Clinical Study Protocol

Protocol Title:	**A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 2a Study to Evaluate the Efficacy and Safety of BBT-401-1S in Patients with Active Ulcerative Colitis**
Short Title:	**Phase 2a Study of BBT401-1S in Active UC**
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GCP Statement

This study is to be performed in full compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

Investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, ICF(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 Synopsis

Title:	A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 2a Study to Evaluate the Efficacy and Safety of BBT-401-1S in Patients with Active Ulcerative Colitis
Study Description:	This will be a randomized, double-blind, placebo-controlled study of orally administered BBT-401-1S to evaluate its efficacy and safety for the treatment of active ulcerative colitis (UC)
Objectives:	Primary Objective: ▪ To assess the efficacy and safety of multiple oral doses of BBT-401-1S in patients with active UC Secondary Objectives: ▪ To assess the plasma and tissue concentration of multiple oral doses of BBT-401-1S in patients with active UC ▪ To evaluate the effects of BBT-401-1S on biomarkers
Endpoints:	Primary Endpoint: ▪ Change from Baseline in Total Mayo Score at Week 8 Secondary Endpoints: ▪ Change from Baseline in Partial Mayo Score at Week 8 ▪ Change from Baseline in Histologic Assessment of Endoscopic Biopsy at Week 8 ▪ Change from Baseline in Ulcerative Colitis Endoscopic Index of Severity (UCEIS) Score at Week 8 ▪ Number and Severity of Treatment Emergent Adverse Events (TEAEs) up to Week 8 ▪ Change from Baseline in Short Inflammatory Bowel Disease Questionnaire (SIBDQ) at Week 8 ▪ Change from Baseline in Concentration of Biomarkers (C-reactive protein [CRP], fecal calprotectin, and fecal lactoferrin) at Week 8 ▪ Plasma and Tissue Concentration of BBT-401-1S in Patients with Active UC
Study Population:	The study plans to enroll up to 48 adult patients with active UC in the United States and South Korea. *Inclusion Criteria* 1) Provision of signed and dated informed consent form 2) Stated willingness to comply with all study procedures and availability for the duration of the study 3) Male or female, aged ≥18 years 4) Diagnosed with active UC for at least 3 months prior to screening 5) Total Mayo score ≥5 and Endoscopic sub-score ≥1 6) Stable dosing regimens of oral drugs (if currently administered) as follows: 5-ASA or sulfasalazine at a stable dose for at least 4 weeks, purine analogues (azathioprine, mercaptopurine, thiopurines) or immunosuppressants (methotrexate, cyclosporine) at a stable dose for at least 12 weeks, and low-dose oral corticosteroid (up to 20 mg prednisone/day or equivalent) for at least 4 weeks prior to the first dose of study treatment. Doses of oral drugs must

	remain stable until the end of study treatment (with possible exception for tapering steroid dose after 8 weeks) 7) For females of reproductive potential: use of highly effective contraception for at least 1 month prior to screening and agreement to use such a method during study participation and for an additional 3 months after the last dose 8) For males of reproductive potential: use of condoms or other methods to ensure effective contraception with partner during study participation and for an additional 3 months after the last dose *Exclusion Criteria* 1) Use of anti-TNF-α biologics, any other biologics, or tofacitinib for treatment of UC within 60 days prior to randomization. 2) Any rectal therapy for treatment of UC or intravenous corticosteroids within 2 weeks prior to randomization. 3) Presence of Crohn's disease, indeterminate colitis, ischemic colitis, fulminant colitis, ulcerative proctitis, or toxic mega-colon 4) Previous extensive colonic resection (subtotal or total colectomy) 5) Ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine 6) 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 randomization 7) Active infection with the HIV or Hepatitis B or C viruses 8) Clinically significant active extra-intestinal infection (e.g., pneumonia, pyelonephritis) 9) Clinically significant abnormal vital signs, physical examination or 12-lead electrocardiogram (ECG) at screening or baseline 10) Clinically significant abnormal results of liver function tests (ALT/AST, bilirubin and alkaline phosphatase) > 2X the upper limit of normal (ULN) at screening 11) Other clinically significant abnormal laboratory results at screening in the investigator's opinion 12) History of any clinically significant medical condition that, in the investigator's opinion, would preclude participation in the study 13) Pregnancy or lactation 14) Treatment with another investigational drug or other intervention within 30 days prior to screening
Phase:	Phase 2a
Description of Study Intervention:	BBT-401-1S, the monosodium salt of BBT-401, will be administered as 200-mg capsules, once a day (q.d.) for 16 weeks

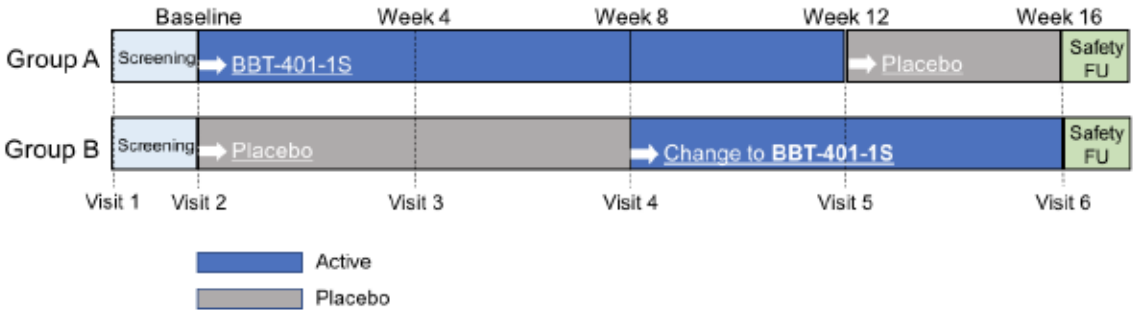
1.2 Schema

Summary

This randomized, placebo-controlled, dose-escalation, multicenter, Phase 2 study consists of three cohorts with 16-week treatment period per cohort that will be conducted sequentially. The first cohort will receive 400 mg of BBT-401-1S (starting dose). Efficacy, safety, and PK data of the

first cohort will be used to select the dose of the subsequent cohort. For the 1st or 2nd cohort, if 12th patient (75%) completes Visit 4 (Week 8), unblinding of 12 patients will be performed within 2 weeks after Visit 4 (Week 8) and the unblinding information will be only provided to the Sponsor for the analysis to determine the dose of next cohort.

Patients will receive a daily oral dose of BBT-401-1S or placebo for the 16 weeks. While patients who are assigned to Active Group will receive BBT-401-1S for the first 12 weeks and then placebo for the last 4 weeks, patients who are assigned to Placebo Group will receive placebo for the first 8 weeks and then BBT-401-1S for last 8 weeks.



Dosing Cohorts

- A total of 16 patients in each cohort will be randomized to either active or placebo group (12 active and 4 placebo).
- Three cohorts will be conducted sequentially. The first cohort will receive 400 mg of BBT-401-1S (starting dose). Efficacy, safety, and PK data of the first cohort will be used to select the dose of the subsequent cohort. A dose level may be repeated or added based on results of the previous cohort(s).
- The highest dose is not to exceed 1,600 mg daily.

Study Visits

- Visit 1 (Screening)
- Visit 2 (Baseline): PK and baseline assessments
- Visit 3 (Week 4): PK, 4-week treatment visit
- Visit 4 (Week 8): PK, 8-week treatment visit
- Visit 5 (Week 12): 12-week treatment visit
- Visit 6 (Week 16): 16-week treatment visit
- Safety Follow-Up (SFU): 2 weeks from the last dose

Efficacy Assessments

- Total Mayo Score (Stool frequency, rectal bleeding, endoscopic findings [flexible proctosigmoidoscopy/colonoscopy], physician's global assessment): Screening and W8
- Partial Mayo Score: Baseline, W4, W8, W12, and W16
- Histologic Assessment of Endoscopic Biopsy: Screening and W8
- Ulcerative Colitis Endoscopic Index of Severity (UCEIS): Screening and W8
- Short Inflammatory Bowel Disease Questionnaire (SIBDQ): Baseline, W4, W8, W12, and W16
- Serum CRP: Baseline, W4, W8, W12, and W16
- Fecal calprotectin: Baseline, W4, W8, W12, and W16
- Fecal lactoferrin: Baseline, W4, W8, W12, and W16

Safety Assessments

- Physical examination: Screening, Baseline, W4, W8, W12, and W16
- Vital signs: All visits (including SFU)
- 12-lead ECG: Screening, Baseline, W4, W8, W12, and W16
- Clinical laboratory testing of serum chemistry/hematology: All visits (including SFU)
- Recording of AEs: Baseline, W4, W8, W12, W16, and SFU

Pharmacokinetic Assessments

- Concentrations of BBT-401-1S in plasma to assess systemic exposure: Baseline, W4, and W8
- Concentration of BBT-401-1S in tissue to assess exposure: Screening and W8

Statistical Analysis

As this is an initial dose-finding study, it is appropriately based on only a limited number of patients in each dose cohort. The number of patients in this study is not based on any statistical power calculations; further, no formal inferential statistics analyses are planned. For the quantitative endpoints (efficacy, biomarker measure, and some safety data) descriptive statistics will be calculated to provide an indication of directional changes in endpoints for each treatment group per dose cohort.

Further, to allow for a direct comparison of BBT-401-1S vs placebo for each cohort, descriptive statistics will be provided for the difference between the treatment groups at Week 8. For the qualitative data, frequency counts and incidence rates will be compiled for each treatment group.

1.3 Schedule of Assessments

	Screening	Treatment Period						SFU
Visit Number	V1	V2	V3	V4	V5	V6	ET	
Visit Period	Up to W-4	Baseline	W4	W8	W12	W16	N/A	W2 from LD
Visit Window	N/A	Within 28 days from V1	±3 days	±3 days	±3 days	±3 days	N/A	+ 7 days from LD
Informed Consent	X							
Demographic Information	X							
Medical/medication History	X	X						
Inclusion/exclusion Criteria	X	X						
Vital Signs	X	X	X	X	X	X	X	X
Physical Examination	X	X[a]	X	X	X	X	X	
12-lead ECG	X	X[a]	X	X	X	X	X	
Clinical Lab Tests and Serum Biomarker[b]	X	X[a]	X	X	X	X	X	X
Endoscopy (biopsy)	X			X			X[c]	
Randomization		X						
Mayo Score	X	X	X	X	X	X	X	
Ulcerative Colitis Endoscopic Index of Severity	X			X			X[c]	
Short Inflammatory Bowel Disease Questionnaire		X	X	X	X	X	X	
Fecal Biomarker[d]		X	X	X	X	X	X	
Plasma Pharmacokinetics[e]		X	X	X				
Tissue Concentration[f]	X			X			X[c]	
Drug Dispensing (with subject diary)		X	X	X	X			
Drug Return and Compliance			X	X	X	X	X	
AE and Concomitant Medication		X	X	X	X	X[g]	X[g]	X

AE = adverse event; ECG = electrocardiogram; SFU = Safety Follow-Up; V = Visit; W = Week; ET = Early Termination; LD = Last Dose

[a] Waived if the screening visit is conducted within 10 days prior to Visit 2 (Baseline).
[b] Serum chemistry, hematology, coagulation test, HIV and hepatitis screens, serum hCG (women with childbearing potential only), and serum CRP (not measured at SFU).
[c] Only if early termination occurs before Visit 4 (W8).
[d] Fecal calprotectin and fecal lactoferrin. A collection container will be dispensed to patients on the previous visit.
[e] Visit 2 (Baseline) and Visit 3 (W4): pre-dose and 3 and 6 hours post-dose; Visit 4 (W8): pre-dose only.
[f] During the endoscopy (flexible proctosigmoidoscopy/colonoscopy) for biopsy.
[g] Reviewing any changes in smoking habits of subject during the study period.

2 INTRODUCTION

2.1 Background and Study Rationale

Ulcerative colitis (UC) is a chronic disorder characterized by inflammation of intestinal mucosa, primarily the colon, as well as the rectum in ~95% of cases. Classic symptomatology in the clinical presentation of UC is bloody diarrhea accompanied by rectal urgency and tenesmus. Individuals with UC may experience periods of active symptoms and of spontaneous or treatment-induced remission (Kornbluth et al, 2010). Diagnosis typically occurs in adulthood, although there are pediatric and adolescent cases of UC (da Silva et al, 2014).

The prevalence of UC in the United States as of 2009 was estimated to be nearly 600,000 (Kappelman et al, 2013). Healthcare utilization for UC is substantial; annual direct medical costs are reported to exceed US$4 billion. Mortality rates associated with UC range between 11% and 30% (Jess et al, 2013). Furthermore, individuals with UC suffer reduced quality of life and have increased rates of anxiety and depression compared with the general population. (Kornbluth et al, 2010).

The goals of treatment of UC are to induce and maintain remission of symptoms. Oral aminosalicylate (e.g., sulfasalazine) therapy comprises the conventional standard of care (SOC) in the pharmacological treatment of mild-to-moderate active UC. Corticosteroids, immunosuppressants, or antibiotics may also be used to treat symptoms. Patients unable to be treated with conventional therapies or those with moderate to severe disease might receive biological therapy (i.e., an anti-TNF-α agent) (Kornbluth et al, 2010).

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 (D'Haens 2016; Curkovic et al, 2013). Biologic therapy is known to have immunocompromising effects that increase patient risks to other diseases and a range of infections (mycobacterial, fungal, viral) (Andersen and Jess, 2014). Reported treatment failures further limit the utility of biologic therapies (Gordon et al, 2015). New therapies with novel mechanisms may help address the unmet needs in treatment of UC.

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. A broader view of the inflammatory process is useful context for this description. Interleukin-1 receptor (IL-1R) has an important role in amplification of the inflammatory response triggered by microbial pathogens. Following IL-1β stimulation, adaptor molecules myeloid

differentiation primary response gene 88 (MyD88), interleukin-1 receptor-associated kinase (IRAK) 4, IRAK1, and TRAF6 are recruited to IL-1R to form the receptor complex. Toll-like receptors (TLRs) and IL-1R have a conserved cytoplasmic Toll–IL-1R domain and share downstream signaling complexes that transduce signals from the receptors (Akira et al, 2001; Janeway et al, 2002).

Binding of the Pellino-1 protein to the receptor complex triggers activation of NF-κB pro-inflammatory responses (Jiang et al, 2003). Lee and colleagues identified the sequence of Smad6 amino acids 422-441 as a sufficient Smad6-derived peptide for alteration of Pellino-1 activity and inhibition of pro-inflammatory reaction. Smad6 inhibits lipopolysaccharide (LPS)/IL1β-induced formation of the MyD88 and/or receptor-interacting protein 1 (RIP1) that act downstream in the signaling pathways involving TLR4 and IL-1β. Pellino-1 was found to be involved in other proinflammatory pathways suggesting a more robust inhibitory activity for the Smad-6-Pellino-1 binding (Choi et al, 2006; Lee et al, 2015).

Based on the idea that Smad6-Pellino-1 binding disrupts Rip1 and MyD88 complex formations in the IL-1R-TLR signaling pathway, 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.

BBT-401-1S is a sodium salt of BBT-401. Nonclinical studies of BBT-401-1S performed to date include in vitro and in vivo evaluations in pharmacology, PK, and toxicology studies. BBT-401-1S was not (or poorly) absorbed following oral administration and drug-drug interaction (DDI) potentials were found to be low in the DDI studies. Safety pharmacology data also have been generated. Nonclinical toxicology studies showed BBT-401-1S to have a benign safety profile with high NOAEL values following oral administration. BBT-401-1S drug product (DP) is composed of BBT-401-1S enteric coated drug substance for oral administration. Phase 1 clinical trial in healthy subjects showed no systemic exposure and an excellent safety/tolerability profile with no serious adverse events (SAEs). Mild diarrhea (usually transient in nature and generally not interfering with normal activities) was the most observed AEs in the 1,600 mg single (SAD) and multiple ascending doses (MAD) cohorts. Please refer to the current Investigator's Brochure (IB) for additional information.

This is the first clinical trial of BBT-401-1S, designed to assess the safety and efficacy of BBT-401 administered in patients with active ulcerative colitis.

2.2 Risk/Benefit Assessment

2.2.1 Known Potential Risks

Nonclinical toxicology of BBT-401-1S is presented in Section 2.1 and described in the IB.

As there may be unknown and potential risks with administration of BBT-401-1S by virtue of its pharmacological action and based on clinical experience with compounds that have inhibitory effects on proinflammatory pathways, all patients will be closely monitored for safety and tolerability.

2.2.2 Known Potential Benefits

Patients participating in this study who are randomized to receive BBT-401-1S may experience therapeutic benefit to symptoms of UC compared with those who receive placebo. Approximately three-quarters of the patients enrolled in this study will be randomized to receive BBT-401-1S.

2.2.3 Assessment of Potential Risks and Benefits

Based on the assessment of potential risks and benefits, there is adequate justification for this study in the planned population.

There is low risk (or low clinical relevance) of drug DDIs between BBT-401-1S and common comedications, including the SOC drugs listed in the inclusion criteria, based on the lack of (or low) systemic exposure and benign safety profiles demonstrated in the nonclinical and Phase 1 clinical studies and on the enteric-coating of BBT-401-1S designed to deliver the API to the colon.

Given the observed safety with no signs of systemic exposure in the Phase 1 trial and the overall favorable safety profile seen in the nonclinical toxicology studies, BBT-401-1S is expected to demonstrate safety and tolerability with minimal systemic absorption in patients with active UC. Accordingly, routine safety monitoring is considered appropriate risk management in this Phase 2a study.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
▪ To assess the efficacy and safety of multiple oral doses of BBT-401-1S in patients with active UC	▪ Change from Baseline in Total Mayo Score (Stool frequency, rectal bleeding, endoscopic findings, physician's global assessment) at Week 8	▪ The Mayo Score is a well-recognized tool for assessing efficacy in UC trials and is an appropriate primary endpoint for a study of this size and nature.
Secondary		
▪ To assess the plasma and tissue concentration of multiple oral doses of BBT-401-1S in patients with active UC ▪ To evaluate the effects of BBT-401-1S on biomarkers	▪ Change from Baseline in Partial Mayo Score at Week 8 ▪ Change from Baseline in histologic assessment of endoscopic biopsy at Week 8 ▪ Change from Baseline in UCEIS at Week 8 ▪ Number and severity of TEAEs up to 8 weeks after the last dose ▪ Change from Baseline in SIBDQ at Week 8 ▪ Change from Baseline in Concentration of Biomarkers (CRP, fecal calprotectin, and fecal lactoferrin) at Week 8 ▪ Plasma and Tissue Concentration of BBT-401-1S	▪ The Mayo Score is an appropriate endpoint for assessing efficacy, as described above. ▪ Histological assessment of endoscopic biopsy is an appropriate method for evaluating mucosal healing (Carbonnel et al, 1994). ▪ Measurement of plasma and tissue BBT-401-1S concentrations is an appropriate method for evaluating systemic exposure. ▪ Changes in concentrations of biomarkers provide non-endoscopic assessment of inflammation (Canani et al, 2008; D'Haens et al, 2012; Lamb et al, 2011).

4 STUDY DESIGN

4.1 Overall Design

This randomized, placebo-controlled, dose-escalation, multicenter, Phase 2 study consists of three cohorts with 16-week treatment period per cohort that will be conducted sequentially. The first cohort will receive 400 mg of BBT-401-1S (starting dose). Efficacy, safety, and PK data of the first cohort will be used to select the dose of the subsequent cohort. For the 1st or 2nd cohort, if 12th patient (75%) completes Visit 4 (Week 8), unblinding of 12 patients will be performed within 2 weeks after Visit 4 (Week 8) and the unblinding information will be only provided to the Sponsor for the analysis to determine the dose of next cohort. A dose level may be repeated or added based on results of the previous cohort(s).

Patients will receive a daily oral dose of BBT 401-1S or placebo for the 16 weeks. While patients who are assigned to Active Group will receive BBT-401-1S for the first 12 weeks and then placebo for the last 4 weeks, patients who are assigned to Placebo Group will receive placebo for the first 8 weeks and then BBT-401-1S for last 8 weeks.

The primary objective of the study is to evaluate the efficacy and safety of multiple oral doses of BBT-401-1S in patients with active UC.

4.2 Scientific Rationale for Study Design

Given the disease pattern of UC, in which remission from active symptoms may be induced by treatment or spontaneously, trials with a placebo control are useful for isolating the treatment effect of an investigational treatment. The use of endoscopy is an important tool for evaluating active disease. Its inclusion in this study as an endpoint and the assessment of change from baseline also may reduce confounding of efficacy results due to placebo effect (Jairath et al, 2016).

4.3 Justification for Dose

In preclinical studies, oral administration of 300 and 400 mg/kg BBT-401-1S reduced clinical colitis scores in mice with DSS-induced colitis. Another preclinical study demonstrated that intra-colonic administration of as low as 3 mg/kg BBT-401-1S decreased the clinical colitis score in rats with DSS-induced colitis. As BBT-401-1S appears to be non-absorbable and is given as the enteric formulation, the data following intra-colonic administration in rats was considered more applicable for determining the lowest effective dose in humans. Consequently, the pharmacologic human equivalent dose of 3 mg/kg BBT-401-1S was calculated as 28.8 mg (FDA, 2005).

The starting dose planned for the trial is 400 mg daily, which is well below the maximum recommended starting dose (830–970 mg with application of safety factor of 10) as determined through preclinical study data. The maximum daily dose in this study (1,600 mg/day) is well below the human equivalent dose (HED) to the NOAEL (2,700 mg HED in dog, the more sensitive species based on oral administration), as determined in 13-week toxicity studies. In Phase 1 clinical trial in healthy subjects to assess the safety and tolerability of single (SAD) and multiple ascending doses (MAD), BBT-401-1S is not systemically absorbed (all plasma concentration values were BLQ, <1 ng/mL) with no SAEs in the SAD up to 1,600 mg per person and in the MAD at doses of 400, 800, and 1,600 mg daily per person for 7 consecutive days. Mild diarrhea (usually transient in nature and generally not interfering with normal activities) was the most observed AEs in the 1,600 mg SAD and MAD cohorts. Please refer to the IB Section 6.1 for additional details.

4.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in Section 1.3 Schedule of Assessments.

The end of the study is defined as completion of the last visit or procedure shown in the Schedule of Assessments in the trial overall.

5 STUDY POPULATION

5.1 Inclusion Criteria

To be eligible to participate in this study, an individual must meet all of the following criteria:

1) Provision of signed and dated informed consent form (ICF)
2) Stated willingness to comply with all study procedures and availability for the duration of the study
3) Male or female, aged ≥18 years
4) Diagnosed with active UC for at least 3 months prior to screening
5) Total Mayo score ≥5 and Endoscopic sub-score ≥1
6) Stable dosing regimens of oral drugs (if currently administered) as follows: 5-ASA or sulfasalazine at a stable dose for at least 4 weeks, purine analogues (azathioprine, mercaptopurine, thiopurines) or immunosuppressants (methotrexate, cyclosporine) at a stable dose for at least 12 weeks, and low-dose oral corticosteroid (up to 20 mg prednisone/day or equivalent) for at least 4 weeks prior to the first dose of study treatment. Doses of oral drugs must remain stable until the end of study treatment (with possible exception for tapering steroid dose after 8 weeks)
7) For females of reproductive potential: use of highly effective contraception for at least 1 month prior to screening and agreement to use such a method during study participation and for an additional 3 months after the last dose
8) For males of reproductive potential: use of condoms or other methods to ensure effective contraception with partner during study participation and for an additional 3 months after the last dose

5.2 Exclusion Criteria

Individuals who meet any of the following criteria will be excluded from this study:

1) Use of anti-TNF-α biologics, any other biologics, or tofacitinib for treatment of UC within 60 days prior to randomization
2) Any rectal therapy for treatment of UC or intravenous corticosteroids within 2 weeks prior to randomization
3) Presence of Crohn's disease, indeterminate colitis, ischemic colitis, fulminant colitis, ulcerative proctitis, or toxic mega-colon
4) Previous extensive colonic resection (subtotal or total colectomy)
5) Ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine
6) 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 randomization
7) Active infection with the HIV or Hepatitis B or C viruses

8) Clinically significant active extra-intestinal infection (e.g., pneumonia, pyelonephritis)
9) Clinically significant abnormal vital signs, physical examination or 12-lead electrocardiogram (ECG) at screening or baseline
10) Clinically significant abnormal results of liver function tests (ALT/AST, bilirubin and alkaline phosphatase) > 2X the upper limit of normal (ULN) at screening
11) Other clinically significant abnormal laboratory results at screening in the investigator's opinion
12) History of any clinically significant medical condition that, in the investigator's opinion, would preclude participation in the study
13) Pregnancy or lactation
14) Treatment with another investigational drug or other intervention within 30 days prior to screening

5.3 Lifestyle Considerations

No new non-pharmacological therapies should be started during the study period. In addition, no elective surgery should be scheduled during the study period. Patients should avoid smoking cessation during the study and should maintain existing habits, such as exercise levels and dietary habits throughout the study. Contraceptive measures for both males and females of childbearing potential should be documented in the source documents.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal screening failure information includes demography, screen failure details, eligibility criteria, and any SAE.

5.5 Strategies for Recruitment and Retention

The study plans to enroll up to 48 adult patients (aged ≥18 years) with active UC in the United States and South Korea.

6 STUDY INTERVENTION

6.1 Study Drug Administration

6.1.1 Study Drug Description

BBT-401-1S is the monosodium salt of BBT-401, an N-terminal lipidated 4aa peptide that targets Pellino E3 ubiquitin protein ligase 1 (Pellino-1) which leads to suppression of NF-κB–mediated inflammatory signals (Choi et al, 2006; Jiang et al, 2003; Lee et al, 2015).

6.1.2 Dosing and Administration

BBT-401-1S or placebo will be administered orally in capsule form. Study medication will be self-administered by the subject. Patients should be advised not to crush, break, chew, or dissolve the capsules. On days with scheduled study visits, patients should not take their dose of study medication at home in order to complete pre-dose study procedures including PK and safety lab. Patients will be instructed to fast for up to eight hours before their scheduled study visits.

Dosing will be determined for 3 cohorts conducted sequentially, starting with the first cohort that will receive BBT-401-1S 400 mg once daily.

Patients will receive a daily oral dose of BBT-401-1S or placebo for the 16 weeks. While patients who are assigned to Active Group will receive BBT-401-1S for the first 12 weeks and then placebo for the last 4 weeks, patients who are assigned to Placebo Group will receive placebo for the first 8 weeks and then BBT-401-1S for last 8 weeks.

Efficacy, safety, and PK data of the first cohort will be used to select the dose of the subsequent cohort. After 75% of patients of the current dose level cohort complete Visit 4 (Week 8), sponsor will review all pertinent data and decide dose level of next cohort. Dose level can be increased within 2-fold of previous dose level. A dose level may be repeated or added based on results of the previous cohort(s). The highest dose is not to exceed 1,600 mg daily.

Based on nonclinical toxicology studies, the safety margin of BBT-401-1S in humans is expected to be high. BBT-401-1S showed no noteworthy findings of drug related AEs at SAD up to 1,600 mg per person and at MAD 400, 800, and 1,600 mg daily per person in the Phase 1 clinical trial in healthy subjects. However, in the absence of an adequate clinical safety database in active UC patients, every investigator should be aware that BBT-401-1S has the potential to cause certain adverse effects by virtue of its pharmacological action and based on clinical experience with compounds of similar pharmacological effect. Please refer to the current IB for additional information regarding expected and anticipated adverse reactions. Please refer to Sections 6.6 of this protocol for additional information regarding reasons for discontinuation of study intervention and participant discontinuation/withdrawal from the study.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and accountability

The investigator will maintain accurate records of the receipt of all study medications. In addition, accurate records will be kept regarding when and how much study medication is dispensed and used by each patient in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. Study medication will be reconciled by the site. The investigator agrees to provide sufficient access to study medication as required for the reconciliation process to be completed in a timely fashion.

6.2.2 Formulation, Appearance, Packaging, and Labeling

The oral drug product, BBT-401-1S capsules for use in the clinic will be administered as a delayed-release (DR) capsule containing 200 mg of BBT-401-1S, the monosodium salt of an N-terminal lipidated tetrapeptide. The formulation has been manufactured so as to selectively fuse particles of an Eudragit®, pH-dependent enteric polymer, with adjacent particles of drug substance and HPMC to form a loose matrix powder. This powder is then blended with magnesium stearate and filled into white, opaque HPMC capsules to provide the labelled active strength.

The BBT-401-1S placebo capsules are intended to mimic the appearance of the active drug product, BBT-401-1S capsules, 200 mg. The content of the BBT-401-1S placebo capsules is a blend mixture of the same quantity of excipients as present in the drug product with the active ingredient replaced by microcrystalline cellulose. BBT-401-1S placebo capsules are filled to the same nominal weight as the drug product and are used as per the clinic dosing regimen.

BBT-401-1S 200 mg or placebo capsules will be provided in HDPE bottles of 32 capsules, sealed with a child-resistant closure. Each bottle of the test products (BBT-401-1S Capsules, 200 mg or Placebo) will be labeled with the following sample labeling:

Protocol Number: BBT401-UC-US02	**IP Code: BBTXXXX**
BBT-401-1S Capsules (200 mg or Placebo)	Quantity: 32 capsules
Lot: L334-01055BOT32/L334-01055ABOT32/L334-01056BOT32	Mfg Date: Sept-2018
For oral administration as directed in the study protocol.	
Store between 59-86°F (15-30°C) and ≤ 60% RH. Protect from exposure to high humidity. Protect from light. Keep out of reach of children.	
Caution: New Drug – Limited by United States law to investigational use.	
Manufactured by Corealis Pharma Inc., Laval (QC), Canada, H7V 4A6	
Sponsor: Bridge Biotherapeutics Inc.	
US Representative: KCRN Research, 20251 Century Blvd. #325, Germantown, MD 20874, Phone: 301-540-2600	

6.2.3 Product Storage and Stability

BBT-401-1S capsules will be stored at controlled room temperature (limited excursions permitted between 59°F and 86°F, 15-30 °C) and ≤ 60% RH. Protect from exposure to high humidity. The bottle should be tightly sealed after use.

6.3 Measures to Minimize Bias: Randomization and Blinding

A total of 16 subjects in each of the 3 dosing cohorts will be randomized to either active or placebo group in a 3:1 ratio (12 active and 4 placebo) using the electronic data capture (EDC) system.

The randomization code will be generated by a unblinded statistician who is not involved with the study. The Sponsor, investigators, patients, and CRO and other relevant personnel involved with the conduct of the study, with the exception of clinical supply staff and the unblinded statistician, will be blinded to the identity of study medication.

For the 1st or 2nd cohort, if the 12th patient (75%) completes Visit 4 (Week 8), the CRO data management (DM) team confirm all clinical data of the 12 patients have no issue and then obtain the written consent from the Sponsor to breaking the code. Per the request of the CRO DM team, the randomization codes of the 12 patients will be opened via the unblinded statistician and notified to the Sponsor for the analysis to determine the next dose. After confirming all clinical data of remaining 4 patients for the 1st or 2nd cohort, the randomization codes will be subsequently opened to the sponsor through the same procedures stated above.

After the last patient of last cohort completes the SFU, the CRO DM team confirm the whole clinical database has no issue and then request the database lock to the Sponsor. Per the Sponsor's approval on the database lock, the randomization code of all patients will be opened via the unblinded statistician and notified to the CRO for the statistical analysis.

Breaking of the randomization code without Company's permission is expressly forbidden except in the event of a medical emergency where the identity of the study medication must be known in order to properly treat the patient. In the event of a medical emergency, it is requested that the investigator make every effort to contact the study monitor or designee prior to breaking the code.

If the blind is broken due to the medical emergency, the subject must be early terminated; a written explanation must be prepared immediately.

6.4 Treatment Compliance

Treatment compliance with the study drugs will be documented by drug dispensing procedures, including a subject diary, on Visits 2–5 and by drug return and compliance assessments conducted on Visits 3–6 and/or Early Termination visit.

The investigator will manage the treatment compliance to be maintained between 80% and 120%. If the subject's drug compliance is deviated from the allowed treatment compliance at a scheduled visit, the investigator should explain the importance of drug compliance to the subject and re-instruct the dosing methods to the patient for appropriate administration of next doses.

6.5 Concomitant Therapy

Concomitant therapy with the following oral drugs is allowed during the study, provided that the dosing regimen has been stable for the specified durations as assessed at screening:

- 5-ASA or sulfasalazine at a stable dose for at least 4 weeks prior to the first dose of study treatment
- Purine analogues (azathioprine, mercaptopurine, thiopurines) or immunosuppressants (methotrexate, cyclosporine) at a stable dose for at least 12 weeks prior to the first dose of study treatment
- Low-dose oral corticosteroid (up to 20 mg prednisone/day or equivalent) at a stable dose for at least 4 weeks prior to the first dose of study treatment

Doses of oral drugs must remain stable until the end of study treatment (with a possible exception for tapering the steroid dose after 8 weeks).

Concomitant therapy with anti-TNF-α biologics, any other biologics, or tofacitinib for treatment of UC within 60 days prior to randomization is not allowed, and individuals receiving such therapy will not be permitted to enroll in the study. Given the effects of anti-TNF-α biologics, other biologics, and tofacitinib on the inflammatory process, there is reasonable potential for interactions and/or confounding effects on the study endpoints.

Concomitant therapy with intravenous corticosteroids or any rectal administration therapy for treatment of UC within 2 weeks prior to randomization is not allowed, and individuals receiving such therapy will not be permitted to enroll in the study.

Assessments of concomitant therapy will be conducted at Visits 3–7.

6.6 Removal of Patients from the Trial or Study Drug

The study may be terminated early if, in the opinion of the Sponsor, investigator, or IRB upon review of key safety data, an unacceptable risk to the safety and welfare of patients is posed by the continuation of the study.

Patients will be free to withdraw from the study at any time if so desired. A patient may be withdrawn from the study for any of the following reasons (including but not limited to):

- Withdrawal of consent - Any patient may withdraw his/her consent from the study at any time. The investigator should make a reasonable attempt to document the specific reason why consent was withdrawn.
- Deviation/noncompliance with the protocol or study drug
- AE
- Lost to follow-up

6.6.1 Handling of Withdrawals

Although a patient is not obliged to give his/her reason for withdrawing prematurely, the investigator will make a reasonable effort to obtain the reason while fully respecting the patient's rights. If there is a medical reason for withdrawal, the patient will remain under the supervision of the study physician until in satisfactory health. Reasonable efforts will be made to contact a patient who fails to attend any follow-up appointments, in order to ensure that he/she is in satisfactory health.

If a patient is prematurely withdrawn or discontinues from this study, every attempt will be made to follow the early termination (ET) visit procedures described in Section 7.4.

6.6.2 Replacements

Patients who terminate early from the study will not be replaced.

7 STUDY ACTIVITIES

7.1 Screening Visit (Day -28 to -1)

Patient's eligibility for the study will be evaluated during this period based on medical history, physical examination, including flexible proctosigmoidoscopy or colonoscopy where indicated, laboratory values and additional tests.

Patients will be screened within 28 days prior to baseline and administration of study medication to confirm that they meet the entrance criteria for the study. The study investigator or appropriate delegate at the site will discuss with each patient the nature of the study, its requirements, risks and benefits. Written informed consent must be obtained prior to performing any protocol-specific procedures, including washout of prohibited medications.

In addition to obtaining informed consent, the following procedures will be performed:

- Collection of demographic information
- Completion of medical history (including prior medication, history of alcohol and drug use, smoking status and weekly alcohol consumption)
- Vital signs (including temperature)
- Physical examination (including weight and height)
- 12-lead ECG
- Mayo score (stool frequency, rectal bleeding, endoscopic findings [flexible proctosigmoidoscopy/colonoscopy], physician's global assessment)
- Review of inclusion/exclusion criteria
- Blood sampling for clinical lab tests (serum chemistry, hematology, pregnancy, and CRP)
- Endoscopy which must be evaluated by a central reader to confirm the endoscopic sub-score for the eligibility.
- Biopsy sampling for histologic assessment and tissue concentration during the endoscopy.
- UCEIS
- Distribution of a fecal sample collection container for V2 (baseline) sample

7.2 Treatment Period

7.2.1 Visit 2 (Baseline, Week 0/Day 1)

Visit 2 will occur within 28 days after Visit 1. In this visit, the eligibility of patients will be confirmed and eligible patients will be randomized to either active or placebo group for 16-week treatments. The following procedures will be performed during Visit 2:

- Confirmation of fecal samples
- Confirmation of medical history
- Vital signs (including temperature)

- Physical examination (including weight), which is waived if the screening visit is conducted within 10 days prior to Visit 2
- 12-lead ECG, which is waived if the screening visit is conducted within 10 days prior to Visit 2
- Confirmation of inclusion/exclusion criteria
- Randomization
- Mayo score (stool frequency, rectal bleeding, physician's global assessment)
- SIBDQ
- Blood sampling for clinical lab tests (serum chemistry, hematology, pregnancy, and CRP), which is waived if the screening visit is conducted within 10 days prior to Visit 2
- Blood sampling for pharmacokinetics: pre-dose, 3 and 6 hours post-dose
- Administration of study drug
- Record of AEs and concomitant medications
- Distribution of a fecal sample collection container for V3 (Week 4) sample
- Distribution of study drugs and subject diary

7.2.2 Visit 3 (Week 4)

Visit 3 will occur at 4 weeks (± 3 days) from the first dosing date. During this visit, the following assessments/procedures will be performed:

- SIBDQ
- Mayo score (stool frequency, rectal bleeding, physician's global assessment)
- Record of AEs and concomitant medications
- Confirmation of fecal samples
- Review of returned study drugs and subject diary
- Vital signs (including temperature)
- Physical examination (including weight)
- 12-lead ECG
- Blood sampling for clinical lab tests (serum chemistry, hematology, pregnancy, and CRP)
- Blood sampling for pharmacokinetics: pre-dose, 3 and 6 hours post-dose
- Administration of study drug
- Distribution of a fecal sample collection containers for V4 (Week 8) sample
- Distribution of study drugs and subject diary

7.2.3 Visit 4 (Week 8)

Visit 4 will occur at 8 weeks (± 3 days) from the first dosing date. During this visit, the following assessments/procedures will be performed:

- SIBDQ
- Mayo score (stool frequency, rectal bleeding, endoscopic findings [flexible proctosigmoidoscopy/colonoscopy], physician's global assessment)

- UCEIS
- Record of AEs and concomitant medications
- Confirmation of fecal samples
- Review of returned study drugs and subject diary
- Vital signs (including temperature)
- Physical examination (including weight)
- 12-lead ECG
- Blood sampling for clinical lab tests (serum chemistry, hematology, pregnancy, and CRP)
- Blood sampling for pharmacokinetics: pre-dose
- Endoscopy which can be performed within 3 days before this visit if it is not feasible at the same date of Visit 4
- Biopsy sampling for histologic assessment and tissue concentration during the endoscopy.
- Distribution of a fecal sample collection containers for V5 (Week 12) sample
- Distribution of study drugs and subject diary

7.2.4 Visit 5 (Week 12)

Visit 5 will occur at 12 weeks (± 3 days) from the first dosing date. During this visit, the following assessments/procedures will be performed:

- SIBDQ
- Mayo score (stool frequency, rectal bleeding, physician's global assessment)
- Record of AEs and concomitant medications
- Confirmation of fecal samples
- Review of returned study drugs and subject diary
- Vital signs (including temperature)
- Physical examination (including weight)
- 12-lead ECG
- Blood sampling for clinical lab tests (serum chemistry, hematology, pregnancy, and CRP)
- Distribution of a fecal sample collection container for Visit 6 (Week 16) sample
- Distribution of study drugs and subject diary

7.2.5 Visit 6 (Week 16)

Visit 6 will occur at 16 weeks (± 3 days) from the first dosing date. During this visit, the following assessments/procedures will be performed:

- SIBDQ
- Mayo score (stool frequency, rectal bleeding, physician's global assessment)
- Record of AEs and concomitant medications
- Review of any changes in smoking habits of subject during the study period
- Confirmation of fecal samples
- Review of returned study drugs and subject diary

- Vital signs (including temperature)
- Physical examination (including weight)
- 12-lead ECG
- Blood sampling for clinical lab tests (serum chemistry, hematology, pregnancy, and CRP)
- Scheduling of the SFU visit at 2 weeks (+ 7 days) from the last dosing

7.3 Safety Follow-Up (SFU) Visit

SFU visit will occur at 2 weeks (+7 days) from the date of last dose. During this visit, the following assessments/procedures should be performed:

- Record of AEs and concomitant medications
- Vital signs (including temperature)
- Blood sampling for clinical lab tests (serum chemistry, hematology, and pregnancy)

7.4 Early Termination (ET) Visit

If a patient will drop-out the study before the last treatment visit, the clinical site will try to schedule an ET visit. During this visit, the following assessments/procedures should be performed:

- SIBDQ
- Mayo score (stool frequency, rectal bleeding, endoscopic findings [flexible proctosigmoidoscopy/colonoscopy] - if applicable, physician's global assessment)
- Record of AEs and concomitant medications
- Review of any changes in smoking habits of subject during the study period
- Confirmation of fecal samples, if applicable
- Review of returned study drugs and subject diary
- Vital signs (including temperature)
- Physical examination (including weight)
- 12-lead ECG
- Blood sampling for clinical lab tests (serum chemistry, hematology, pregnancy, and CRP)
- Endoscopy (biopsy), only if this ET occurs before Visit 4 (Week 8), which can be performed within 3 days before or after this visit if it is not feasible at the same date of ET Visit (if applicable)
- UCEIS (if the endoscopy is performed)
- Scheduling of SFU visit at 2 weeks (+ 7 days) from the last dosing unless this ET visit occurs after 2 weeks from the last dosing.

8 STUDY PROCEDURES

8.1 Informed Consent and Medical History

8.1.1 Informed Consent

The investigator will obtain informed consent and complete an ICF for each patient screened for this study. All patients will be informed in writing of the nature of the protocol and investigational therapy, their possible hazards, and their right to withdraw at any time, and will sign an ICF indicating their consent to participate prior to the initiation of study procedures. The patient's medical record should contain written documentation indicating that informed consent was obtained. The ICF must be reviewed and approved by the investigator's designated IRB and by the Sponsor. The ICF should include all the elements as outlined in Section 4.8.10 of the ICH guideline for GCP (E6).

8.1.2 Medical History

At screening, a complete medical history including a full history of UC will be collected by patient interview. Concomitant medications, recent blood donations, illnesses, and participation in other investigational drug studies will also be recorded.

Prior therapies related to UC and a detailed history of UC, including date of diagnosis, disease severity, hospitalizations, and extraintestinal manifestations will be collected during screening.

8.2 Safety Assessments

- Physical examination: Screening, Baseline, W4, W8, W12, and W16
- Vital signs: All visits (including SFU)
- 12-lead ECG: Screening, Baseline, W4, W8, W12, and W16
- Clinical laboratory testing of serum chemistry/hematology: All visits (including SFU)
- Recording of AEs: W4, W8, W12, W16, and SFU

8.2.1 Physical Examination

Complete physical examination including weight, general appearance, examination of skin, HEENT (head, ears, eyes, nose, throat), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs, peripheral edema), abdomen (palpation and auscultation), neurology (mental status, station, gait, reflexes, motor and sensory function, coordination), and lymph nodes will be performed.

Any clinically significant changes from the baseline examination should be recorded as AEs.

8.2.2 Vital Signs

Vital signs will be recorded throughout the study as per the Schedule of Assessments. Blood pressure (BP) will be measured in the patient's dominant arm and recorded to the nearest mmHg. The same arm will be used throughout the study. All BP in this study will be measured with the patient in the sitting position after resting for at least 5 minutes. The use of automated devices for measuring BP and pulse rate are acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. On visits when a blood sample is collected, the BP and pulse rate should be obtained prior to blood sample collection.

Temperature will be recorded as either oral, axillary or tympanic temperature, with the same method used throughout the study.

8.2.3 Electrocardiogram (ECG)

Twelve (12)-lead ECGs will be obtained on all patients as per Schedule of Assessments. All scheduled ECGs should be performed after the patient has rested quietly for at least 10 minutes in a supine position.

ECG measurement collected at the Screening visit will serve as the patient's baseline value if conducted within 10 days prior to baseline. To ensure patient safety, a qualified individual at the investigator site will make comparisons to the baseline measurement.

If the QTc measurement at a time post-dose is > 45 msec increase from the baseline; or an absolute QTc value is ≥ 500 msec for any scheduled ECG, a single ECG will be repeated at least hourly until QTc values from successive ECGs fall below the threshold value that triggered the repeat measurement.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as a factor of the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTc values are in the acceptable range.

8.2.4 Clinical Laboratory Tests

All details regarding clinical laboratory sample collection, preparation, and shipment are included in the laboratory manual provided by the CRO. In the event of abnormal clinical laboratory values,

the physician will make a judgment as to whether or not the abnormality is clinically significant and/or is deemed an AE.

8.2.4.1 Laboratory Parameters

Clinical safety laboratory tests will be conducted as outlined in the Schedule of Assessments, and should be completed pre-dose. Laboratory tests will include the following:

Serum Chemistry

Albumin
Alkaline phosphatase
Alanine aminotransferase (ALT; SGPT)
Amylase
Aspartate aminotransferase (AST; SGOT)
Bicarbonate
Blood urea nitrogen
Calcium
Chloride
Creatinine
Creatine kinase and MB subtype (if elevated) (% and total MB)
Gamma-glutamyl transferase
Glucose
Lactate dehydrogenase
Lipase
Magnesium
Phosphate
Potassium
Sodium
Total bilirubin
Total cholesterol
Total protein
Triglycerides

Hematology

Hematocrit
Hemoglobin
Mean corpuscular hemoglobin
Mean corpuscular volume
Platelet count
Red blood cell count
White blood cell count with differential (% and absolute counts)

Coagulation

Prothrombin time
Activated partial thromboplastin time
International Normalized Ratio

Additional Tests

Serum hCG (women with childbearing potential only)
Serum FSH (women only)
HIV test
HBsAg
Anti-HCV
VZV IgG

8.2.4.2 Additional Tests

- Serum hCG will be performed at every visit for women with childbearing only.
- Serum FSH test can be performed to confirm postmenopausal status at screening only.
- Human immunodeficiency virus (HIV), hepatitis B (HBsAg), hepatitis C virus (RIBA 2 or 3), and VZV IgG antibody will be performed at screening only.

8.2.4.3 Sample Collection, Storage, and Shipping

Blood samples for hematology, coagulation parameters, serum chemistry, HIV and hepatitis screens, serum hCG (women with childbearing potential only), and serum CRP will be collected according to the laboratory manual provided by the CRO and according to the Schedule of Assessments and descriptions of visits.

8.2.4.4 Blood Volume

The total blood volume to be collected for clinical laboratory tests during the study is less than 150 mL.

8.3 Efficacy Assessments

- Total Mayo Score (Stool frequency, rectal bleeding, endoscopic findings [flexible proctosigmoidoscopy/colonoscopy], physician's global assessment): Screening and W8
- Partial Mayo Score: Baseline, W4, W8, W12, and W16
- Histologic Assessment of Endoscopic Biopsy: Screening and W8
- UCEIS score: Screening and W8
- SIBDQ: Baseline, W4, W8, W12, and W16
- Serum CRP: Baseline, W4, W8, W12, and W16
- Fecal calprotectin: Baseline, W4, W8, W12, and W16
- Fecal lactoferrin: Baseline, W4, W8, W12, and W16

8.3.1 Mayo Score

The Total Mayo score is an instrument designed to measure disease activity of ulcerative colitis, 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 (Mayo scoring system is listed in Appendix 1). For the endoscopic subscore, the Modified Mayo Endoscopic Score will be used to exclude any friability from Grade 1 per the FDA guidance.

- Stool frequency (0-3)
- Rectal bleeding (0-3)
- Findings of endoscopy (0-3)
- Physician global assessment (PGA) (0-3)

The Partial Mayo score consists of 3 subscores (stool frequency, rectal bleeding, and PGA). The subscores of stool frequency and rectal bleeding will be answered by a patient and the subscore of PGA will be assessed by an investigator.

8.3.2 Endoscopy with Biopsy Procedure

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

Endoscopy examination (flexible proctosigmoidoscopy/colonoscopy) will be required at screening in order to establish the Mayo endoscopic subscore and confirm patient eligibility for the study at baseline. Mayo endoscopic subscores will be assessed by both local and central reader. If the single central reader and local reader assessment results do not match, another central reader will score for adjudication.

Any patient who has not had a colonoscopy performed within 10 years since the onset of symptoms will be required to undergo a colonoscopy for screening surveillance. Therefore, in such cases, a colonoscopy will be required at screening (a flexible proctosigmoidoscopy will not be an option).

An appropriately trained endoscopist should perform the flexible proctosigmoidoscopy/ colonoscopy. Where possible the same endoscopist should perform the endoscopy for both screening and Week 8 visits. If this is not possible, it should be clearly documented who performed each endoscopy procedure.

8.3.3 Ulcerative Colitis Endoscopic Index of Severity (UCEIS)

The Ulcerative Colitis Endoscopic Index of Severity (UCEIS) is the first validated index for the assessment of overall endoscopic activity (Appendix 2). 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.

8.3.4 Quality of Life Questionnaire: Short Inflammatory Bowel Disease Questionnaire (SIBDQ)

The SIBDQ is a health-related quality of life (HRQoL) tool measuring physical, social, and emotional status. Scores range between 10 and 70, reflecting poor to good HRQoL. The SIBDQ has been predominantly used in trials for Crohn's disease, and further validation of the SIBDQ is desirable in UC patients. A sample of the SIBDQ is provided in Appendix 3.

8.3.5 Biomarkers

The following biomarkers will be analyzed to support the efficacy assessments:

- Serum C-reactive protein (CRP)
- Fecal calprotectin
- Fecal lactoferrin

Instructions for storage and shipment of biomarker samples will be provided by the CRO.

8.4 Pharmacokinetic Assessments

8.4.1 Plasma Pharmacokinetics

For all patients, blood samples (approximately 4 mL) for analysis of BBT-401-1S pharmacokinetics will be collected in blood collection tubes containing K_2EDTA as anticoagulant at the following scheduled time points:

- Visit 2 (Baseline) and Visit 3 (W4): pre-dose and 3 hour (± 15 minutes) and 6 hour (- 30 to + 150 minutes) post-dose.
- Visit 4 (W8): pre-dose only

Blood tubes will be gently inverted several times to ensure mixing and placed on wet ice. Plasma will be obtained within 2 hours of blood collection by centrifugation approximately at 3200 g and at 4 °C for 10 minutes. Plasma will be transferred into two labeled plasma collection tubes each containing approximately 0.8 mL and stored in freezing conditions (-20 °C or below) until shipment to an analytical lab. Blood sampling, centrifuge time, storage condition, and storage time will be documented.

Instructions for sample shipment will be provided in a separate document by the Sponsor. Plasma sample analysis will be performed using a validated bioanalytical method.

8.4.2 Tissue Concentration

For all patients, biopsy samples for analysis of BBT-401-1S concentration will be collected in tissue collection tubes during the endoscopy following Visit 1 (Screening) and prior to Visit 4 (W8).

The collection tubes will be stored in freezing conditions (-20 °C or below) until shipment to an analytical lab. Tissue sampling, storage condition, and storage time will be documented.

Instructions for sample shipment will be provided in a separate document by the Sponsor. Tissue sample analysis will be performed using a non-validated bioanalytical method.

8.5 Adverse Events and Serious Adverse Events Reporting

8.5.1 Definition of Adverse Events (AE)

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of study drug.

Note that progression of the ulcerative colitis investigated in this protocol, including secondary events that are subsumed under a unifying diagnosis of disease progression, will NOT be considered an AE unless the investigator judges the progression to be related to treatment with study drug.

An AE includes, but is not limited to, the following:

- Any clinically significant worsening of a pre-existing condition
- An AE occurring from overdose (i.e., a dose higher than that indicated in the protocol) of a study drug, whether accidental or intentional
- An AE occurring from abuse (e.g., use for nonclinical reasons) of a study drug
- An AE that has been associated with the discontinuation of the use of a study drug
- Any treatment-emergent abnormal laboratory result that is clinically significant, i.e., meeting 1 or more of the following conditions, should be recorded as a single diagnosis on the AE page in the eCRF:
  - Accompanied by clinical symptoms
  - Leading to a change in study medication (e.g., dose modification, interruption or permanent discontinuation)
  - Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

8.5.2 Definition of Serious Adverse Events (SAE)

A serious adverse event (SAE) is any AE, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening “Life-threatening” means that the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that hypothetically might have caused death had it occurred in a more severe form.
- Requires inpatient hospitalization or prolongation of existing hospitalization (see clarification in the paragraph below on planned hospitalizations)

- Results in persistent or significant disability/incapacity "Disability" is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly/birth defect
- Is an important medical event
  An "important medical event" is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Clarification should be made between the terms "serious" and "severe" because they are not synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); however, the event itself may be of relatively minor medical significance (such as a severe headache). This is NOT the same as a "serious" adverse event (SAE), which is based on patient/event outcome or action criteria described above. An SAE is usually an event that poses a threat to a patient's life or ability to function. In contrast, an AE assessed as "severe" is not automatically considered "serious" in nature (i.e., an SAE). For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild, but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Other Reportable Information: certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes:

- A case involving a pregnancy exposure to a test article, unless the product is indicated for use during pregnancy e.g., prenatal vitamins. Information about use in pregnancy encompasses the entire course of pregnancy and delivery and perinatal and neonatal outcomes, even if there were no abnormal findings. If a pregnancy is confirmed, test article must be discontinued immediately in female patients. All reports of pregnancy must be followed for information about the course of the pregnancy and delivery, as well as the condition of the newborn. When the newborn is healthy, additional follow-up is not needed. Pregnancies occurring up to 3 months after completion of the study treatment must also be reported to the investigator.
- Overdose (e.g., a dose higher than that indicated in the protocol) with or without an AE.
- Abuse (e.g., use for nonclinical reasons) with or without an AE
- Inadvertent or accidental exposure with or without an AE
- Device malfunction with or without an AE

8.5.3 Classification of an Adverse Event

8.5.3.1 Severity of Event

The severity of AEs should be graded as follows:

- Mild – Usually transient in nature and generally not interfering with normal activities
- Moderate – Sufficiently discomforting to interfere with normal activities
- Severe – Inability to perform normal daily activities

Medically significant AEs considered related to the study drug by the investigator or Sponsor will be followed until resolved or considered stable.

It will be left to the investigator's clinical judgment to determine whether an AE is related and of sufficient severity to require the patient's removal from treatment or from the study. A patient may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these situations arises, the patient should be strongly encouraged to undergo an end-of-study assessment and be under medical supervision until symptoms cease or the condition becomes stable.

8.5.3.2 Relationship to Study Intervention

The following AE attributes must be assigned by the investigator: AE diagnosis or syndrome(s) (if known, signs or symptoms if not known); event description (with detail appropriate to the event); dates of onset and resolution; severity; assessment of relatedness to study drug and action taken. The investigator may be asked to provide follow-up information, discharge summaries, and extracts from medical records or eCRFs.

Relatedness to study drug administration will be determined by the investigator responding to the question, 'Is there a reasonable possibility that the AE is associated with the study drug?' Relatedness to study drug administration will be graded as "related", "probably," "possibly," or "not related," as follows:

- Not Related
  - Another cause of the event is most plausible, or
  - Clinically plausible temporal sequence is inconsistent with the onset of the event and the study treatment administration, or
  - A causal relationship is considered biologically implausible.
- Possibly Related
  - An event that follows a reasonable temporal sequence from administration of the study treatment or a known or expected response pattern to the suspected drug, but that could readily have been produced by a number of other factors.

- Probably Related
  - An event that follows a reasonable temporal sequence from administration of the study treatment, and
  - There is a biologically plausible mechanism for study treatment causing or contributing to the AE, and
  - The event could not be reasonably explained by the known characteristics of the patient's clinical state.
- Related
  - An event that occurs in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals.
  - The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

In addition, the relationship may be confirmed by improvement on stopping the study treatment and reappearance of the event on repeated exposure.

8.5.3.3 Expectedness

The Sponsor will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.5.4 Adverse Event Reporting

All AEs and SAEs will be collected and recorded from the time of the patient receives the first dose of study drug until the end-of-study visit for all subjects with informed consent. The Investigator will assess all AEs and SAEs and record the following information where appropriate on the CRF:

- Event description
- Date of onset
- Date of resolution or stabilization
- Assessment of severity
- Relationship to study drug
- Action taken with study medication

The Investigator should employ best medical judgment in determining how to manage AEs and SAEs. Any questions regarding AE or SAE management should be directed to the Medical Monitor.

The Sponsor will be responsible for notifying the FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the Sponsor's initial receipt of the information. In addition, the Sponsor must notify the FDA and all participating investigators in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the Sponsor determines that the information qualifies for reporting.

8.5.5 Reporting Events to Patients

Not applicable.

8.5.6 Events of Special Interest

Not applicable.

8.5.7 Reporting of Pregnancy

Serum pregnancy testing will be conducted for all female patients with child-bearing potential at screening and all treatment visits. If a female patient becomes pregnant during clinical study, the investigator should prepare and submit an initial pregnancy report to the Sponsor within 24 hours of becoming aware of the pregnancy. The investigator should follow up and document all progresses and results of pregnancy, even if the patient withdraws consent or terminate the clinical study. In addition, the investigator should prepare and submit the pregnancy outcome report within 24 hours of becoming aware of all results of pregnancy.

Pregnancy itself is not considered as an AE if the pregnancy is not related to the investigational product.

All SAEs that occur during pregnancy will be recorded in an SAE report and the reporting will be performed according to the SAE reporting procedures.

9 STATISTICAL CONSIDERATIONS

The statistical analysis of the data obtained from this study will be the responsibility of the CRO. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP) which will be finalized before the first individual unblinding. If, after the study has been unblinded, changes are made to the pre-specified statistical analysis plan, the changes will be listed along with an explanation as to why they occurred in the Clinical Study Report.

9.1 General Methodology

No formal inferential statistical analyses are planned. Rather, for the quantitative endpoints (efficacy, biomarker measure, and some safety data) descriptive statistics will be calculated to provide an indication of directional changes in endpoints for each treatment group. For the qualitative data, frequency counts and incidence rates will be compiled for each treatment group.

Summary of tabulations will be presented by treatment group displaying the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent per category for categorical data.

9.2 Blinding and Randomization

The study is double blind, with patients randomized to either the active or placebo group. The randomization will be conducted to produce a 3:1 ratio of active to placebo—each cohort will include 12 active and 4 placebo patients.

9.3 Sample Size and Power

As this is an initial dose-escalation study, it is appropriately based on only a limited number of patients in each dose cohort. The size of the study is not based on any statistical power calculations and no formal sample size calculations have been done. Based on experience from previous studies and the use of a sequential dose-escalation design for this study, a total of 48 patients (16 patients per dose cohort) is considered appropriate for the study.

9.4 Population for Analyses

The analyses of the efficacy endpoints will be based on a modified Intent-to-Treat (mITT) population. The mITT population consists of all randomized patients who receive at least 1 dose of study medication. Note that, for the analysis of an individual endpoint, it must have a baseline measurement and at least one post-randomization measurement. Therefore, the patients included in an analysis can vary with endpoints since some patients may have the needed data for inclusion in the mITT analysis for some endpoints but not for others. For the efficacy analyses, patients are

counted in the treatment group to which they were randomized, regardless of the treatment received during the course of the trial.

The analysis of the safety endpoints will be based on a Safety population which will include all randomized patients who received at least 1 dose of study medication. Patients are counted in the treatment group based on the treatment they receive.

PK population consists of all randomized patients who receive at least 1 dose of the study medication and have plasma and tissue concentration data.

9.4.1 General Approach Procedures for Handling Missing, Unused, and Spurious Data

All available efficacy and safety data will be included in the data listings and tabulations. No imputation of values for missing data will be performed.

9.4.2 Demographic and Baseline Descriptive Statistics

The baseline value is defined as the last value obtained on or before the date and time of the first study drug dose.

9.4.3 Subject Disposition

Subject disposition will be summarized for subjects who complete the study or discontinue early. The overall summary will comprise the number and percentage of subjects for each analysis population, as well as the number and percentage of subjects who completed the study parts and treatment, and discontinued early with reasons for discontinuation.

9.4.4 Prior and Concomitant Medications

Medications administered prior to and concomitantly with study drug will be tabulated and listed.

9.4.5 Protocol Deviations

A list of subjects with protocol deviations will be compiled based on entry criteria deviations as well as deviations from study conduct and assessments.

9.5 Statistical Analyses

No formal inferential statistics are planned for this study. Descriptive statistics will be calculated to summarize the changes from baseline in the primary and secondary endpoints. Frequency counts will be compiled for qualitative safety analysis.

- Primary Endpoint(s):
  - Change from Baseline in Total Mayo Score at Week 8
- Secondary Endpoint(s):
  - Change from Baseline in Partial Mayo Score at Week 8
  - Change from Baseline in Histologic Assessment of Endoscopic Biopsy at Week 8
  - Change from Baseline in UCEIS Score at Week 8
  - Number and Severity of treatment-emergent AE (TEAEs) up to Week 8
  - Change from Baseline in SIBDQ at Week 8
  - Change from Baseline in Concentration of Biomarkers (serum CRP, fecal calprotectin, and fecal lactoferrin) at Week 8
  - Plasma and Tissue Concentration of BBT-401-1S in Patients with Active UC

9.5.1 Analysis of Primary Endpoint

The primary objective is to determine the efficacy of BBT-401-1S in patients with active Ulcerative Colitis. Response to treatment will be evaluated using the change from baseline in Total Mayo score at week 8 based on the mITT population. The baseline value is defined as the last value obtained on or before the date and time of the first study drug dose. Descriptive statistics will be presented including mean, standard deviation (SD), median, max, and min by treatment and cohort group (and overall cohort) at each timepoint. However, to allow for a direct comparison of BBT-401-1S vs placebo for each cohort, descriptive statistics will be provided for the difference in the change from baseline between the treatment groups during the double-blind portion of the study.

9.5.2 Analysis of Secondary Endpoints

The secondary efficacy analyses will be based on the mITT population. Analysis on the TEAEs and other safety endpoints is discussed under the Safety Analysis section below.

For each efficacy endpoint, descriptive statistics will be presented by treatment and cohort group (and overall cohort) at each timepoint, including mean, SD, median, max, and min as there is no formal inferential statistical analysis is planned.

9.5.3 Safety Analyses

All analyses based on safety data (AEs, laboratory data, ECGs, vital signs, and physical exam data) will be based on the Safety population.

AE terms recorded on the eCRFs will be mapped to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA®) version 17.0 or later. AEs included in summary tables will be restricted to treatment-emergent AEs (TEAEs). A TEAE is defined as an AE that occurs (or worsens) after study drug is received. TEAEs will be summarized for each treatment group by the

number and percentage of patients who experienced the event, according to the system organ class and preferred term. Additional summaries will also be provided by severity and relationship to study drug. Listings of deaths, SAEs and AEs leading to early termination of study drug or premature withdrawal from study will also be provided.

Descriptive statistics will be provided for laboratory results by scheduled time of evaluation and by treatment group, as well as for change from baseline. Laboratory variables will be evaluated using mean change in value from baseline to scheduled time points. The baseline value of a variable is defined as the last value obtained on or before the date and time of the first study drug dose. Individual laboratory test results that are outside the normal range for that test will be flagged as high (H) or low (L), as appropriate, in the listings.

ECGs, vital sign measurements and weight will be summarized by change from baseline to scheduled time points using descriptive statistics.

9.5.4 Planned Interim and Subgroup Analyses

Not applicable.

9.5.5 Tabulation of Individual Participant Data

All available efficacy and safety data will be included in the data listings and tabulations.

9.5.6 Pharmacokinetic Analysis

Not applicable.

9.5.7 Pharmacodynamic Analyses

No formal statistical analysis of PD endpoints (i.e. biomarkers) will be performed. PD data from each assay will be listed, and possible relationships between clinical response and PD variables will be explored. Any biological activity will be described. The exploratory analyses will 1) assess ulcerative colitis biomarkers and cell growth and 2) correlate clinical outcomes with response and ulcerative colitis parameters.

10 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1 Informed Consent Process

In obtaining and documenting informed consent, the investigator must comply with applicable regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and should adhere to ICH GCP. Prior to the beginning of the trial, the investigator should have the IRB's written approval for the protocol and the written ICF(s) and any other written information to be provided to the participants.

10.2 Consent/assent and Other Informational Documents Provided to Participants

The IRB-approved ICF describing in detail the study intervention, study procedures, potential benefits and risks is to be given to the participant, and written documentation of informed consent is required prior to administering the study intervention.

The ICF contains a statement that consent is freely given, that the patient is aware of the risks of entering the study, and that the patient is free to withdraw from the study at any time. Informed consent must be given by the patient and/or legal representative after the receipt of detailed information on the study.

10.3 Consent Procedures and Documentation

The Investigator is responsible for ensuring that informed consent is obtained from each patient or legal representative and that the ICF is completed (i.e., signed and dated) prior to the performance of any protocol procedures and prior to the administration of study drug.

Patients will be asked to read and review the IRB-approved ICF. The investigator will explain the study purpose, procedures, and potential risks, as well as the patient's rights as a research participant, in clear terms suited to the patient's comprehension. It should be noted that the quality of the patient's medical care will not be adversely affected if he or she declines to participate in the study.

Patients will have the opportunity to carefully review the written consent form and ask questions prior to signing. The patient should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate.

Patients must be informed that participation is voluntary and that they may withdraw from the study at any time. A copy of the ICF will be given to the participants for their records.

10.4 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated by the Sponsor if there is sufficient reasonable cause. Written notification documenting the reason for study suspension or termination by the Sponsor or PI will be provided to investigators or the Sponsor, respectively, study participants, the IRB, and regulatory authorities. Study participants will be contacted, as applicable, and be informed of any changes to the study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns are addressed to the satisfaction of the Sponsor, IRB and/or regulatory authorities.

10.5 Confidentiality and Privacy

Patient confidentiality and privacy is held by the participating investigators, their staff, and the Sponsor. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. The study monitor and other authorized representatives of the Sponsor, IRB, or regulatory agencies may inspect all documents and records required to be maintained by the investigator. The clinical study site will permit access to such records.

No information concerning the study or the data will be released to patients, any insurance company, employer, family member, general physician, or other unauthorized third party unless required by law or with prior written approval of the Sponsor. In exceptional circumstances, certain individuals might see both the medical data and personal identifiers of a patient. For example, in the case of a medical emergency, or Sponsor or representative physician or an investigator might become aware of a patient's identity and have access to his or her medical data.

Patient contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or Sponsor requirements. Patient research data will not include the patient's contact or identifying information but will be labeled with a unique study identification number. The study data entry and study management systems used by clinical sites and by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

10.6 Future Use of Stored Specimens and Data

The US FDA regulations (21 CFR §312.62[d]) and the ICH Guideline for GCP require that records and documents pertaining to the conduct of this study and the distribution of study drug, including eCRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the investigator for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational drug. Patient identification codes (patient names and corresponding study numbers) will be retained for this same period of time. The Sponsor will notify the Principal Investigator of these events. These documents may be transferred to another responsible party, acceptable to the Sponsor, who agrees to abide by the retention policies. Permission to transmit data to another responsible party will be included in the ICF. Written notification of transfer must be submitted to the Sponsor. The investigator must contact the Sponsor prior to disposing of any study records.

As part of understanding the PK of the study drug, plasma samples may be used for metabolite identification and profiling evaluation. As part of understanding the efficacy and safety of the study drug, biopsy samples may be used for gene expression and profiling evaluation. Residual plasma and biopsy samples may be stored up to 2 years. If the residual samples are used, the results will be reported to the regulatory agencies.

10.7 Safety Oversight

The study will be monitored by the Safety Monitoring Committee (SMC) comprised of the Principal Investigator for each site, the Medical Monitor, and Sponsor representative(s) or designee. During the study period, all SAEs or safety issues will be sent to the SMC on a continual basis. The SMC will be responsible for reviewing all SAEs or safety issues and making the decision of proceeding to a new dose level after completing each cohort based on the relevant safety data. If at any point a safety concern arises, an ad hoc meeting of the SMC can be performed.

Further information describing a scope of work and procedures for the SMC will be provided in the SMC Charter.

10.8 Clinical Monitoring

The Sponsor has engaged the services of a CRO, to perform all monitoring functions within this clinical study. CRO monitors will work in accordance with CRO SOPs and have the same rights and responsibilities as monitors from the Sponsor organization. Monitors will establish and maintain regular contact between the Investigator and the Sponsor.

Monitors will evaluate the competence of each study center, informing the Sponsor about any problems relating to facilities, technical equipment or medical staff. During the study, monitors will check that written informed consent has been obtained from all patients correctly and that data are recorded correctly and completely. Monitors are also entitled to compare entries in eCRFs with corresponding source data and to inform the Investigator of any errors or omissions. Monitors will

also control adherence to the protocol at the study center. They will arrange for the supply of investigational product and ensure appropriate storage conditions are maintained.

Monitoring visits will be conducted according to all applicable regulatory requirements and standards. Regular monitoring visits will be made to each center while patients are enrolled in the study. The monitor will make written reports to the Sponsor on each occasion contact with the Investigator is made, regardless of whether it is by phone or in person.

During monitoring visits, entries in the eCRFs will be compared with the original source documents (source data verification). For the following items, this check will be 100%:

- Patient identification number.
- Patient consent obtained.
- Patient eligibility criteria (inclusion and exclusion criteria).
- Efficacy variables.
- Medical record of AE.

10.9 Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and at each stage of data handling. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

The Sponsor is responsible for implementing and maintaining quality assurance and QC systems with written Standard Operating Procedures (SOPs). In accordance with the written SOPs, monitors will verify that the clinical trial is conducted, data are generated, and biological specimens are collected, recorded, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)). The Sponsor and monitor will determine the frequency of monitoring visits.

In addition, during the study the Sponsor may conduct audits separately from routine monitoring. The investigational site will provide direct access to all trial-related sites, source data/documents including medical history and concomitant medication documentation, and reports for both routine monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

10.10 Data Handling and Record Keeping

The US FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of this study and the

distribution of study drug, including eCRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Investigator for 15 years after the last marketing application approval in an ICH region or after at least 15 years have elapsed since formal discontinuation of clinical development of the investigational drug. Patient identification codes (patient names and corresponding study numbers) will be retained for this same period of time. The Sponsor will notify the Principal Investigator of these events. These documents may be transferred to another responsible party, acceptable to Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to Sponsor. The Investigator must contact the Sponsor prior to disposing of any study records.

10.11 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol. The noncompliance may be on the part of the patient, the investigator, or the study site/CRO staff. Corrective actions in response to deviations are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to timely identify and report deviations. All deviations must be addressed in study source documents and reported to the monitor and/or Sponsor. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

For minor protocol deviations deemed to have no influence on the interpretation of study results, the level and reason of deviation or delay will be accurately described and comprehensively considered by the Investigator, Sponsor, monitor or statistician when preparing the study report.

10.12 Publication and Data Sharing Policy

The data generated by this study are the proprietary information of the Sponsor. The Sponsor will make the results of the study publicly available, which may include publication in a peer-reviewed journal. The publication policy with respect to the investigator and clinical site will be set forth in the Clinical Trial Agreement. This trial will be registered at ClinicalTrials.gov, and data from this trial will be submitted to ClinicalTrials.gov.

10.13 Conflict of Interest Policy

Actual or perceived conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed.

10.14 Abbreviations

AE	Adverse Event
ALT	Alanine Transaminase

API	Active Pharmaceutical Ingredient
ASA	5-aminosalicylic acid
AST	Aspartate Transaminase
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRP	C-Reactive Protein
DDI	Drug-drug Interaction
DP	Drug Product
ECG	Electrocardiogram
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HBsAg	Hepatitis B Surface Antigen
HED	Human Equivalent Dose
HIV	Human Immunodeficiency Virus
HRQoL	Health-related Quality of Life
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IND	Investigational New Drug Application
ICF	Informed Consent Form
IL-1R	Interleukin-1 Receptor
IRAK	Interleukin-1 Receptor-associated Kinase
IRB	Institutional Review Board
ITT	Intent-To-Treat
LPS	Lipopolysaccharide
MAD	Multiple Ascending Dose
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-To-Treat
MyD88	Myeloid Differentiation Primary Response Gene 88
NOAEL	No-observed-adverse-effect Level
PD	Pharmacodynamics
PGA	Physician Global Assessment
PI	Principal Investigator
PK	Pharmacokinetics
QC	Quality Control
RIP1	Receptor-interacting Protein 1
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SFU	Safety Follow-Up
SIBDQ	Short Inflammatory Bowel Disease Questionnaire

SMC	Safety Monitoring Committee
SOC	Standard of Care
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
TNF	Tumor Necrosis Factor
TLR	Toll-like Receptor
UC	Ulcerative Colitis
UCEIS	Ulcerative Colitis Endoscopic Index of Severity
ULN	Upper Limit of Normal

10.15 Protocol Amendment History

Version	Date	Description of Change	Brief Rationale
V1.1	Dec 24, 2018	• Updated the 2nd paragraph of Section 10.6 like the following: *As part of understanding the PK of the study drug, plasma samples may be used for metabolite identification and profiling evaluation. As part of understanding the efficacy and safety of the study drug, biopsy samples may be used for gene expression and profiling evaluation. Residual plasma and biopsy samples may be stored up to 2 years. If the residual samples are used, the results will be reported to the regulatory agencies.*	Clarification request from the IRB
		• Updated a term of 'dosing diary' to 'subject diary'. • Clarified the conditions of repeat ECG on Section 8.2.3 like the following: *If the QTc measurement at a time post-dose is > 45 msec increase from the baseline; or an absolute QTc value is ≥ 500 msec for any scheduled ECG*	Updated for the clarifications
		• Removed PK sampling procedures from an early termination (ET) visit. • Distributed a subject diary at screening. • Added a procedure to review any changes in smoking habits of subject during the study period at Visit 6 (Week 16) or ET visit.	Updated the study design
V2.0	Jan 20, 2019	• Using the Modified Mayo Endoscopic Score for the Mayo Endoscopic Subscores in Section 8.3.1 and Appendix 1 like the following (new text in **bold**; deleted text in ~~strikethrough~~): 8.3.1 Mayo Score The Total Mayo score is an instrument designed to measure disease activity of ulcerative colitis, with scores ranging	Updated per the FDA guidance

		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 (Mayo scoring system is listed in Appendix 1). **For the endoscopic subscore, the Modified Mayo Endoscopic Score will be used to exclude any friability from Grade 1 per the FDA guidance.** 'Findings of Endoscopy' of Appendix 1 **Findings of Endoscopy** 0 = Normal or inactive disease 1 = Mild disease (erythema, decreased vascular pattern~~, mild friability~~) 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions) 3 = Severe disease (spontaneous bleeding, ulceration)	
		• Updated the section of 'Bleeding' of Appendix 1 like the following (new text in **bold**; deleted text in ~~strikethrough~~): **Bleeding** 0 = None (**No visible blood**~~Normal vascular pattern with arborisation of capillaries clearly defined, or with blurring or patchy loss of capillary margins~~) 1 = Mucosal (**Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope that can be washed away**~~Patchy obliteration of vascular pattern~~) 2 = Luminal mild (**Some free liquid blood in the lumen**~~Complete obliteration of vascular pattern~~) 3 = Luminal moderate or severe (Frank blood in the lumen ahead of endoscope or visible oozing from mucosa after washing intraluminal blood, or visible oozing from a hemorrhagic mucosa)	Updated the definition of bleeding
V3.0	Apr 10, 2019	• Added tissue sampling and analysis for the tissue concentration of BBT-401-1S into the study design and procedures	Updated the study design
		• Added clinical sites located in South Korea.	Updated the study region
		• Updated the concomitant medications in Sections 5.1, 5.2, and 6.5	Updated for the clarification
		• Removed misleading sentence for the subject compensation in Section 5.5	Updated for the clarification

		• Added the allowed treatment compliance range as 80 to 120% in Section 6.4	Updated for the clarification
		• Removed an unnecessary procedure from Section 7.2.5	Updated for the correction
		• Updated the definitions of causality in Section 8.5.3.2	Updated for the clarification
		• Updated the sponsor address	Updated the sponsor information
V3.1	Jul 19, 2019	• Removed a screening diary from screening procedures.	Updated for the correction
		• Moved UCEIS procedure from V2 Baseline to V1 Screening.	Updated for the clarification
		• Indicated the endoscopy means flexible proctosigmoidoscopy/colonoscopy for this study (Section 1.3)	Updated for the clarification
		• Added 'Early Termination Visit' to visits when the treatment compliance is performed (Section 6.4)	Updated for the correction
		• Updated concomitant therapies in Section 6.5	Updated for the clarification
		• Clarified who will answer or assess sub-scores of Partial Mayo Score (Section 8.3.1).	Updated for the clarification
		• Deleted the central reading of UCEIS from Section 8.3.2.	Updated for the correction
		• Updated the scoring sheets of Mayo Score with actual scoring sheets to be used for the study (Appendix 1).	Updated for the correction

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Appendix 1. Mayo Score (Modified)

< Partial Mayo Score >

Subject ID _____ Initials _____ Visit No _____ Date _____

Partial Mayo Scoring Index Assessment for Ulcerative Colitis Activity

Patient, please enter number of daily bowel movements you would have when in remission or before your diagnosis or symptoms of ulcerative colitis began. **This number will be Your Normal**. ☐

Patient, please complete Questions 1 and 2.

Q1. Stool Frequency* (based on the past 3 days)

- ☐ Normal number of stools = 0
- ☐ 1-2 stools more than normal = 1
- ☐ 3-4 stools more than normal = 2
- ☐ 5 or more stools more than normal = 3

☐

Q2. Rectal Bleeding* (based on the past 3 days)

- ☐ No blood seen = 0
- ☐ Streaks of blood with stool less than half the time = 1
- ☐ Obvious blood with stool most of time = 2
- ☐ Blood alone passed = 3

☐

** Patient will choose the highest stool frequency and the most severe bleeding of the past 3 days.*

Investigator, please complete Question 3.

Q3. Physician's Global Assessment**

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

☐

*** Physician's Global Assessment acknowledges the sub scores, the daily records of abdominal discomfort and functional assessment, and other observations such as physical findings and patient's performance status.*

< Comments >

Partial Mayo Score (Sum of all above items) ☐

BBT401-UC-US02, Partial May Scoring
V1.2, 12Apr2019

Investigator _____ Date _____

< Mayo Endoscopic Score >

BBT401-UC-US02
Mayo Endoscopic Score

Site Number:		Principal Investigator:	

Subject No and Initials: _____ / _____

Endoscopy

Type (Cycle one): Screening Visit 4 (Week 8)

Date: _____

Name of GI Doctor: _____

Mayo Endoscopic Score

Score: _____

0 = Normal or inactive disease
1 = Mild disease (erythema, decreased vascular pattern)
2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3 = Severe disease (spontaneous bleeding, ulceration)

_____ _____
Investigator Signature* **Date (dd/mmm/yyyy)**

Appendix 2. Ulcerative Colitis Endoscopic Index of Severity

Patient ID _____ Initials _____ Visit No _____ Date _____

Vascular Pattern Score: _____

0 = Normal	(Normal vascular pattern with arborisation of capillaries clearly defined, or with blurring or patchy loss of capillary margins)
1 = Patchy obliteration	(Patchy obliteration of vascular pattern)
2 = Obliterated	(Complete obliteration of vascular pattern)

Bleeding Score: _____

0 = None	(No visible blood)
1 = Mucosal	(Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope that can be washed away)
2 = Luminal mild	(Some free liquid blood in the lumen)
3 = Luminal moderate or severe	(Frank blood in the lumen ahead of endoscope or visible oozing from mucosa after washing intraluminal blood, or visible oozing from a hemorrhagic mucosa)

Erosions and Ulcers Score: _____

0 = None	(Normal mucosa, no visible erosions or ulcers)
1 = Erosions	(Tiny [≤ 5mm] defects in the mucosa, of a white or yellow color with a flat edge)
2 = Superficial ulcer	(Larger [> 5mm] defects in the mucosa, which are discrete fibrin-covered ulcers when compared with erosions, but remain superficial)
3 = Deep ulcer	(Deeper excavated defects in the mucosa, with a slightly raised edge)

Investigator _____ Date _____

Appendix 3. Short Inflammatory Bowel Disease Questionnaire

Patient ID _____ Initials _____ Visit No _____ Date _____

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. Please check the box of your choice below each question.

1. How often has the feeling of fatigue or being tired and worn out been a problem for you during the past 2 weeks?
   - All of the time
   - Most of the time
   - A good bit of the time
   - Some of the time
   - A little of the time
   - Hardly any of the time
   - None of the time

2. How often during the last 2 weeks have you delayed or canceled a social engagement because of your bowel problem?
   - All of the time
   - Most of the time
   - A good bit of the time
   - Some of the time
   - A little of the time
   - Hardly any of the time
   - None of the time

3. As a result of your bowel problems, how much difficulty did you experience doing leisure or sports activities during the past 2 weeks?
   - A great deal of difficulty; activities made impossible
   - A lot of difficulty
   - A fair bit of difficulty
   - Some difficulty
   - A little difficulty
   - Hardly any difficulty
   - No difficulty; the bowel problem did not limit sports or leisure activities

4. How often during the past 2 weeks have you been troubled by pain in the abdomen?
   - All of the time
   - Most of the time
   - A good bit of the time
   - Some of the time
   - A little of the time
   - Hardly any of the time
   - None of the time

5. How often during the past 2 weeks have you felt depressed or discouraged?
   - All of the time
   - Most of the time
   - A good bit of the time
   - Some of the time
   - A little of the time
   - Hardly any of the time
   - None of the time

6. Overall, in the past 2 weeks, how much of a problem have you had with passing large amounts of gas?
   - A major problem
   - A big problem
   - A significant problem
   - Some problem
   - A little trouble
   - Hardly any trouble
   - No trouble

7. Overall, in the past 2 weeks, how much of a problem have you had maintaining or getting to the weight you would like to be?
   - A major problem
   - A big problem
   - A significant problem
   - Some problem
   - A little trouble

Hardly any trouble
No trouble

8. How often during the past 2 weeks have you felt relaxed and free of tension?
   All of the time
   Most of the time
   A good bit of the time
   Some of the time
   A little of the time
   Hardly any of the time
   None of the time

9. How much of the time during the past 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty?
   All of the time
   Most of the time
   A good bit of the time
   Some of the time
   A little of the time
   Hardly any of the time
   None of the time

10. How often during the past 2 weeks have you felt angry as a result of your bowel problem?
    All of the time
    Most of the time
    A good bit of the time
    Some of the time
    A little of the time
    Hardly any of the time
    None of the time

Study Coordinator _____ Date _____