (up to 400 mg/kg/day in mice and 100 mg/kg/day in rats, which correspond to human equivalent doses of 2000 and 970 mg/day, respectively).

[redacted]

Clinical studies of single doses of up to 1600 mg and multiple doses of up to 1600 mg/day for 7 days in healthy subjects indicated that BBT-401-1S is not absorbed systemically (plasma concentrations were below the lower limit of quantification [<1 ng/mL]). No SAEs were reported in this study. Additionally, in an exploratory study of the efficacy in subjects with UC, orally administered BBT-401-1S was generally well tolerated at 400 mg/day for up to 12 weeks.

## 4. SELECTION OF STUDY POPULATION

### 4.1. Inclusion Criteria

Subjects must satisfy all the following criteria at the screening visit, unless otherwise stated:

1. Male or female, of any race, ≥18 and ≤60 years of age.
    a. Females will not be pregnant or lactating.
    b. Females of childbearing potential will agree to abide by the contraception requirements from the time of signing the informed consent form (ICF) until 3 months after the last dose of study drug (Appendix 3).
    c. Males will agree to abide by the contraception requirements from Day 1 until 3 months after the follow-up visit (Appendix 3).
2. Have been diagnosed with active UC for ≥3 months prior to Day 1, as determined by clinical and endoscopic evidence and documented in a histopathology evaluation.
3. Have a total Mayo score ≥6, an endoscopic subscore ≥2, rectal bleeding subscore ≥1, and a stool frequency subscore ≥1, regardless of standard of care history.

4. Able to comprehend and willing to voluntarily sign an ICF and to abide by the study restrictions.

### 4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria at the screening visit, unless otherwise stated:

1. Have received:
    a. intravenous or rectally administered corticosteroids within 3 weeks, or
    b. Janus kinase (JAK) inhibitors within 2 weeks, or
    c. cyclosporine, mycophenolate, tacrolimus, or methotrexate within 5 weeks, or
    d. anti-TNF-α biologics within 9 weeks, or
    e. any other biologics (including ustekinumab and vedolizumab) for the treatment of UC within 12 weeks.
2. Have received orally administered azathioprine or 6-mercaptopurine that has been stable for <8 weeks. Doses of oral drugs must remain stable until the last dose of study drug.
3. Have received orally or rectally administered 5-aminosalicylic acid, or orally administered sulphasalazine or low-dose corticosteroids (prednisolone ≤20 mg/day or equivalent), that have been stable for <5 weeks. Doses must remain stable until the last dose of study drug.
4. Have received any other concomitant medications for UC that have been stable (ie, have not started dosing with a new drug or had a change to their dosing regimen) for <7 days or 5 half-lives, whichever is longer.
5. Have Crohn's disease, indeterminate colitis, ischaemic colitis, fulminant colitis, toxic megacolon, chronic (as determined by the investigator) pancolitis, confined proctitis (distal, ≤15 cm), or symptomatic intestinal stenosis.
6. Have a history of extensive colonic resection (subtotal or total colectomy) or are anticipated to require surgical intervention for UC.
7. Have an ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine.
8. Have a positive test for *Clostridium difficile*, or have evidence of treatment for *Clostridium difficile* infection or other pathogenic bowel infection within 60 days or for another intestinal pathogen within 30 days prior to Day 1.
9. Have active infection with the human immunodeficiency virus or hepatitis B or C viruses.
10. Have clinically significant active extraintestinal infection (eg, pneumonia, pyelonephritis).
11. Have, in the opinion of the investigator, clinically significant abnormal vital signs, physical examination findings, or 12-lead electrocardiograms (ECGs) at screening or Day 1.

12. Have a history of any disease or condition (including mental and emotional conditions) that, in the opinion of the investigator (or designee), would affect participation in this study.
13. Have clinically significant abnormal liver function tests, including:
    a. estimated glomerular filtration rate ≤50 mL/min/1.73m$^2$
    b. alanine aminotransferase or aspartate aminotransferase >2 × the upper limit of normal (ULN)
    c. direct bilirubin >1.5 × ULN.

    **Note:** Liver function tests may be repeated once, at the discretion of the investigator (or designee).

14. Have other clinically significant abnormal clinical laboratory results that, in the opinion of the investigator, preclude participation in the study, including:
    a. platelet count <100,000/µL
    b. haemoglobin <8.5 g/dL
    c. neutrophils <1500/µL
    d. lymphocytes <500/mm$^3$
    e. absolute white blood cells count <3000/µL.

    **Note:** Clinical laboratory evaluations may be repeated once, at the discretion of the investigator (or designee).

15. Have participated in a clinical study involving administration of an investigational drug in the past 30 days prior to Day 1.
16. Have previously participated in any study of BBT-401-1S.
17. In the opinion of the investigator (or designee) or the sponsor, should not participate in this study.

### 4.3. Subject Number and Identification

Subjects will be assigned a subject number prior to the first dosing occasion. Subjects will be identified only by a subject number on all study documentation. A list identifying the subjects by subject number will be kept in the site master file.

### 4.4. Rescreening

Subjects may be rescreened once, at the discretion of the investigator (or designee), providing that the reason for screen failure was not due to a safety concern or non-eligibility based on exclusion criteria related to clinical laboratory evaluations. If a subject is considered to be eligible for rescreening, this will be discussed with the sponsor prior to rescreening. Subjects who are rescreened will be identified by a new subject number.

### 4.5. Screen Failures

Subjects who consent to participate in the study but are not subsequently enrolled will be considered screen failures. A minimal set of screen failure information, including demographics, eligibility criteria, SAEs, and details of the screen failure, will be collected to ensure transparent reporting of screen failures and to respond to queries from regulatory authorities.

### 4.6. Subject Withdrawal

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn from dosing if any of the following criteria are met:

- change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects subject safety as determined by the investigator (or designee)
- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the investigator (or designee)
- any clinically relevant sign or symptom (including disease worsening) that, in the opinion of the investigator (or designee), warrants subject withdrawal.

If a subject is withdrawn from dosing, the sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic case report form. If a subject is withdrawn from the study, efforts will be made to perform all early termination assessments, if possible (Appendix 11). Other procedures may be performed at the investigator's (or designee's) and/or sponsor's discretion. The investigator (or designee) may also request that the subject return for an additional follow-up visit. All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the investigator (or designee) to have stabilised.

### 4.7. Study Termination

The study may be discontinued at the discretion of the sponsor if any of the following criteria are met:

- AEs unknown to date (ie, not previously reported in any similar investigational study drug trial with respect to their nature, severity, and/or duration)
- increased frequency, severity, and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined predose on Day 1 as baseline signs and symptoms)
- medical or ethical reasons affecting the continued performance of the study
- difficulties in the recruitment of subjects
- cancelation of drug development.

# 5. STUDY TREATMENTS

## 5.1. Description, Storage, Packaging, and Labelling

BBT-401-1S and placebo will be supplied by the sponsor (or designee) in bottles, along with the batch/lot numbers and certificates of analysis.

[redacted]

Study drug will be stored according to the instructions on the label, and when stored at the site, will be stored in a location that is locked with restricted access.

## 5.2. Study Treatment Administration

Study drug will be administered orally. At each dosing occasion, subjects will receive a total of 4 capsules, comprising a combination of BBT-401-1S and/or placebo capsules to maintain the blind (Table 1). Subjects will receive study drug in the morning and evening during the induction and extension phases.

**Table 1: Study Drug Administration**

| Dose Level | Morning Dose | | Evening Dose | |
|---|---|---|---|---|
| | Number of BBT-401-1S Capsules | Number of Placebo Capsules | Number of BBT-401-1S Capsules | Number of Placebo Capsules |
| Placebo BID | 0 | 4 | 0 | 4 |
| 800 mg BBT-401-1S QD and placebo QD | 4 | 0 | 0 | 4 |
| 800 mg BBT-401-1S BID | 4 | 0 | 4 | 0 |

Abbreviations: BID = twice daily; QD = once daily.

## 5.3. Randomisation

Subjects will be randomised to placebo BID, 800 mg BBT-401-1S QD and placebo QD, or 800 mg BBT-401-1S BID during the induction phase using an interactive voice/web response system.

## 5.4. Blinding

The following controls will be employed to maintain the double-blind status of the study:

- The placebo capsules will be identical in appearance to BBT-401-1S.
- The same number of capsules will be administered at each dosing occasion.
- There will be the same number of dosing occasions within the induction and extension phases.

- Subjects, investigators, and other members of staff involved with the study (including those involved in clinical operations and study site monitoring) will remain blinded to the treatment randomisation. **Note**: Sponsor representatives who are not involved in monitoring of the study may be unblinded.

The interactive voice/web response system will be programmed with unblinding instructions. The study blind may be broken if, in the opinion of the investigator, it is in the subject's best interest to know the assigned treatment. Whenever possible, and providing it does not interfere with or delay any decision in the best interest of the subject, the investigator will discuss the intended unblinding with the sponsor. If it becomes necessary to unblind during the study, the date, time, and reason will be recorded in the subject's source data.

## 5.5. Treatment Compliance

Where doses are administered at the study site, all doses will be administered under the supervision of suitably qualified study site staff and treatment administration will be documented at the study site.

Where doses are administered away from the study site, subjects will document treatment administration using subject diaries that will be reviewed at study site visits. Additionally, unused study drug will be returned to the study site for assessment of treatment compliance.

## 5.6. Rescue Therapy

A rescue treatment is defined as any procedure or medication (new medications or medications that have been increased in dose) used for the treatment of new or persistent symptoms of UC.

If a subject who does not exhibit a clinical response experiences worsening of disease (ie, worsening of clinical status or symptoms of UC that require rescue treatment) or disease relapse, study drug must be discontinued, and subjects should be treated as clinically appropriate with conventional treatments for active disease, as determined by the investigator. These subjects should continue in the study for safety assessments but will be considered treatment failures with respect to the intent-to-treat population.

A subject will be considered to have disease relapse when they meet all of the following criteria:

- an increase in UC disease activity after achievement of a clinical response, defined as an increase from nadir or Day 57 in partial Mayo score of ≥2 points and an absolute partial Mayo score ≥4 points, and
- an endoscopic subscore of ≥2 points, and
- exclusion of other causes of increased disease activity that are unrelated to UC (eg, infections or changes in medication).

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

### 5.7. Drug Accountability

The investigator (or designee) will maintain an accurate record of the receipt of study drug. In addition, an accurate drug accountability record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the sponsor upon request.

At the completion of the study, all unused study drug will be returned to the sponsor or disposed of by the study site, per the sponsor's written instructions.

## 6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

Allowed concomitant medications for UC should be maintained at a stable dose until the last dose of study drug.

The following medications are specifically excluded:

- cyclosporine, mycophenolate, tacrolimus, methotrexate, JAK inhibitors, and intravenous and rectally administered corticosteroids
- anti-TNF-α biologics or any other biologics (including ustekinumab and vedolizumab) for the treatment of UC
- orally administered azathioprine or 6-mercaptopurine that has been stable for <8 weeks prior to screening
- orally or rectally administered 5-aminosalicylic acid, or orally administered sulphasalazine or low-dose corticosteroids (prednisolone ≤20 mg/day or equivalent), that have been stable for <5 weeks prior to screening
- any other medications for UC that have been stable for <7 days or 5 half-lives, whichever is longer, prior to screening
- over-the-counter and prescription antidiarrhoeals and probiotics
- treatments for *Clostridium difficile*.

Oral, implantable, injectable, or intrauterine contraceptives are acceptable concomitant medications.

Any medication administered by a subject during the study and the reason for its use will be documented in the source data.

## 7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time provided in Appendix 11, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

At the discretion of the investigator, subjects may be requested to attend unscheduled visits for additional assessments or procedures, including, but not limited to, safety assessments and prescription of rescue medications.

## 7.1. Efficacy Assessments

### 7.1.1. Endoscopy with Biopsy

All details regarding endoscopic examination, standardised performing procedures, video recordings, assessment, biopsy sampling procedures, storage, and shipping will be provided in the laboratory manual.

Endoscopic examination will be required in order to establish the Mayo endoscopic subscore. Mayo endoscopic subscores will be assessed by both a local reader and a qualified central reader. Locally read Mayo endoscopic subscores will be used to determine the subject's clinical remission status, and treatment to be assigned in the extension phase. Centrally read Mayo endoscopic subscores will be used to evaluate the subject's eligibility and the objectives of the study. Further details of the endoscopy procedures and their standardisation will be documented in a separate charter.

Subjects will be required to undergo a full colonoscopy at screening; a flexible proctosigmoidoscopy will not be an option. Subsequent endoscopies may comprise a full colonoscopy or a flexible proctosigmoidoscopy; this will be at the investigator's discretion, based on the extent of disease.

An appropriately trained endoscopist should perform the flexible proctosigmoidoscopy/colonoscopy. Where possible, the same endoscopist should perform the endoscopy at all visits. It should be clearly documented who performed each endoscopy procedure.

On each occasion, every attempt should be made to collect biopsy samples from the same area. Biopsies will be collected from 2 locations, from the rectum and from the most proximal lesion in the colon (if the disease extends beyond the sigmoid colon). For biopsies collected from the rectum, if the disease extends <20 cm from the anal verge, the biopsy will be collected at the most proximal lesion of the disease. If the disease extends >20 cm from the anal verge, the biopsy will be collected at 15 to 20 cm from the anal verge.

### 7.1.2. Ulcerative Colitis Endoscopic Index of Severity

The UCEIS is the first validated index for the assessment of overall endoscopic activity (Appendix 5). The final model incorporates the vascular pattern, the presence of bleeding, and the presence of ulcerations with accurate definitions and 3 or 4 levels of severity as measurable parameters, which explain almost 90% of variations in determining overall activity.

### 7.1.3. Mayo Score

The total Mayo score (Appendix 6) is an instrument designed to measure disease activity of UC, with scores ranging from 0 to 12 points. The total Mayo score consists of 4 subscores, each graded from 0 to 3 with higher scores indicating more severe disease. For the

endoscopic subscore, the modified Mayo endoscopic score will be used to exclude any friability from Grade 1.

- stool frequency (0 to 3)
- rectal bleeding (0 to 3)
- findings on endoscopy (0 to 3)
- physician's global assessment (PGA; 0 to 3).

The total Mayo score (including the findings on endoscopy subscore) measured at screening will be used as the total Mayo baseline score.

The partial Mayo score (Appendix 7) consists of 3 subscores (stool frequency, rectal bleeding, and PGA).

The modified Mayo score (Appendix 8) consists of 3 subscores (stool frequency, rectal bleeding, and findings on endoscopy).

Where applicable, the subscores of stool frequency and rectal bleeding will be answered by the subject, subscores of PGA will be assessed by the investigator who has observed the subject, and findings on endoscopy will be assessed by designated reader.

#### 7.1.4. Inflammatory Bowel Disease Questionnaire

The IBDQ is a health-related quality-of-life (HRQoL) tool measuring bowel, systemic, emotional, and social function (Appendix 10). Scores for each question range between 1 and 7, reflecting poor to good HRQoL, for a range of possible total scores from 32 to 224.

#### 7.1.5. Histopathology

Mucosal biopsy samples will be collected during endoscopy for the histologic assessment of disease and healing. Measurements of histologic improvement will be performed by a central reader guided by the Geboes score (Appendix 9). Further details of the histologic procedures and their standardisation will be documented in a separate charter.

Biopsy samples will be used to explore the efficacy and safety of BBT-401-1S using gene expression and profiling; tissue blocks may be used for RNA analysis and/or immunohistochemistry. The biomarkers to be investigated will include, but will not be limited to: interleukin (IL)-8, granulocyte-macrophage colony-stimulating factor, IL-6, IL1-β, TNF-α, IL-23, IL-17, and retinoic acid receptor-related orphan receptor C.

### 7.2. Biomarkers

Serum C-reactive protein and faecal calprotectin will be measured to support the efficacy assessments.

## 7.3. Pharmacokinetic Assessments

Biopsy samples will be collected for analysis of tissue concentrations of BBT-401-1S. Procedures for the collection and shipping of tissue samples will be detailed in a separate document.

## 7.4. Safety Assessments

### 7.4.1. Adverse Events

Adverse event definitions, assignment of severity and causality, and procedures for reporting SAEs are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF to final discharge from the study. Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as "How have you been feeling since you were last asked?", at each study visit. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the study.

Any AEs and remedial action required will be recorded in the subject's source data. The nature, time of onset, duration, and severity will be documented, together with an investigator's (or designee's) opinion of the relationship to study drug.

Adverse events recorded during the study that are possibly related or related to the study drug or study procedures will be followed up, where possible, to resolution or until the unresolved AEs are judged by the investigator (or designee) to have stabilised. This will be completed at the investigator's (or designee's) discretion.

### 7.4.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations. Clinical laboratory evaluations are listed in Appendix 2. For all subjects, a *Clostridium difficile* test will be performed at screening. For all female subjects of childbearing potential, a serum pregnancy test will be performed at screening and urine pregnancy tests performed at all other timepoints. An investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

### 7.4.3. Vital Signs

Supine or sitting blood pressure, supine or sitting pulse rate, and tympanic temperature will be assessed. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required. All measurements will be performed singly and repeated once if outside the relevant clinical reference range.

Subjects must be supine or sitting for at least 5 minutes before blood pressure and pulse rate measurements. For individual subjects, the same posture and same arm should be used for all measurements throughout the study. Vital signs should be assessed prior to blood sampling.

### 7.4.4. 12-Lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes. Single 12-lead ECGs will be repeated once if either of the following criteria apply:

- QT interval corrected for heart rate using Fridericia's method (QTcF) >500 ms
- QTcF change from the baseline (predose) is >60 ms.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The investigator (or designee) will perform an assessment of each 12-lead ECG to determine any clinically significant findings.

### 7.4.5. Physical Examination

Physical examinations will be performed. Body weight will be measured as part of physical examinations.

## 7.5. Guidelines, Study Assessments, and Procedures During the Coronavirus Disease-19 Pandemic

In view of the coronavirus disease -19 (COVID-19) worldwide pandemic, the safety and wellbeing of study subjects is of primary importance. Study sites must comply with local public health rules.

Although every effort should be made to follow the protocol, subject safety is paramount and the investigator should continue to reassess the risks and benefits of continued study participation for each subject.

If a subject is diagnosed with COVID-19 or is suspected to have COVID-19, they should follow the local treatment and quarantine guidances.

- All diagnoses, procedures, assessments, dosing interruptions, and sequelae should be recorded in the electronic case report form (eCRF).
- Adverse events and SAEs should be reported in accordance with instructions in Appendix 1. If an AE or SAE related to COVID-19 is reported, the investigator should determine whether study drug administration should continue, be interrupted, or stopped.

If a subject is unable to attend study site visits and/or receive study drug, site staff should keep contact with the subject, preferably via telephone calls, to maintain awareness of subject status. If the subject is unable to attend the site, the following options may be considered:

- Subjects may be visited at their home by study staff or other trained professionals (where possible due to social distancing requirements).
- Visits may be performed by telephone or telemedicine to provide continuous medical care and oversight and to identify AEs.

- Blood samples may be collected and analysed at an alternative healthcare facility, at the discretion of the investigator. Although results of these analyses may not necessarily be collected or documented in the study database, it will allow the investigator to assess subject safety.
- If the endoscopy at the end-of-treatment visit can not be performed, the partial Mayo score may be collected by telephone or telemedicine (preferred).

# 8. SAMPLE SIZE AND DATA ANALYSIS

## 8.1. Determination of Sample Size

There has not been any formal statistical assessment of the sample size. However, the number of subjects is common in early clinical studies and is considered sufficient to achieve the objectives of the study.

## 8.2. Analysis Populations

The **intent-to-treat population** will include all subjects who received at least 1 dose of study drug, have a partial Mayo score recorded on Day 1, and at least 1 post-baseline Mayo score recorded.

The **safety population** will include all subjects who received at least 1 dose of study drug.

## 8.3. General Principles

Continuous variables will be summarised by the standard descriptive statistics: number of subjects (n), mean, standard deviation, median, minimum, and maximum. Frequency of subjects or events and percentages will be summarised in categorical variables.

## 8.4. Efficacy Analyses

### 8.4.1. Primary and Secondary Efficacy Analysis

All subjects in the intent-to-treat population will be included in the primary and secondary efficacy analyses. Descriptive summaries will be presented for clinical response, clinical remission, and endoscopic remission rates. The estimate and 95% confidence interval (CI) of clinical response, clinical remission, and endoscopic remission rates at Day 57 will be calculated using the exact binomial method for each treatment. The Fisher's exact test will be used to evaluate any differences between treatments.

Missing data will be deemed as "unresponsive". If any event that was not initially anticipated demands to reconsider data handling, then the method of handling the relevant data will be established in the statistical analysis plan.

### 8.4.2. Exploratory Efficacy Analysis

All subjects in the intent-to-treat population will be included in the exploratory efficacy analysis. The estimate and 95% CI of endoscopic response rate and histological improvement at Day 57, and clinical response rate and the percentage of subjects with clinical remission at

Day 112 will be calculated using the exact binomial method for each treatment. Actual values and change from baseline in Mayo scores, UCEIS scores, IBDQ total score, C-reactive protein, and faecal calprotectin over time will be summarised descriptively. No formal hypothesis will be tested on the exploratory efficacy endpoints.

### 8.5. Safety Analysis

All subjects in the safety population will be included in the safety analysis. All AEs will be listed and summarised using descriptive methodology. Each AE will be coded using the Medical Dictionary for Regulatory Activities. Observed values for clinical laboratory test data, 12-lead ECGs, vital signs, and physical examination findings will be listed.

### 8.6. Interim Analysis

No formal interim analyses are planned for this study. However, an assessment of clinical remission will be performed at Day 57 to determine whether a subject will progress into the extension phase and the dose to be administered.

## 9. REFERENCES

1. Kornbluth A, Sachar DB. Ulcerative Colitis Practice Guidelines in Adults: American College of Gastroenterology, Practice Parameters Committee: Am J Gastroenterol. 2010 Mar;105(3):501–23.

2. D'Haens G. Systematic review: second-generation vs. conventional corticosteroids for induction of remission in ulcerative colitis. Aliment Pharmacol Ther. 2016;44(10):1018–29.

3. Curkovic I, Egbring M, Kullak-Ublick GA. Risks of Inflammatory Bowel Disease Treatment with Glucocorticosteroids and Aminosalicylates. Dig Dis. 2013;31(3–4):368–73.

4. Andersen NN, Jess T. Risk of infections associated with biological treatment in inflammatory bowel disease. World J Gastroenterol. 2014;20(43):16014.

5. Gordon JP, McEwan PC, Maguire A, Sugrue DM, Puelles J. Characterizing unmet medical need and the potential role of new biologic treatment options in patients with ulcerative colitis and Crohn's disease: a systematic review and clinician surveys. Eur J Gastroenterol Hepatol. 2015 Jul;27(7):804–12.

## 10. APPENDICES

## Appendix 1: Adverse Event Reporting

### Definitions

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and/or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug.

### Assessment of Severity

The investigator will be asked to provide an assessment of the severity of the AE using the following categories:

- **Mild**: Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate**: Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
- **Severe**: Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

### Relationship to Study Treatment

The investigator (or designee) will decide the relationship of the AE to the study drug using a 4-category system according to the following guidelines:

- **Not Related**: The AE is definitely caused by the subject's clinical state or the study procedure/conditions.
- **Unlikely Related**: The temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
- **Possibly Related**: The AE follows a reasonable temporal sequence from the time of drug administration, but could have been produced by the subject's clinical state or the study procedures/conditions.
- **Related**: The AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesised cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

### Follow-up of Adverse Events

Every reasonable effort will be made to follow up with subjects who have AEs. Any subject who has an ongoing AE that is possibly related or related to the study drug or study procedures at the follow-up visit will be followed up, where possible, until resolution or until the unresolved AE is judged by the investigator (or designee) to have stabilised. This will be

completed at the investigator's (or designee's) discretion. Any subject who has an ongoing AE that is not related or unlikely related to the study drug or study procedures at the follow-up visit can be closed out as ongoing at the investigator's discretion.

**Adverse Drug Reactions**

All noxious and unintended responses to a study drug (ie, where a causal relationship between a study drug and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, investigator's brochure for an unapproved study drug).

**Serious Adverse Events**

A serious AE (SAE) is defined as any untoward medical occurrence that at any dose either:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- results in a congenital anomaly/birth defect
- results in an important medical event (see below).

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered SAEs when, based upon appropriate medical judgement, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Instances of death or congenital abnormality, if brought to the attention of the investigator at any time after cessation of the study drug and considered by the investigator to be possibly related to the study drug, will be reported to the sponsor.

Definition of Life-threatening

An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred (ie, does not include a reaction that might have caused death if it had occurred in a more serious form). For instance, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Definition of Hospitalisation

Adverse events requiring hospitalisation should be considered serious. In general, hospitalisation signifies that the subject has been detained (usually involving an overnight

stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate at the study site. When in doubt as to whether hospitalisation occurred or was necessary, the AE should be considered as serious.

Hospitalisation for elective surgery or routine clinical procedures, which are not the result of an AE, need not be considered AEs and should be recorded on a clinical assessment form and added to the electronic case report form. If anything untoward is reported during the procedure, this must be reported as an AE and either 'serious' or 'nonserious' attributed according to the usual criteria.

**Serious Adverse Event Reporting**

The investigator will complete an SAE report form and forward it by facsimile or email to Labcorp Drug Safety Services (DSS) and the sponsor immediately (within 24 hours) upon becoming aware of an SAE.

The responsibilities of Labcorp DSS include the following:

- Prepare an AE reporting plan prior to the start of the study. Where this plan differs from the applicable study site standard operating procedure on SAE reporting, the Safety Management Plan will always take precedence.
- Receive and review SAE report forms from the study site and inform the sponsor of the SAE within 1 working day of the initial notification to Labcorp DSS. Drug Safety Services will delete any information from the SAE report forms that may identify the subject.
- Write case narratives and enter the case into Labcorp's safety database as defined in the AE reporting plan.
- Produce appropriate reports of all suspected unexpected serious adverse reactions and forward to the ethics committee, principal investigator, and the sponsor.

The responsibility for reporting SAEs will be transferred to the sponsor 28 days after the end of the study.

**Pregnancy**

Pregnancy (maternal or paternal exposure to study drug) does not meet the definition of an AE. However, to fulfil regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and foetus. A separate consent form will be signed by the pregnant female partner in order to gather information on the pregnancy and foetus.

## Appendix 2: Clinical Laboratory Evaluations

| Clinical chemistry: | Haematology: | Urinalysis: |
|---|---|---|
| Alanine aminotransferase<br>Albumin<br>Alkaline phosphatase<br>Amylase<br>Aspartate aminotransferase<br>Bicarbonate<br>Blood urea nitrogen<br>Calcium<br>Chloride<br>Cholesterol<br>Creatine kinase<br>Creatinine<br>Direct bilirubin<br>Gamma-glutamyl transferase<br>Glucose<br>Lipase<br>Potassium<br>Sodium<br>Total bilirubin<br>Total protein<br>Triglycerides<br>Uric acid | Hematocrit<br>Haemoglobin<br>Mean cell haemoglobin<br>Mean cell haemoglobin concentration<br>Mean cell volume<br>Platelet count<br>Red blood cell count<br>White blood cell (WBC) count<br>WBC differential:<br>Basophils<br>Eosinophils<br>Lymphocytes<br>Monocytes<br>Neutrophils | Bilirubin<br>Blood<br>Colour and appearance<br>Glucose<br>Ketones<br>Leukocyte esterase<br>Nitrite<br>pH<br>Protein<br>Specific gravity<br>Urobilinogen<br>Microscopic examination |
| **Serology:** | **Hormone panel - females only:** | **Coagulation** |
| Hepatitis B surface antigen<br>Hepatitis B virus surface antibody<br>Hepatitis B virus core antibody<br>Hepatitis C antibody<br>Human immunodeficiency (HIV-1 and HIV-2) antibodies and p24 antigen | Follicle-stimulating hormone (postmenopausal females only)<br>Serum pregnancy test (human chorionic gonadotropin; screening only; females of childbearing potential only)<br>Urine pregnancy test (all timepoints except screening; females of childbearing potential only) | Prothrombin time<br>Activated partial thromboplastin time<br>International normalized ratio |
| **Other:** | | |
| *Clostridium difficile* test | | |

## Appendix 3: Contraception Guidance

### Definitions

**Females of Childbearing Potential**: premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

**Females of Nonchildbearing Potential:**

1. **Surgically sterile**: females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilisation to have occurred a minimum of 6 weeks, or at the investigator's discretion, prior to screening.
2. **Postmenopausal**: females at least 45 years of age with amenorrhoea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone levels of ≥40 mIU/mL. The amenorrhoea should not be induced by a medical condition, such as anorexia nervosa, hypothyroid disease, or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhoea, such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-oestrogens, or selective oestrogen receptor modulators.

**Fertile male**: a male that is considered fertile after puberty.

**Infertile male**: permanently sterile male via:

- bilateral orchiectomy, or
- vasectomy performed at least 90 days prior to the screening visit with confirmation of surgical success.

### Contraception Guidance

### Female Subjects

Female subjects who are of nonchildbearing potential will not be required to use contraception.

Female subjects of childbearing potential who have a fertile male partner must be willing to use 2 methods (1 primary and 1 secondary method) of birth control from the time of signing the informed consent form (ICF) until 3 months after the last dose of study drug. Primary (non-barrier) methods of contraception include:

- hormonal injection (as prescribed)
- combined oral contraceptive pill or progestin/progestogen-only pill (as prescribed)
- combined hormonal vaginal ring (as prescribed)
- surgical method performed at least 3 months prior to the screening visit:
    - bilateral tubal ligation

    - Essure® (hysteroscopic bilateral tubal occlusion) with confirmation of occlusion of the fallopian tubes
- hormonal implant
- hormonal or non-hormonal intrauterine device.

Secondary (barrier) methods of contraception include:

- male condom
- female condom
- diaphragm (as prescribed).

Female subjects of childbearing potential who have an infertile male partner are not required to use contraception, providing that the infertile male is the sole partner of the female subject. A barrier method of contraception may be encouraged but is not required.

Female subjects of childbearing potential should refrain from donation of ova from Day 1 until 3 months after the last dose of study drug.

**Male Subjects**

Infertile male subjects must use a barrier method of contraception from Day 1 until 3 months after the follow-up visit.

Fertile male subjects with partners of childbearing potential must use a barrier method of contraception in addition to a second method of acceptable contraception from Day 1 until 3 months after the follow-up visit.

Barrier methods of contraception include:

- male condom
- female condom
- diaphragm (as prescribed).

Acceptable secondary methods of contraception for female partners include:

- hormonal injection
- combined oral contraceptive pill or progestin/progestogen-only pill
- combined hormonal vaginal ring
- surgical method (bilateral tubal ligation or Essure® [hysteroscopic bilateral tubal occlusion])
- hormonal implant
- hormonal or non-hormonal intrauterine device.

For male subjects, sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from Day 1 until 3 months after the follow-up visit.

Male subjects are required to refrain from donation of sperm from Day 1 until 3 months after the follow-up visit.

**Sexual Abstinence and Same-sex Relationships**

Subjects who practice true abstinence, because of the subject's lifestyle choice (ie, the subject should not become abstinent just for the purpose of study participation), are exempt from contraceptive requirements. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. If a subject who is abstinent at the time of signing the ICF becomes sexually active, they must agree to use contraception as described previously.

For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply. If a subject who is in a same-sex relationship at the time of signing the ICF becomes engaged in a heterosexual relationship, they must agree to use contraception as described previously.

## Appendix 4: Regulatory, Ethical, and Study Oversight Considerations

### Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, informed consent form (ICF), investigator's brochure, and other relevant documents must be submitted to an ethics committee (EC) by the investigator and reviewed and approved by the EC before the study is initiated.

Any substantial protocol amendments, likely to affect the safety of the subjects or the conduct of the study, will require EC and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects or any nonsubstantial changes, as defined by regulatory requirements.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the EC annually or more frequently in accordance with the requirements, policies, and procedures established by the EC.
- Notifying the EC of serious adverse events or other significant safety findings as required by the EC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the EC, European Directive 2001/20/EC for clinical studies (if applicable), and all other applicable local regulations.

### Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

### Informed Consent

Prior to starting participation in the study, each subject will be provided with a study-specific ICF giving details of the study drugs, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the investigator (or designee) and that their participation is voluntary and that they are free to withdraw from the study at any time. Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation.

Following discussion of the study with study site personnel, subjects will sign 2 copies of the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving their informed consent. One copy will be given to the subject, and the other will be maintained in the subject's records.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

**Subject Data Protection**

Subjects will be assigned a unique identifier and will not be identified by name in eCRFs, study-related forms, study reports, or any related publications. Subject and investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual subjects or investigators will be redacted according to applicable laws and regulations.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her study-related data may be examined by the sponsor or contract research organisation (CRO) auditors or other authorised personnel appointed by the sponsor, by appropriate EC members, and by inspectors from regulatory authorities.

**Disclosure**

All information provided regarding the study, as well as all information collected and/or documented during the study, will be regarded as confidential. The investigator (or designee) agrees not to disclose such information in any way without prior written permission from the sponsor.

**Data Quality Assurance**

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs, unless directly transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, EC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a data management plan.

- A study monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator in the study site archive for at least 5 years after the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

**Investigator Documentation Responsibilities**

All individual, subject-specific study data will also be entered into a 21 CFR Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to the sponsor or designee electronically, will be integrated with the subject's eCRF data in accordance with the data management plan.

An eCRF must be completed for each enrolled subject who undergoes any screening procedures, according to the eCRF completion instructions. The sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

**Publications**

- Publications will be addressed in a separate agreement.The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

## Appendix 5: Ulcerative Colitis Endoscopic Index of Severity

| Descriptor | Likert scale (anchor points) | Definition |
|---|---|---|
| **Vascular pattern** | Normal (0) | Normal vascular pattern with arborisation of capillaries clearly defined, or with blurring or patchy loss of capillary margins |
| | Patchy obliteration (1) | Patchy obliteration of vascular pattern |
| | Obliterated (2) | Complete obliteration of vascular pattern |
| **Bleeding** | None (0) | No visible blood |
| | Mucosal (1) | Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope, which can be washed away |
| | Luminal mild (2) | Some free liquid blood in the lumen |
| | Luminal moderator severe (3) | Frank blood in the lumen ahead of endoscope or visible oozing from mucosa after washing intraluminal blood or visible oozing from a haemorrhagic mucosa |
| **Erosions and ulcers** | None (0) | Normal mucosa, no visible erosions or ulcers |
| | Erosions (1) | Tiny (≤5 mm) defects in the mucosa, of a white or yellow colour with a flat edge |
| | Superficial ulcer (2) | Larger (>5 mm) defects in the mucosa, which are discrete fibrin-covered ulcers in comparison with erosions, but remain superficial |
| | Deep ulcer (3) | Deeper excavated defects in the mucosa with a slightly raised edge |

Adapted from Travis SP, Schnell D, Krzeski P et al. Reliability and initial validation of the Ulcerative Colitis Endoscopic Index of Severity. *Gastroenterology* 2013;145:987–95.

## Appendix 6: Total Mayo Score

| Question | Subject-reported | | Investigator-reported | |
|---|---|---|---|---|
| | Stool frequency* | Rectal bleeding* | Physician's Global Assessment† | Findings on endoscopy |
| **Score** | | | | |
| 0 | Normal number of stools | No blood seen | Normal | Normal or inactive disease |
| 1 | 1-2 stools more than normal | Streaks of blood with stool less than half the time | Mild disease | Mild disease (erythema, decreased vascular pattern) |
| 2 | 3-4 stools more than normal | Obvious blood (more than just streaks) or streaks of blood with stool most of time | Moderate disease | Moderate disease (marked erythema, absent vascular pattern, friability, erosions) |
| 3 | ≥ 5 stools more than normal | Blood alone passed | Severe disease | Severe disease (spontaneous bleeding, ulceration) |

* Subject will document the stool frequency and the rectal bleeding score daily in the subject diary. The stool frequency and rectal bleeding subscores will use the average of the last 3 non-missing assessments recorded in the subject diary. If an endoscopy is performed, the average of the last 3 non-missing assessments recorded in the subject diary prior to bowel preparation should be used. If the subscore is not an integer, the subscore should be rounded to the nearest integer.
† Physician's Global Assessment acknowledges the subscores, the daily records of abnormal discomfort and functional assessment, and other observations such as physical findings and the subject's performance status.
Adapted from Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomised study. *N Engl J Med*. 1987;317(26):1625.

## Appendix 7: Partial Mayo Score

| Question | Subject-reported | | Investigator-reported |
|---|---|---|---|
| | Stool frequency* | Rectal bleeding* | Physician's Global Assessment† |
| **Score** | | | |
| 0 | Normal number of stools | No blood seen | Normal |
| 1 | 1-2 stools more than normal | Streaks of blood with stool less than half the time | Mild disease |
| 2 | 3-4 stools more than normal | Obvious blood (more than just streaks) or streaks of blood with stool most of time | Moderate disease |
| 3 | ≥5 stools more than normal | Blood alone passed | Severe disease |

* Subject will document the stool frequency and the rectal bleeding score daily in the subject diary. The stool frequency and rectal bleeding subscores will use the average of the last 3 non-missing assessments recorded in the subject diary. If an endoscopy is performed, the average of the last 3 non-missing assessments recorded in the subject diary prior to bowel preparation should be used. If the subscore is not an integer, the subscore should be rounded to the nearest integer.
† Physician's Global Assessment acknowledges the subscores, the daily records of abnormal discomfort and functional assessment, and other observations such as physical findings and the subject's performance status.
Adapted from Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomised study. *N Engl J Med*. 1987;317(26):1625.

## Appendix 8: Modified Mayo Score

| Question | Subject-reported | | Investigator-reported |
|---|---|---|---|
| | Stool frequency* | Rectal bleeding* | Findings on endoscopy |
| **Score** | | | |
| 0 | Normal number of stools | No blood seen | Normal or inactive disease |
| 1 | 1-2 stools more than normal | Streaks of blood with stool less than half the time | Mild disease (erythema, decreased vascular pattern) |
| 2 | 3-4 stools more than normal | Obvious blood (more than just streaks) or streaks of blood with stool most of time | Moderate disease (marked erythema, absent vascular pattern, friability, erosions) |
| 3 | ≥5 stools more than normal | Blood alone passed | Severe disease (spontaneous bleeding, ulceration) |

* Subject will document the stool frequency and the rectal bleeding score daily in the subject diary. The stool frequency and rectal bleeding subscores will use the average of the last 3 non-missing assessments recorded in the subject diary. If an endoscopy is performed, the average of the last 3 non-missing assessments recorded in the subject diary prior to bowel preparation should be used. If the subscore is not an integer, the subscore should be rounded to the nearest integer.
Adapted from Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomised study. *N Engl J Med*. 1987;317(26):1625.

## Appendix 9: Geboes Score

| | |
|---|---|
| **Grade 0: Architectural changes** | 0.0 No abnormality<br>0.1 Mild abnormality<br>0.2 Mild/moderate diffuse or multifocal abnormalities<br>0.3 Severe diffuse or multifocal abnormalities |
| **Grade 1: Chronic inflammatory infiltrate** | 1.0 No increase<br>1.1 Mild but unequivocal increase<br>1.2 Moderate increase<br>1.3 Marked increase |
| **Grade 2A: Eosinophils in lamina propria** | 2A.0 No increase<br>2A.1 Mild but unequivocal increase<br>2A.2 Moderate increase<br>2A.3 Marked increase |
| **Grade 2B: Neutrophils in lamina propria** | 2B.0 No increase<br>2B.1 Mild but unequivocal increase<br>2B.2 Moderate increase<br>2B.3 Marked increase |
| **Grade 3: Neutrophils in epithelium** | 3.0 None<br>3.1 < 5% crypts involved<br>3.2 < 50% crypts involved<br>3.3 > 50% crypts involved |
| **Grade 4: Crypt destruction** | 4.0 None<br>4.1 Probable: local excess of neutrophils in part of the crypts<br>4.2 Probable: marked attenuation<br>4.3 Unequivocal crypt destruction |
| **Grade 5: Erosions and ulcerations** | 5.0 No erosion, ulceration or granulation tissue<br>5.1 Recovering epithelium + adjacent inflammation<br>5.2 Probable erosion: focally stripped<br>5.3 Unequivocal erosion<br>5.4 Ulcer or granulation tissue |

Adapted from Geboes K Riddell R Ost A Jensfelt B Persson T Lofberg R. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. *Gut* 2000;47:404–9.

**Appendix 10: Inflammatory Bowel Disease Questionnaire**

INSTRUCTIONS FOR SELF-ADMINISTERED IBDQ

This questionnaire is designed to measure the effects of your inflammatory bowel disease on your daily function and quality of life. You will be asked about symptoms you have been having as a result of your bowel disease, the way you have been feeling in general, and how your mood has been.

There are two versions of this questionnaire, the IBDQ and IBDQ-Stoma. If you have a colostomy or ileostomy, you should complete the IBDQ-Stoma. Questions 1, 5, 17, 22, 24 and 26 are slightly different in each version. Be sure you have the correct questionnaire.

On this questionnaire there are 32 questions. Each question has a graded response numbered from 1 through 7. Please read each question carefully and select the number which best describes how you have been feeling in the past 2 weeks.

EXAMPLE

**How often have you felt unwell as a result of your bowel problem in the past 2 weeks?**

(1) ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

If you are having trouble understanding a question, **STOP** for a moment! Think about what the question means to you. How is it affected by your bowel problem? Then answer the question as best you can. You will have the chance to ask the research assistant questions after completing the questionnaire. This takes only a few minutes to complete.

**QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)**

**This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.**

1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last two weeks by picking one of the options from

1 BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN
2 EXTREMELY FREQUENT
3 VERY FREQUENT
4 MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
5 SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
6 SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
7 NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

3. How often during the last 2 weeks have you felt frustrated, impatient, or restless? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

5. How much of the time during the last 2 weeks have your bowel movements been loose? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

6. How much energy have you had during the last 2 weeks? Please choose an option from

1 NO ENERGY AT ALL
2 VERY LITTLE ENERGY
3 A LITTLE ENERGY
4 SOME ENERGY
5 A MODERATE AMOUNT OF ENERGY
6 A LOT OF ENERGY
7 FULL OF ENERGY

7. How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

8. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

9. How often during the last 2 weeks have you been troubled by cramps in your abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

10. How often during the last 2 weeks have you felt generally unwell? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

11. How often during the last 2 weeks have you been troubled because of fear of not finding a washroom? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from

1 A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
2 A LOT OF DIFFICULTY
3 A FAIR BIT OF DIFFICULTY
4 SOME DIFFICULTY
5 A LITTLE DIFFICULTY
6 HARDLY ANY DIFFICULTY
7 NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES

13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

14. How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

15. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

16. How often during the last 2 weeks have you had to avoid attending events where there was no washroom close at hand? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

17. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

18. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to, the weight you would like to be at? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

21. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option from

1 NONE OF THE TIME
2 A LITTLE OF THE TIME
3 SOME OF THE TIME
4 A GOOD BIT OF THE TIME
5 MOST OF THE TIME
6 ALMOST ALL OF THE TIME
7 ALL OF THE TIME

22. How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

23. How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

25. How much of the time during the last 2 weeks have you felt tearful or upset? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

28. To what extent has your bowel problem limited sexual activity during the last 2 weeks? Please choose an option from

1 NO SEX AS A RESULT OF BOWEL DISEASE
2 MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE
3 MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE
4 SOME LIMITATION AS A RESULT OF BOWEL DISEASE
5 A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE
6 HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE
7 NO LIMITATION AS A RESULT OF BOWEL DISEASE

29. How much of the time during the last 2 weeks have you been troubled by nausea or feeling sick to your stomach? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

30. How much of the time during the last 2 weeks have you felt irritable? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

31. How often during the past 2 weeks have you felt a lack of understanding from others? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

32. How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks? Please choose one of the following options from

1 VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
2 GENERALLY DISSATISFIED, UNHAPPY
3 SOMEWHAT DISSATISFIED, UNHAPPY
4 GENERALLY SATISFIED, PLEASED
5 SATISFIED MOST OF THE TIME, HAPPY
6 VERY SATISFIED MOST OF THE TIME, HAPPY
7 EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASED

## Appendix 11: Schedule of Assessments

| | | Induction Phase | | | | |
|---|---|---|---|---|---|---|
| | **Visit 1** | **Visit 2** | **Visit 3** | **Visit 4** | **Visit 5** | **Visit 6[a]** |
| | **Screening** | **Baseline** | | | **EOT/ET** | **Follow-up** |
| | **≤28 days prior to Day 1** | **Day 1** | **Day 8[b] (± 3 d)** | **Day 29 (± 3 d)** | **Day 57 (± 3 d)** | **Day 71 (± 7 d)** |
| Informed consent | X | | | | | |
| Inclusion/exclusion | X | P | | | | |
| Demographics | X | | | | | |
| Medical history | X | P | | | | |
| Concomitant medication | X | | | | | |
| Subject diary completion | X | | | | | |
| **Study drug** | | | | | | |
| Randomisation | | X | | | | |
| Study drug administration | | X | | | | |
| Compliance review | | | X | X | X | |
| **Safety** | | | | | | |
| Follicle-stimulating hormone[c] | X | | | | | |
| Pregnancy test[d] | X | P | | X | X | |
| Viral serology | X[e] | | | | | |
| *Clostridium difficile* test | X | | | | | |
| Chemistry, haematology, coagulation, and urinalysis | X | P | | X | X | X |
| Vital signs | X | P | | X | X | X |
| 12-lead ECGs | X | P | | X | X | X |
| Physical examination | X | | | X | X | X |
| Adverse event monitoring | X | | | | | |
| **Endoscopic and clinical assessments** | | | | | | |
| UCEIS | X | | | | X | |
| Total Mayo score[f] | X | | | | X | |
| Partial Mayo score[f,g] | X | P | | X | X | |
| Modified Mayo score[f,h] | X | | | | X | |
| **Health-related quality of life** | | | | | | |
| IBD questionnaire | | P | | X | X | |
| **Biomarkers** | | | | | | |
| C-reactive protein | X | P | | X | X | |
| Faecal calprotectin | X | P | | X | X | |
| **Endoscopy/biopsy** | | | | | | |
| Endoscopy | X[i] | | | | X[j] | |
| Histopathology | X | | | | X | |
| Tissue concentration | | | | | X | |

Abbreviations: d = days; ECG = electrocardiogram; EOT = end of treatment; ET = early termination; IBD = inflammatory bowel disease; P = predose; UCEIS = Ulcerative Colitis Endoscopic Index of Severity.

a Only for subjects who do not agree to participate in the extension phase.

b Telephone visit; however, at the discretion of the investigator, subjects may be requested to attend the study site.

c Postmenopausal females only.

d Females of childbearing potential only. A serum pregnancy test will be performed at screening and urine pregnancy tests performed at all other timepoints.

e At a minimum comprises HBV (includes HBV surface antigen, HBV surface antibody, and HBV core antibody), antibodies to hepatitis C virus, and human immunodeficiency virus.

f Mayo scores collected from 1 week prior to each visit (including endoscopy visit).

g Rectal bleeding, stool frequency, and Physician's global assessment.

h Rectal bleeding, stool frequency, and findings on endoscopy.

i Conducted within 7 days of Day 1.

j Endoscopy will be performed ≤7 days prior to the Day 57 visit or on the same day as the other Day 57 procedures/assessments.

| | Extension Phase | | |
|---|---|---|---|
| | Visit 7 | Visit 8 | Visit 9 |
| | | | EOS/ET visit |
| | Day 71 (± 3 d)[a] | Day 85 (± 3 d) | Day 112 (± 3 d) |
| Concomitant medication | X | | |
| Subject diary completion | X | | |
| **Study drug** | | | |
| Study drug administration | X | | |
| Compliance review | X | X | X |
| **Safety** | | | |
| Urine pregnancy test[b] | | X | X |
| Chemistry, haematology, coagulation, and urinalysis | | X | X |
| Vital signs | | X | X |
| 12-lead ECGs | | X | X |
| Physical examination | | X | X |
| Adverse event monitoring | X | | |
| **Endoscopic and clinical assessments** | | | |
| UCEIS | | | X[d] |
| Total Mayo score[c] | | | X[d] |
| Partial Mayo score[c,e] | | X | X |
| Modified Mayo score[c,f] | | | X[d] |
| **Health-related quality of life** | | | |
| IBD questionnaire | | X | X |
| **Biomarkers** | | | |
| C-reactive protein | | X | X |
| Faecal calprotectin | | X | X |
| **Endoscopy/biopsy** | | | |
| Endoscopy | | | X[g] |
| Histopathology | | | X[d] |

Abbreviations: d = days; ECG = electrocardiogram; EOS = end of study; ET = early termination; IBD = inflammatory bowel disease; UCEIS = Ulcerative Colitis Endoscopic Index of Severity.

a Telephone visit; however, at the discretion of the investigator, subjects may be requested to attend the study site for safety assessments.

b Females only.

c Mayo scores collected from 1 week prior to each visit (including endoscopy visit).

d If endoscopy is performed.

e Rectal bleeding, stool frequency, and Physician's global assessment.

f Rectal bleeding, stool frequency, and findings on endoscopy.

g Endoscopy performed at the discretion of the investigator. If an endoscopy is performed, it should be performed ≤7 days prior to the EOS/ET visit or on the same day as the other EOS/ET procedures/assessments.

**Appendix 12: Summary of Changes**

The following changes were implemented in Protocol Version 2:

- It was clarified that the Mayo endoscopic subscore will be assessed by both a local and qualified central reader. Locally read Mayo endoscopic subscores will be used to determine the subject's eligibility, clinical remission status, and treatment to be assigned in the extension phase. Centrally read Mayo endoscopic subscores will be used to evaluate the objectives of the study.
- Measurements of the tissue concentration of BBT-401-1S at screening were removed.
- The time window for the Day 57 endoscopy was updated.
- The time windows for visits in the extension phase were updated.
- The fasting requirements were removed.
- It was clarified that stool frequency and rectal bleeding will be documented daily by the subject.
- The unit of glomerular filtration rate was corrected.

The following changes were implemented in Protocol Version 3:

- Protocol Version 2 incorrectly stated that locally read Mayo endoscopic subscores would be used to determine the subject's eligibility. This was corrected to state that centrally read Mayo endoscopic subscores will be used to evaluate the objectives of the study.

The following changes were implemented in Protocol Version 4:

- Clarified that subjects who test positive for *Clostridium difficile* at screening will be excluded.
- Added that clinical laboratory evaluations, including liver function tests, may be repeated once, at the discretion of the investigator (or designee), to determine eligibility.
- Added that subjects may be rescreened once, at the discretion of the investigator (or designee), providing that the reason for screen failure was not due to a safety concern or non-eligibility related to clinical laboratory evaluations.
- Updated that the study treatments will be provided in bottles.
- Added locations from which biopsies will be collected.
- Added that the total Mayo score measured at screening will be used as baseline.
- Clarified that subscores of physician's global assessment component of the Mayo score will be assessed by the investigator who has observed the subject
- Updated the definition of 'obvious blood' for subject-reported rectal bleeding within the total, partial, and modified Mayo scores according to Food and Drug

Administration (FDA) interpretation of the FDA Guidance on Clinical Trial Endpoints of Ulcerative Colitis.

- Clarified that the subject will document stool frequency and the rectal bleeding score **daily in the subject diary** and subscores will be calculated as the average of the last 3 non-missing assessments.
- Added histopathology on Day 112, if endoscopy is performed.
- Minor editorial and formatting changes were made.

The following changes were implemented in Protocol Version 5:

- Updated the sponsor's medical contact.
- The name of the organisation Covance was changed to Labcorp.
- Updated that rectally administered 5-aminosalicylic acid that has been stable for <5 weeks is exclusionary.
- Clarified in Section 6 that concomitant medications for ulcerative colitis should be maintained at a stable dose until the last dose of study drug for consistency with the exclusion criteria in Section 4.2.
- Added that over-the-counter and prescription antidiarrhoeals and probiotics are excluded for the duration of the study.
- Added guidelines for performing assessments and procedures during the coronavirus disease-19 pandemic.
- Minor editorial and formatting changes were made.