Statistical Analysis Plan

Bridge Biotherapeutics, Inc.

BBT401-UC-005

[redacted]

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Glossary of Abbreviations

Abbreviation	Term
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
BID	Twice daily
CI	Confidence interval
CRF	Case report form
ECG	Electrocardiogram
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	Inform consent form
ITT	Intention-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
PR	Pulse rate
PT	Preferred term
QD	Once a day
QTcF	Fridericia corrected QT interval
RBS	Rectal Bleeding Score
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SFS	Stool Frequency Score
SI	International system of units
SOC	System organ class
STEAE	Serious treatment emergent adverse event

TEAE	Treatment emergent adverse event
TFLs	Tables, figures and listings
UC	Ulcerative colitis
UCEIS	Ulcerative Colitis Endoscopic Index of Severity
mMCS	Modified Mayo Clinical Score
mESS	Modified Mayo Endoscopic Score

1. Source Documents

The Statistical Analysis Plan (SAP) was written based on the following documentation:

Document	Date	Version
Protocol for Korea	02-Aug-2021	5.1 (Korea)
Protocol for other countries	02-Aug-2021	5.0 (Other countries)
[redacted]	[redacted]	[redacted]

2. Protocol Details

2.1 Study Objectives

The primary objective of this study is to explore the efficacy of orally administered BBT-401-1S in inducing a clinical response in subjects with active ulcerative colitis (UC) which is defined as have been diagnosed with active UC for ≥3 months prior to Day 1, have an inadequate response or disease relapse despite treatment of UC based on the local standard of care prior to screening, or have a total Mayo score ≥6, and endoscopic subscore ≥2, rectal bleeding subscore ≥1, and a stool frequency subscore ≥1, regardless of standard of care history.

The secondary objectives of the study are:

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

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

2.2 Overall Study Design

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

Induction Phase

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

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

Extension Phase

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

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

Subjects will attend the study site on Days 85, 112 (last dose of treatment), and 126 (for Korean sites only). Additionally, subjects will be contacted by telephone on Day 71 for safety and compliance monitoring; however, at the discretion of the investigator, subjects may be requested to attend a study site visit on this day.

The total planned study duration (screening to follow-up) is approximately 20 and 22 weeks for subjects who are enrolled into the extension phase in the sites of Korea and other countries respectively, and approximately 14 weeks for subjects who are not enrolled into the extension phase.

2.3 Sample Size and Power

Approximately 36 subjects will be randomised. There has not been any formal statistical assessment of the sample size. However, the number of subjects is common in early clinical studies and is considered sufficient to achieve the objectives of the study.

3. Efficacy and Safety Variables

3.1 Primary Endpoint(s)

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

The primary safety endpoints are adverse events (AEs) and serious adverse events (SAEs).

3.2 Secondary Endpoints

The secondary efficacy endpoints are:

- Clinical remission at Day 57, as measured by a total Mayo score of ≤2 points, with no individual subscore exceeding 1 point
- Achievement of endoscopic remission at Day 57, as measured by a Mayo endoscopic subscore of 0 or 1.
- Change from baseline to Day 57 in the total Mayo score

3.3 Exploratory Endpoints

The exploratory efficacy endpoints are:

- Endoscopic response rate at Day 57, as defined by a ≥2-point reduction from baseline in Ulcerative Colitis Endoscopic Index of Severity (UCEIS) score
- Endoscopic response rate at Day 57, as defined by a reduction of ≥1 grade in the Mayo endoscopic subscore
- Modified Mayo remission rate at Day 57, as defined by modified Mayo Clinical Score (mMCS) ≤2, Rectal Bleeding Score (RBS) =0, modified Mayo Endoscopic Score (mESS) ≤1, Stool Frequency Score (SFS) =0 or (1 if at least 1 point drop from baseline)
- Symptomatic remission rate at Day 57, as defined by RBS =0, SFS = 0
- Inflammatory Bowel Disease Questionnaire (IBDQ) total score, as measured by change from baseline
- Histological improvement, as guided by change from baseline in Geboes score
- Biomarkers, including C-reactive protein and faecal calprotectin, as measured by change from baseline
- Clinical remission at Day 112, as measured by a total Mayo score of ≤2 points, with no individual subscore exceeding 1 point
- Percentage of subjects with sustained remission at Day 112
- Clinical response rate at Day 112.
- Change from baseline to Day 57 in the partial Mayo score

4. Analysis populations

4.1 Intent-to-treat Population

The intent-to-treat (ITT) population will include all subjects who receive at least 1 dose of study drug, and who have a partial Mayo score recorded on Day 1 and at least 1 post-baseline Mayo score recorded. Subjects are categorized in the treatment group to which they are randomized.

4.2 Safety Population

The safety population will include all subjects who receive at least 1 dose of study drug. Subjects are categorized in the treatment group of the treatment they actually receive.

4.3 Pharmacokinetic Population

The pharmacokinetic population will include all subjects who received at least 1 dose of study drug and have at least 1 evaluable tissue concentration without a protocol deviation considered to significantly affect the pharmacokinetics.

4.4 Per Protocol Population

The per protocol population will include all subjects in the ITT who do not have pre-defined major protocol deviations that may affect the primary efficacy endpoint and have completed the study until Visit 5 (Day 57).

5. Data Handling

Unless otherwise specified, the baseline value which is not related to the efficacy analysis is defined as the last value obtained before the date and time of the first dose of study drug. Post-baseline values are defined as value obtained after the first dose of study drug.

The efficacy related baseline value (such as Total Mayo Score) is defined as the measurement taken at screening.

Change from baseline is defined as a post-baseline value minus the baseline value.

5.1 Time points and Visit Windows

Day 1 is defined as the day of first dose of treatment. Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1.

All data will be analyzed using nominal study visits as defined in the Study Schedule and case report form (CRF). No visit windows will be applied for summary and analysis.

5.2 Handling of Dropouts, Missing Data, and Outliers

For the primary and secondary efficacy responder analysis based on the total Mayo score, subjects with missing data will be deemed as "unresponsive". For subjects who received rescue therapy after the first dose of study drug and prior to Day 57, the response status will be deemed as "unresponsive" regardless of the Mayo score value at Day 57.

In terms of the exploratory endpoints, for the endoscopic response rate by total Mayo score, if a subject has no Mayo endoscopic subscore on Day 57, then the last post-baseline measurement prior to Day 57 will be used and the analysis will be based on the imputed value. If a subject does not have any post-baseline Mayo endoscopic subscore measurement, then the subject will be deemed as "unresponsive".

For modified Mayo remission rate at Day 57, if a subject has more than or equal to 2 questions are not answered, then the subject will be considered as "unresponsive". If a subject has only 1 question is not answered, then the last post-baseline question answered prior to Day 57 will be used to calculate the modified Mayo remission rate at Day 57.

For systemic remission rate at Day 57 based by total Mayo score, if a subject has 2 questions are not answered, then the subject will be considered as "unresponsive". If a subject has only 1 question is not answered, then the last post-baseline question answered prior to Day 57 will be used to calculate the systemic remission rate at Day 57.

For the clinical remission at Day 112, the percentage of subjects with sustained remission on Day 112, and the clinical response rate at Day 112 which are all based on the total Mayo score, if a subject has more than or equal to 3 questions are not answered, then the subject will be considered as "unresponsive". If a subject has less than 3 questions are not answered, then the last post-baseline question(s) answered prior to Day 112 will be used to calculate the total Mayo score and information relevant to derive hose Day 112 related exploratory endpoints.

For the UCEIS exploratory endpoint, if a subject has 1 unanswered UCEIS descriptor for the Day 57 visit, the last post-baseline value for the UCEIS descriptor prior to Day 57 will be used to calculate the final index score and to classify the achievement of endoscopic response by Day 57. If a subject has more than 1 unanswered UCEIS descriptor for the Day 57 visit, the last post-baseline value of the UCEIS index score prior to Day 57 will be used to classify the achievement of endoscopic response by Day 57. If a subject does not have any post-baseline measurement, then the subject will be deemed as "unresponsive".

In terms of handling missing/incomplete IBDQ, the following rule (as shown in the table below) will be followed before any imputation to be taken into a place:

	Number of Missing Values				Comments /Actions
	Subscore 1	Subscore 2	Subscore 3	Subscore 4	
Scenario A	0	0	0	0	You can compute 4 subscores and the full IBDQ

Scenario B	1	0	0	0	You can compute both the full IBDQ and the 4 subscores, by replacing the missing value with the average mean (computed on the data available for its own subscore)
Scenario C	1	1	1	1	You can compute both the full IBDQ and the 4 subscores, by replacing the missing values with the average means (each one computed on the data available for its own subscore)
Scenario D	2	0	0	0	You can compute the full IBDQ by replacing the 2 missing values with the average mean (computed on the data available for its own subscore). You can compute only 3 subscores
Scenario E	2	1	0	1	You can compute the full IBDQ by replacing the missing values with the average means (each one computed on the data available for its own subscore). You can compute only 3 subscores
Scenario F	2	1	1	1	You cannot compute the full IBDQ (more than 4 missing values). You can compute only 3 subscores
Scenario G	2	2	0	0	You cannot compute the full IBDQ because in more than one subscore there are 2 missing values (even though the total missing value is not exceeding 4). You can compute only 2 subscores.
Scenario H	0	0	3	0	You cannot compute the full IBDQ because there is one subscore with more than 2 missing values. You can compute only 3 subscores.

If the IBDQ missing value scenario is not covered via the process described above, the last post-baseline measurement will be used and analysis will be based on the imputed value.

Missing histopathology data will be considered as non-remission when analysis is performed.

Missing biomarkers data will not be imputed.

Handling of missing/incomplete concomitant medication start/stop date will be documented in Section 6.4.2 Previous and Concomitant Medication.

Handling of missing/incomplete AE start/stop date will be documented in Section 6.7.2 Adverse Events.

6. Statistical Methods

6.1 General Principles

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

Frequency of subjects or events and percentages will be summarised in categorical variables.

All data processing, summarization and analyses will be performed using Labcorp's SAS Environment / Version 9.4 (or later) of the SAS® statistical software package.

The following principles will be applied to all TFLs unless otherwise stated:

Principle	Value	Suggested Alternative Values
Significant tests	The significance testing will be performed and the 95% confidence interval will be reported where applicable.	
Treatment group labels and order presented	• 800 mg BBT-401-1S QD and placebo QD • 800 mg BBT-401-1S BID • Placebo BID	• BBT-401-1S QD +Placebo QD • BBT-401-1S BID • Placebo BID
Tables	Data in summary tables presented by phase, assessment and visit (where applicable).	
Listings	All data collected presented by phase, subject, assessment and visit (where applicable), unless otherwise specified	
Descriptive summary statistics for continuous variables	Number of subjects (n), mean, standard deviation (SD), minimum, median, and maximum.	
Descriptive summary statistics for categorical variables	Frequency counts and percentages [n (%)]	
Denominator for percentages	Number of subjects in the analysis population, unless stated otherwise in table shell(s)	
Include "Missing" as category	Demographics and Other Baseline Characteristics only	
Display for 0 percentages	0	
Display to one more decimal place than collected value	Mean Mean Difference Median	
Display to two more decimal places than collected value	Standard Deviation Standard Error Confidence Interval	
Limit of precision for displays	3 decimal places for non-derived variables and 5 decimal places for derived variables	
Date Format	DDMMMYYYY	

For subjects who progress into the extension phase and have achieved clinical remission in the induction phase, subjects will continue with the same treatment in the extension phase. If subjects have not achieved clinical remission in the induction phase, then a treatment will be assigned follows the described in Section 2.2. Data display will be summarised/listed by study phase where it is applicable as subjects may switch treatments between induction phase and extension for the Safety Population.

6.2 Subject Disposition and Data Sets Analyzed

Subject disposition will be listed and summarised and will include the number and percentage of subjects:

- screened
- enrolled
- treated
- included in each study population (ITT, Safety, PK and Per Protocol Population).

The number and percentage of subjects who complete the treatment/study at induction phase and who discontinue early from induction phase including primary reasons for discontinuation, will be presented by treatment group [redacted]

Additionally, a separate disposition for the extension will be summarised by treatment group [redacted] and will include the number and percentage of subjects:

- enter the extension phase
- treatment received during the extension phase
- early discontinue from extension phase with primary reason
- complete the extension phase

Screen failures will be listed with the reasons for failing the screen.

6.3 Protocol Deviations

All protocol deviations will be listed. In addition, all important protocol deviations will be summarised separately for each phase and by treatment group for the ITT Population.

6.4 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be listed and summarised by treatment group for the ITT Population. Standard descriptive statistics will be presented for the continuous variables of:

- age (years) [as collected on the CRF]

- weight (kg)

The total counts and percentages of subjects will be presented for the categorical variables of:

- sex
- race
- ethnicity

6.4.1 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [Version 23.1 (or a later version if updated during the study)]. All medical history will be listed, and the number and percentage of subjects with any medical history will be summarised by system organ class (SOC) and preferred term (PT) by treatment group for ITT.

6.4.2 Previous and Concomitant Medications

Medications received prior to or concomitantly with treatment will be coded by Labcorp using the WHODrug Dictionary [Sep2020 B3 (or a later version if updated during the study)], Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows:

Prior medications are taken with a start and stop dates prior to the first dose date and time of treatment.

Concomitant medications are those with a start date on or after the first dose date and time of treatment, or those with a start date before the first dose date of treatment and a stop date on or after the first dose date and time of treatment or ongoing end of study.

If there are missing/partial medication start/end dates, the following rule will be used to determine whether the medication is a concomitant medication:

- If month/year of the start date is after the month/year of Day 1, the medication will be considered as concomitant medication.
- If month/year of the start date is equal or before the month/year of Day 1, and the end date is present, the end date will be used to determine whether the medication is prior or concomitant. If the end date is on or after Study Day 1, the medication will be considered as concomitant medication. Otherwise, if the medication stopped before Study Day 1, then the medication is a prior medication.
- If month/year of the start date is equal to the month/year of Day 1, and the end date is a partial date, the medication will be considered as concomitant medication.

If a medication cannot be classified as "prior" or "concomitant" after applying imputation rules for missing/incomplete dates, it will be classified as concomitant.

Prior medications and concomitant medications will be listed together and summarised by treatment group for the ITT Population.

The number and percentage of subjects using each medication will be displayed together with the number and percentage of subjects using at least one medication within each therapeutic class (ATC-Level 2), chemical subgroup (ATC-Level 4), and generic term.

Medication starting date which is within the induction phase will be summarised under the induction phase. Similarly, a medication starting date which is within the extension phase will be summarised under the extension phase.

6.4.3 Concomitant Procedure

Procedure received concomitantly with treatment will be coded [redacted]

Concomitant procedures will be documented on the CRF. The number and percentage of subjects using each procedure will be displayed together with the number and percentage of subjects using at least one medication [redacted] for each phase and by treatment group for the Safety Population.

6.4.4 Rescue Therapy

Rescue medications and rescue procedures are both considered as rescue therapy for this study. Both rescue medication and rescue procedure will be documented on the CRF.

6.4.4.1 Rescue Medication

Rescue medication will be coded by Labcorp using the WHODrug Dictionary [Version Sep2020 B3 (or a later version if updated during the study)], ATC Classification codes.

The number and percentage of subjects using each therapy will be displayed together with the number and percentage of subjects using at least 1 medication within each therapeutic class (ATC-Level 2), chemical subgroup (ATC-Level 4), and generic term for each phase and by treatment group for the Safety Population.

6.4.4.2 Rescue Procedure

Rescue procedure will be coded by Labcorp using the Medical Dictionary for Regulatory Activities (MedDRA) [Version 23.1 (or a later version if updated during the study)].

The number and percentage of subjects with any rescue procedue will be summarised by system organ class (SOC) and preferred term (PT) for each phase and by treatment group for the Safety Population.

6.5 Measurements of Treatment Compliance

Percentage compliance is calculated as:

Overall Compliance:

100 * actual dose (capsules) taken/expected dose (capsules) administered

[redacted]

The expected dose administered is defined as number of days * 8 (capsules). Where number of days is calculated as the last treatment date – the first treatment date +1.

Compliance under Induction Phase:

100 * actual dose (capsules) taken/expected dose (capsules) administered

[redacted]

The expected dose administered is defined as number of days * 8 (capsules). Where number of days is calculated as the last treatment date – the first treatment date +1 during the induction phase.

Compliance under Extension Phase:

100 * actual dose (capsules) taken/expected dose (capsules) administered

[redacted]

The expected dose administered is defined as number of days * 8 (capsules). Where number of days is calculated as the last treatment date – the first treatment date +1 during the extension phase.

Percentage compliance will be summarised descriptively for each study phase by treatment group for the Safety Population. A pooled overall percentage compliance

will also be summarised descriptively by induction assigned treatment for the Safety Population.

The number and percentage of compliant subjects will be presented for each study phase by treatment group and pooled overall labelled by induction assigned treatment for the Safety Population, where compliant is defined as percentage compliance between 80.0% and 120.0% inclusive. The following percentage compliance categories will also be presented for overall and each study phase:

- <80.0%
- 80.0% - 120.0%
- >120.0%

6.6 Efficacy

6.6.1 Primary Efficacy Analysis

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

The stool frequency and rectal bleeding subscores will use the average of the last 3 non-missing assessments recorded in the subject diary. If an endoscopy is performed, the average of the last 3 non-missing assessments recorded in the subject diary prior to bowel preparation should be used. If the subscore is not an integer, the subscore should be rounded to the nearest integer. Subjects with missing values will be considered as unresponsive as described in Section 5.2.

Total Mayo Score will be calculated based on the response achieved from all 4 subscores ranged from 0-3 each out of a total sum of 12.

For example: If stool frequency = 2, rectal bleeding = 1, physician's global assessment = 2 and findings on endoscopy = 2 then total mayo score is 7 (2+1+2+2=7).

The percentage of improvement at day 57 is calculated as:

((Baseline Sum of the Total Mayo Score – Day 57 Sum of the Total Mayo Score)/ Baseline Sum of the Total Mayo Score) x 100%.

Subjects with a reduction of ≥3 points and ≥30% improvement from baseline of total Mayo score as well as a decrease in rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore ≤1 will be considered as slowing a clinical response at Day 57.

The number and proportion of subjects with the 95% confidence interval (CI) of clinical response rate at Day 57 will be calculated using the exact binomial method for each treatment. The Fisher's exact test will be used to evaluate any differences between treatments at Day 57 and will be summarised for the induction phase by treatment group for the ITT Population. No adjustments will be made for multiple comparisons.

6.6.2 Secondary Efficacy Analysis

Centrally read Mayo endoscopic subscores will be used to evaluate the secondary objectives of the study.

The stool frequency and rectal bleeding subscores will use the average of the last 3 non-missing assessments recorded in the subject diary. If an endoscopy is performed, the average of the last 3 non-missing assessments recorded in the subject diary prior to bowel preparation should be used. If the subscore is not an integer, the subscore should be rounded to the nearest integer. Missing values will be considered as unresponsive as described in Section 5.2.

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

  Total Mayo Score will be calculated based on the response achieved from all 4 subscores ranged from 0-3 each out of a total sum of 12.

  Subjects who have a sum of total Mayo score ≤2 points, with no individual subscore exceeding 1 point at Day 57, will be considered as achieving clinical remission.

  The number and proportion of subjects with the 95% confidence interval (CI) of clinical remission rate at Day 57 will be calculated using the exact binomial method for each treatment. The Fisher's exact test will be used to evaluate any differences between treatments at Day 57 will be summarised for the induction phase by treatment group for then ITT Population.

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

  The number and proportion of subjects achieving endoscopic remission at Day 57 with the 95% CI will be calculated using the exact binomial method for each treatment. The Fisher's exact test will be used to evaluate any differences between treatments at Day 57 will be summarised for the induction phase by treatment group for the ITT Population.

- **Change from baseline to Day 57 in the Total Mayo score.**

Analysis of covariance (ANCOVA) with change from baseline as the dependent variable and baseline value as the covariate variable will be used to compare the change from baseline to Day 57 in the total Mayo score between each treated group and the placebo group. The 95% CI for the treatment differences in the change from baseline will be calculated, and the p-value will be provided.

The normality assumption will be checked through the Shapiro-Wilk test of the residuals from the ANCOVA. If the normality assumption is violated at the 0.01 level of significance, an additional nonparametric analysis [redacted] will be used to compare each treated group to the placebo group.

6.6.3 Sensitivity Analysis

The following sensitivity analysis will be performed on the primary efficacy endpoint (the clinical response rate at Day 57) and the first secondary efficacy endpoint (the clinical remission rate at Day 57).

For these analyses, the following rules will apply.

[redacted]

In addition, the primary efficacy analysis will also be performed for the per-protocol population.

6.6.4 Subgroup Analysis

There is no pre-specified subgroup analysis for this study.

6.6.5 Exploratory Analysis

- **Endoscopic response rate by Day 57, as defined by a ≥2-points reduction from baseline in UCEIS score via central reading.**

  The UCEIS score will be calculated as the sum of the scores of all descriptors. The higher the score, the worse the UC. Baseline total UCEIS score minus Day 57 UCEIS score will be used to calculate the number of subjects who have a ≥2 points reduction. With a difference ≥2 points will be considered as endoscopic response. Missing value will be imputed based on the description from Section 5.2.

The actual and change from baseline will be presented. The number and proportion of subjects with the 95% CI of endoscopic response rate at Day 57 will be calculated using the exact binomial method for each treatment. The Fisher's exact test will be used to evaluate any differences between treatments at Day 57 and will be summarised for the induction phase by treatment group for ITT Population.

- **Endoscopic response rate at Day 57, as defined by a reduction of ≥1 grade in the Mayo endoscopic subscore**

  The Mayo endoscopic subscore will be based on Part 4 of the total Mayo score - "Investigator-reported Findings on endoscopy". The change in endoscopic score is calculated as the difference between the baseline and Day 57 scores. A difference of ≥1 grade is considered as endoscopic response. Missing values will be imputed based on the description from Section 5.2.

  The number and proportion of subjects with the 95% CI of endoscopic response rate at Day 57 will be calculated using the exact binomial method for each treatment. The Fisher's exact test will be used to evaluate any differences between treatments at Day 57 and will be summarised for the induction phase by treatment group for ITT Population.

- **Modified Mayo remission rate at Day 57, as defined by a mMCS≤2, RBS=0, mESS≤1, SFS=0 or (1 if at least 1 point drop from baseline)**

  The modified Mayo remission will be based on the Total Mayo Score with all the following 4 conditions are satisfied: 1. mMCS≤2, and 2. Rectal Bleeding Score=0, and 3. mESS≤1, and 4. Stool Frequency Score=0 or (1 if at least 1 point drop from baseline), where mMCS will be collected in the Modified Mayo Score form as the sum of RBS, mESS and SFS. Missing values will be imputed based on the description from Section 5.2.

  The number and proportion of subjects with the 95% CI of modified Mayo remission rate at Day 57 will be calculated using the exact binomial method for each treatment. The Fisher's exact test will be used to evaluate any differences between treatments at Day 57 and will be summarised for the induction phase by treatment group for ITT Population.

- **Symptomatic remission rate at Day 57, as defined by RBS=0, SFS=0**

  The symptomatic remission rate at Day 57 will be based on the Rectal Bleeding Score =0 and Stool Frequency Score=0 from Total Mayo Scoare. Missing values will be imputed based on the description from Section 5.2.

The number and proportion of subjects with the 95% CI of symptomatic remission rate at Day 57 will be calculated using the exact binomial method for each treatment. The Fisher's exact test will be used to evaluate any differences between treatments at Day 57 and will be summarised for the induction phase by treatment group for ITT Population.

- **Inflammatory Bowel Disease Questionnaire (IBDQ) total score, as measured by change from baseline**

  The IBDQ is a health-related quality-of-life (HRQoL) tool measuring bowel, systemic, emotional, and social function. Scores for each question range between 1 and 7, reflecting poor to good HRQoL, for a range of possible total scores from 32 to 224. In terms of the 4 aspects of patients live and their corresponding questions, it is summarised in the following table.

Aspects	Questions	Range of Score
Bowel	1, 5, 9, 13, 17, 20, 22, 24, 26, 29	10 to 70
Systemic	2, 6, 10, 14, 18	5 to 35
Emotional	3, 7, 11, 15, 19, 21, 23, 25, 27, 30, 31, 32	12 to 84
Social Function	4, 8, 12, 16, 28	5 to 35
Total Score	1~32	32 to 224

  Descriptive statistics on total score and its four aspects: bowel, systemic, emotional, and social function at each scheduled visit as well as change from baseline will be calculated for each phase and by treatment group for the ITT Population.

  The following categories with number and percentage of subjects will also be presented for total score at each post-baseline visit:

  - change >= 16 points from baseline
  - total score >= 170

  Mixed Model Repeated Measures (MMRM), with repeated change from baseline values as the dependent variable and baseline values as the covariate variable, will be used to compare the change from baseline to Day 29 and 57 in the IBDQ score between treatment and placebo group. The sample SAS code is provided in Apendix 2. The 95% CI for the difference in the change from baseline will be calculated for each treatment, and the p-value will be provided.

The normality assumption will be checked through the Shapiro-Wilk test. If the normality assumption is violated at the 0.01 level of significance, an additional nonparametric analysis [redacted] will be used to compare each treated group to the placebo group.

- **Histologic remission using histologic category**

  Subjects will be dichotomized as "histological remission" versus "histological non-remission" based on the option recorded on the CRF. Subjects with histologic category recorded as "histologic near remission" and "Other" will be categorised as "histologic non-remission". On the other hand, those recorded with "histologic healing", "histologic remission", "histologic remission without basal plasmacytosis", and "histologic remission without basal plasmacytosis or increased mucosal eosinophils" will be grouped to "histologic remission".

  A shift table (i.e., cross-tabulations "histologic remission" and "histologic non-remission" at screening versus Day 57) in a form of 2 x 2 table will be presented for each treatment.

  The number and proportion of subjects within each combined category will be summarised by treatment group for the ITT Population.

- **Biomarkers, including C-reactive protein and faecal calprotectin, as measured by change from baseline**

  Descriptive statistics on biomarkers at each scheduled visit as well as change from baseline will be calculated for each phase by treatment group for the ITT Population.

- **Clinical remission at Day 112, as measured by a total Mayo score of ≤2 points, with no individual subscore exceeding 1 point.**

  Total Mayo Score will be evaluated. Subjects who have a total Mayo score ≤2 points, with no individual subscore exceeding 1 point at Day 112, will be considered as achieving clinical remission.

  The number and proportion of subjects with the 95% CI of clinical remission rate at Day 112 will be calculated using the exact binomial method for each treatment. The Fisher's exact test will be used to evaluate any differences between treatments at Day 112 for the extension phase by treatment group for the ITT Population.

- **Sustained remission at Day 112.**

  Total Mayo Score will be evaluated. Subjects who have a total Mayo score ≤2 points, with no individual subscore exceeding 1 point at day 57 and day 112 will be considered as achieving sustained remission at day 112.

  The number and proportion of subjects with the 95% CI of sustained remission at Day 112 will be calculated using the exact binomial method for each treatment.

The Fisher's exact test will be used to evaluate any differences between treatments at Day 112 for the extension phase by treatment group for the ITT Population.

- **Clinical response rate at Day 112.**

  The number and proportion of subjects with the 95% CI of clinical response rate at Day 112 will be calculated using the exact binomial method for each treatment. The Fisher's exact test will be used to evaluate any differences between treatments at Day 112 for the extension phase by treatment group for the ITT Population.

- **Change from baseline to Day 57 in the Partial Mayo score.**

  Mixed Model Repeated Measures (MMRM), with repeated change from baseline values as the dependent variable and baseline values as the covariate variable, will be used to compare the change from baseline to Day 29 and 57 in the partial Mayo score between treatment and placebo group. The sample SAS code is provided in Apendix 2. The 95% CI for the difference in the change from baseline will be calculated for each treatment, and the p-value will be provided.

  The normality assumpltion will be checked through Shapiro-Wilk test of the residuals during the use of MMRM. If the normality assumption is violated at the 0.01 level of significance, an additional nonparametric analysis [redacted] will be used to compare each treated group to the placebo group.

6.7 Safety

6.7.1 Extent of Exposure

Duration of exposure will be defined in days as:

Overall Exposure:

(date of the last dose – date of the first dose) + 1-off-drug days

If date of the first dose date is missing, then the date of the first dose dispensed will be used. If the last dose date is missing then, then the last available dose date will be used.

Induction Phase Exposure:

(date of the last dose from the induction phase – date of the first dose from the induction phase) + 1-off-drug days

If date of the first dose date is missing, then the date of the first dose dispensed in the induction phase will be used. If the last dose date is missing then, then the last available dose date in the induction phase will be used.

Extension Phase Exposure:

(date of the last dose from the extension phase – date of the first dose from the extension phase) + 1-off-drug days

If date of the first dose date is missing, then the date of the first dose dispensed in the extension phase will be used. If the last dose date is missing then, then the last available dose date in the extension phase will be used.

Duration of exposure will be listed and summarised using descriptive statistics for each phase and overall by treatment group for the Safety Population.

The number and percentage of subjects with an overall duration of exposure in the following categories will be summarised for each phase and by treatment group for the Safety Population:

- <22 days
- ≥22 and <57 days
- ≥57 days

Overall duration will be summarised by treatment received during the induction phase. Exposure during each study phase will be summarised by the actual treatment received respectively during each study phase.

6.7.2 Adverse Events

All AEs recorded on the CRF will be coded using the MedDRA dictionary [Version 23.1 (or a later version if updated during the study)] and treatment – emergent AEs (TEAEs) are defined as follows:

- TEAEs are events with start date on or after the date and time of the first dose of treatment or events with start date prior to the date and time of the first dose of treatment whose severity worsens on or after the date and time of the first dose of treatment.

If an event where AE start/stop date is missing/partial, the following imputation rule will be applied:

Imputation rules for start date of AEs:

- If start date is completely missing, start date will be imputed to be the first dose date of study treatment;
- For a partial start date (day is missing, or day and month are both missing):

  - none missing part of the partial date < the first dose date: the last day of the month/year

  - none missing part of the partial date = the first dose date: the first dose date

  - none missing part of the partial date > the first dose date: the first day of the month/year

Imputation rules for end date of AEs:

- If end date is completely missing, then end date remains missing (assuming ongoing event);
- For a partial end date, the last day/month will be imputed. If only day is missing, the last day of the month will be imputed; if both day and month are missing, then the last day of the year will be imputed. If the imputed end date is after the end of study date, then imputed end date will be set as the end of study date.

If imputed AE start date is after the imputed AE stop date, then start date will be set to the imputed AE stop date.

Imputed dates will be used to determine whether an AE is treatment-emergent and will not be displayed in data listings.

All AE data will be listed. Treatment-emergence status will be flagged in the listing. In addition, corresponding listings of SAEs, AEs leading to discontinuation of treatment and AEs resulting in death will be produced.

Summary tables of TEAEs will be produced for each phase by treatment group for the Safety Population. AE starting date which is within the induction phase will be summarised under the induction phase. Similarly, an AE starting date which is within the extension phase will be summarised under the extension phase.

The severity of all AEs is recorded as mild, moderate, or severe. If severity is missing for a TEAE, it will be considered severe only in the overall category in the summary tables.

The relationship between an AE and treatment is assessed as not related, unlikely related, possible related, or related. A treatment-related AE is an AE considered by the investigator as possibly related, or related to treatment or with unknown/missing relationship to treatment.

An overview table will summarize the number and percentage of subjects with at least one of the following TEAEs, where subjects with more than one TEAE in a particular category are counted only once in that category:

- Any TEAE;
- Treatment-Related TEAE;
- TEAE Leading to Treatment Discontinuation;
- Serious Treatment Emergent Adverse Event (Serious TEAE);
- Treatment-Related Serious TEAE;
- Serious TEAE Leading to Death;
- Treatment-Related Serious TEAE Leading to Death;
- Serious TEAE Leading to Treatment Discontinuation;

- Treatment-Related Serious TEAE Leading to Treatment Discontinuation

The number and percentage of subjects reporting each AE will be summarised by System Organ Class (SOC) and Preferred Term (PT) for each phase and by treatment group for the Safety Population. Tables will be sorted alphabetically by SOC. PTs will be sorted by descending overall total. The following summaries will be produced:

- TEAEs, by SOC and PT;
- Treatment-Related TEAEs, by SOC and PT;
- TEAEs by Relationship to Treatment, by SOC and PT;
- TEAEs by Maximum Severity, by SOC and PT;
- TEAEs Related to Treatment by Maximum Severity, by SOC and PT;
- TEAEs Causing Discontinuation from Treatment, by SOC and PT;
- Treatment-Related TEAEs Causing Discontinuation from Treatment, by SOC and PT;
- Serious TEAEs, by SOC and PT;
- Treatment-Related Serious TEAEs, by SOC and PT;
- TEAEs Leading to Death, by SOC and PT;

In the above summaries, subjects with more than one AE within a particular SOC are counted only once for that SOC. Similarly, subjects with more than one AE within a particular PT are counted only once for that PT. For summaries by maximum severity, subjects with multiple AEs within a particular SOC or PT will be counted under the category of their most severe AE within that SOC or PT. AEs with missing severity will be included (as severe) in the overall count of subjects with AEs, but will not be included in the counts of subjects with AEs within a SOC or PT.

6.7.3 Laboratory Evaluations

Data for the following hematology, blood chemistry, and urinalysis analytes received recorded in the CRF will be summarised and listed and by visit for each study phase and by treatment group for the Safety Population.

Hematology	Clinical Chemistry	Urinalysis
Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell count White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Alanine aminotransferase Albumin Alkaline phosphatase Amylase Aspartate aminotransferase Bicarbonate Blood urea nitrogen Calcium Chloride Cholesterol Creatine kinase Creatinine Direct bilirubin Gamma-glutamyl transferase Glucose Lipase Potassium Sodium Total bilirubin Total protein Triglycerides Uric acid	Bilirubin Blood Colour and appearance Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urobilinogen Microscopic examination <u>Coagulation</u> Prothrombin time Activated partial thromboplastin time International normalised ratio

All laboratory data will be reported in International System of Units (SI)/Conventional units. Out-of-reference-range values will be flagged as high (H) or low (L) in the listings.

6.7.4 Vital Signs

The following vital signs will be summarised and listed by visit for each study phase and by treatment group for the Safety Population.

- systolic and diastolic blood pressure (mmHg);
- pulse rate (beats/min);
- tympanic temperature (°C).

6.7.5 12-Lead Electrocardiograms

The following quantitative ECG measurements will be taken during the study:

- heart rate (beats/min);
- PR interval (ms);
- QRS duration (ms);
- QT interval (ms);
- QTcF interval (ms);
- RR interval (ms);

An overall Investigator assessment of ECG will be provided (categories "normal", "abnormal, not clinically significant" and "abnormal, clinically significant").

The ECG measurements and investigator assessment will be summarised and be listed by visit for each study phase and by treatment group for the Safety Population.

6.7.6 Physical Examination

Physical examination results (normal/ abnormal, not clinically significant/ abnormal, clinically significant) will be summarised and listed for each subject for each study phase and by treatment group for the Safety Population.

6.8 PK Analysis

Tissue concentrations data for the biopsy samples collected on Day 57 will be summarized and listed by treatment group for the PK population.

6.9 Interim Analysis

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

7. Changes in Planned Analysis

- **histopathology healing using the Geboes score, as measured by change from baseline**

During the study design stage, it was determined that this study should be as similar as the BBT401-UC-004. Therefore, the same endpoint was kept as it is. During the BBT401-UC-004 CRF design, it was determined that it is difficult to record and compare Geboes Score directly and hence the study team decided to use histologic category as the tool for histopathology.

To be consistent with the BBT401-UC-004, it is decided the way of analysis and the endpoint should be modified accordingly. Therefore, a change in histopathology analysis is amended to be consistent with the BBT401-UC-004.

- **Change from baseline to Day 57 in the Total Mayo score**

The study team decided to present the absolute change from baseline to Day 57 in the Total Mayo score.

- **Modified Mayo remission rate at Day 57, as defined by a mMCS <=2, RBS=0, mESS<=1, SFS=0 or (1 if at least 1 point drop from baseline)**

The study team decided to summarize the modified Mayo remission rate to better evaluate the effects of BBT-401-1S.

- **Symptomatic remission rate at Day 57, as defined by RBS=0, SFS=0**

The study team decided to add an additional analysis to summarize the symptomatic remission rate to investigate how symptoms improve over the study duration.

- **Change from baseline to Day 57 in the partial Mayo score**

The study team decided to also present the change from baseline to Day 57 in the partial Mayo score to better evaluate the effects of BBT-401-1S.

8. Data Issues

No known data issues at the time of preparing this SAP.

9. References

1 CPMP. Points to Consider on Missing Data. EMEA: London, 2001. Available at https://www.ema.europa.eu/en/documents/scientific-guideline/points-consider-missing-data_en.pdf

2 ICH. *ICH E3 Guideline: Structure and Content of Clinical Study Reports Questions & Answers*, 2012. Available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_QAs_R1_Step4.pdf

3 R K. Pai, V Jairath, N Casteele, F Rieder, C E. Parker, G Y. Lauwers. *The Emerging Role of Histologic Disease Activity Assessment in Ulcerative Colitis*. Gastrointest Endosc 2018;88: 887-98.

4 G Guyatt, A Mitchell, E. J. Irvine, J Singer, N Williams, R Goodacre, C Tompkins. A New Measure of Health Status for Clinical Trials in Inflammatory Bowel Disease. Gastroenterology 1989;96:804-10

10. Appendices

Appendix 1: Document History

Document Version, Status, Date	Summary/Reason for Changes
Version XXX, DDMMMYYYY	Not applicable; the first version

Appendix 2: Sample SAS Code for MMRM

[redacted]

[redacted]

[redacted]

[redacted]