Statistical Analysis Plan

NCT04700449

CBP-307CN002

Multicenter, randomized, double-blind, placebo-controlled phase II clinical trial to evaluate the effectiveness and safety of CBP-307 in subjects with moderate to severe ulcerative colitis (UC)

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.1 (Dated 18Jan2023) for Protocol CBP-307CN002 V6.0 (Dated 25Dec2020).

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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Output Templates Signature Page

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	15FEB2022	Boran Zheng	Not Applicable – First Version
1.1	18Jan2033	Boran Zheng	Add definition of per-protocol set and 0.2mg only analysis sets

Contents

Abbreviations

Abbreviation	Meaning
AE	Adverse event
ALC	Absolute lymphocyte count
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BLQ	Below the lower limit of quantification
BMI	Body mass index
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRP	C-reactive protein
CS	Clinically Significant
CTCAE	Common terminology criteria for adverse events
DBP	Diastolic Blood Pressure
DLCO	Diffusing capacity of the lung for carbon monoxide
DMC	Data monitoring committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
FAS	Full analysis set
FCS	Fully Conditional Specification
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus

HIV	Human immunodeficiency virus
HR	Heart Rate
IBDQ	Inflammatory bowel disease questionnaire
ICH	International Conference on Harmonization
Ig	Immunoglobulin
LOCF	Last observation carried forward
LSMEANS	Least square mean
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full Analysis Set
MI	Multiple Imputation
MNAR	Missing Not at Random
n	Number of subjects
NCS	Not Clinically Significant
NE	Not Evaluable
NRI	Non Responder Imputation
OCT	Optical coherence tomography
PD	Pharmacodynamics
PFT	Pulmonary Function Test
PK	Pharmacokinetics
PPS	Per protocol set
PT	Preferred term
Q1	First quartile
Q3	Third quartile
QD	Once a day
QTcF	Fridericia's corrected QT interval
RR	Respiratory Rate
SAE	Serious adverse event
SAP	Statistical analysis plan

SBP	Systolic Blood Pressure
SD	Standard deviation
SE	Standard error
SOC	System organ class
SS	Safety set
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosis factor
UC	Ulcerative colitis
VZV	Varicella zoster virus
WBC	White blood cell count
WHO	World Health Organization

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol CBP-307CN002. It describes the data to be summarized and analyzed, including the specific statistical analyses to be performed. The Pharmacokinetics (PK)/Pharmacodynamics (PD) will be performed by the third-party vendor. A separate analysis plan will be provided for PK/PD analysis by the third-party vendor.

This statistical analysis plan (SAP) is based on protocol version 6.0, dated 25Dec2020. Protocol version 5.0, dated 17Dec2019, will be also mentioned.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

To compare clinical efficacy of CBP-307 vs placebo by evaluating the change of adapted Mayo score after 12 consecutive weeks treatment in subjects with moderate to severe UC.

2.2. SECONDARY OBJECTIVES

The secondary objectives are:

- To compare clinical efficacy of CBP-307 vs placebo by evaluating the clinical response rate, clinical remission rate and mucosal healing rate after 12 consecutive weeks treatment in subjects with moderate to severe UC
- To compare the clinical safety and tolerability of CBP-307 with those of placebo administered for 12 weeks in subjects with moderate to severe UC

2.3. EXPLORATORY OBJECTIVES

The exploratory objectives are:

- To evaluate the PK/PD of CBP-307 orally administered in subjects with moderate to severe UC in study stage 1
- To evaluate inflammatory bowel disease questionnaire (IBDQ) in study stage 1 and stage 2
- To evaluate the safety and tolerability of CBP-307 after medium or long-term administration (in study stage 2) in subjects with moderate to severe UC
- To evaluate clinical remission, clinical response and mucosal healing in subjects with moderately to severely active UC who respond after 12 weeks of induction therapy in the stage 1 study, thereby to evaluate the efficacy of CBP-307 orally administered for maintenance treatment compared with placebo in sub-study 1 of the study stage 2
- To evaluate clinical remission, clinical response and mucosal healing in subjects with moderately to severely active UC who do not achieve clinical response after 12 weeks of induction therapy in the study stage 1, thereby to evaluate the efficacy of CBP-307 when orally administered for treatment in the sub-study 2 of the study stage 2.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This study is a multicenter, randomized, double-blind, placebo-controlled phase II clinical trial to evaluate the efficacy and safety of CBP-307 in subjects with moderate to severe ulcerative colitis (UC). This study includes stage 1 and stage 2.

Stage 1:

After screening, subjects will enter randomized, double-blind, placebo-controlled induction

therapy for 12 weeks, i.e., stage 1. Subjects will be given CBP-307 capsules 0.2 mg (or placebo) orally once daily for 12 consecutive weeks. The eligible patients are planned to be enrolled and randomized at a ratio of 1:1 into the 2 groups (approximately 52 subjects per each group) and stratified according to whether the subject failed in a previous tumor necrosis factor (TNF)-α antagonist therapy. Subjects will be screened at 1-21 days prior to the baseline visit. Subjects with moderate to severe UC (adapted Mayo score >= 4) who meet all inclusion criteria and do not meet any exclusion criteria will be randomized into one of the following 2 groups at the baseline visit: a group treated with CBP-307 0.2 mg once daily (2 capsules of CBP-307 0.1 mg), and a placebo group (treated with 2 capsules of placebo). Placebo capsules are completely identical with the CBP-307 capsules in appearance and weight.

The study includes a one-week titration period:

For the subjects 0.2 mg group: subjects will be given 0.05mg CBP-307 till day 4, and 0.1 mg CBP-307 for the following 3 days, from day 8, the subjects will be given 0.2 mg CBP-307.

The subjects in placebo group will perform simulated titration. Both CBP-307 and placebo are administered through the oral route.

Those patients who were randomized to 0.1mg according to protocol 5.0 or earlier should continue the previously assigned treatment till week 12.

Subjects will be screened at 1-21 days prior to the baseline visit. Administration will be continued for 12 weeks. At the same time, if subjects who complete 12 weeks of induction therapy in stage 1 study meet the criteria, they can be selected to enter stage 2 study to further evaluate the safety and efficacy of CBP-307 after medium or long-term administration in subjects with moderate to severe UC. 4 weeks of safety follow-up will be performed in subjects who complete stage 1 study but not enter stage 2 study or early withdraw from the study.

Stage 2:

All subjects who complete 12 weeks of induction therapy (with CBP-307 or placebo) in stage 1

study and complete all examinations (including colonoscopy) at visits week 12 can be selected to enter stage 2 for a total of 40 weeks, including 36 weeks of continuous administration and 4 weeks of safety follow-up after the last dose. Subjects selected to enter stage 2 will be required to sign an updated informed consent form and be rescreened for eligibility.

Stage 2 contains two sub-studies: sub-study 1 and sub-study 2. Subjects entering stage 2 will enter one of sub-studies based on their results of efficacy evaluation in stage 1.

Sub-study 1: Subjects who have **clinical response** shown by efficacy evaluation at week 12 in stage 1 and meet the eligibility criteria for stage 2 will enter sub-study 1 and continue on the double-blind maintenance treatment for 36 weeks (weeks 13 to 48), i.e., the therapeutic regimen for them in stage 1 study will be maintained. Safety follow-up is scheduled at 4 weeks after the last dose. Subjects who present with UC relapse during maintenance treatment period are required to terminate treatment and be withdrawn from the study.

Note: Patients previously enrolled by protocol 4.0/5.0 would have the chance to receive 0.1mg, then they will continue 0.1mg in stage 2 sub-study 1. But there is no 0.1 mg group in protocol version 6.0 now.

Definition of disease relapse (UC recurrence): Increased activity of UC, defined as

a repeated (occurring at 2 consecutive visits) partial Mayo score that is at least 5 points and is also >=3 points higher than the score at week 12 (the end of induction therapy), and where the possibility of increased disease activity being due to other potential factors unrelated to UC can be excluded (e.g., infection, medication changes).

Sub-study 2 : Subjects who **do not achieve clinical response** at week 12 efficacy evaluation in stage 1 and meet the eligibility criteria for stage 2 will enter open-label treatment with CBP-307 0.2 mg. Subjects who receive CBP-307 0.2 mg or placebo in stage 1 study will receive CBP-307 once daily an oral dose of 0.2 mg in sub-study 2 of stage 2.

For subjects who enter sub-study 2 of stage 2, one-week dose titration will be performed at the first week (week 13) of stage 2. Dose titration involves administration of CBP 0.05 mg initiated on day 1 and used for 4 consecutive days, followed by administration of CBP-307 0.1 mg for 3

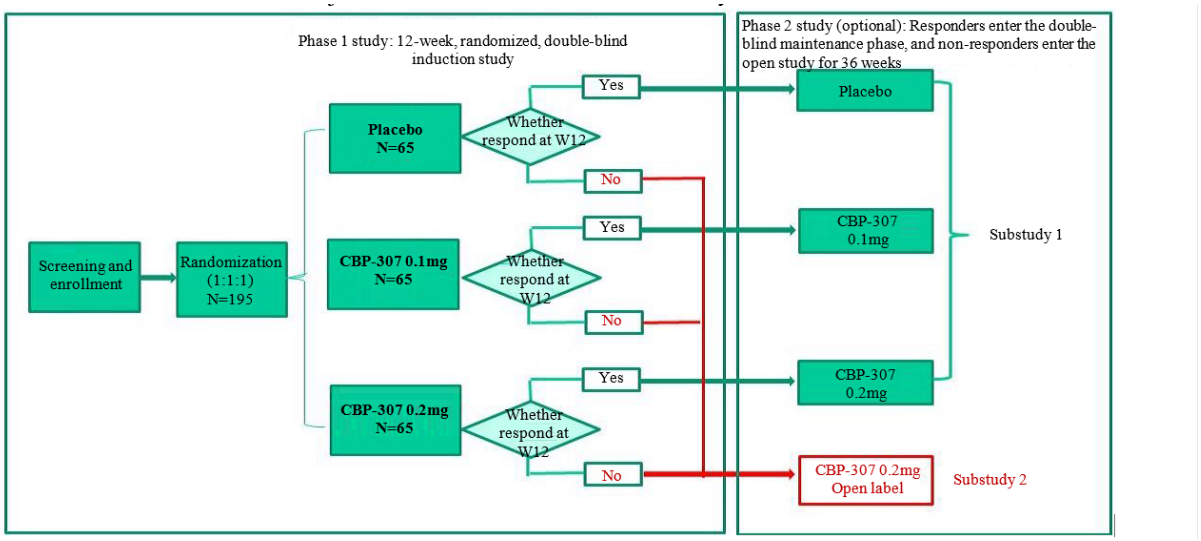
days, and administration of CBP-307 at a target dose of 0.2 mg initiated on day 8. After dose titration is completed, subjects will receive oral treatment with CBP-307 0.2 mg once daily, for 36 weeks. Safety follow-up of is scheduled at 4 weeks after the last dose.

At week 24, subjects will undergo efficacy evaluation involving colonoscopy. If the subjects have not achieved clinical response, the treatment will be discontinued, and the subjects will be withdrawn from the study. See Figure 1 for the overall design of the clinical study.

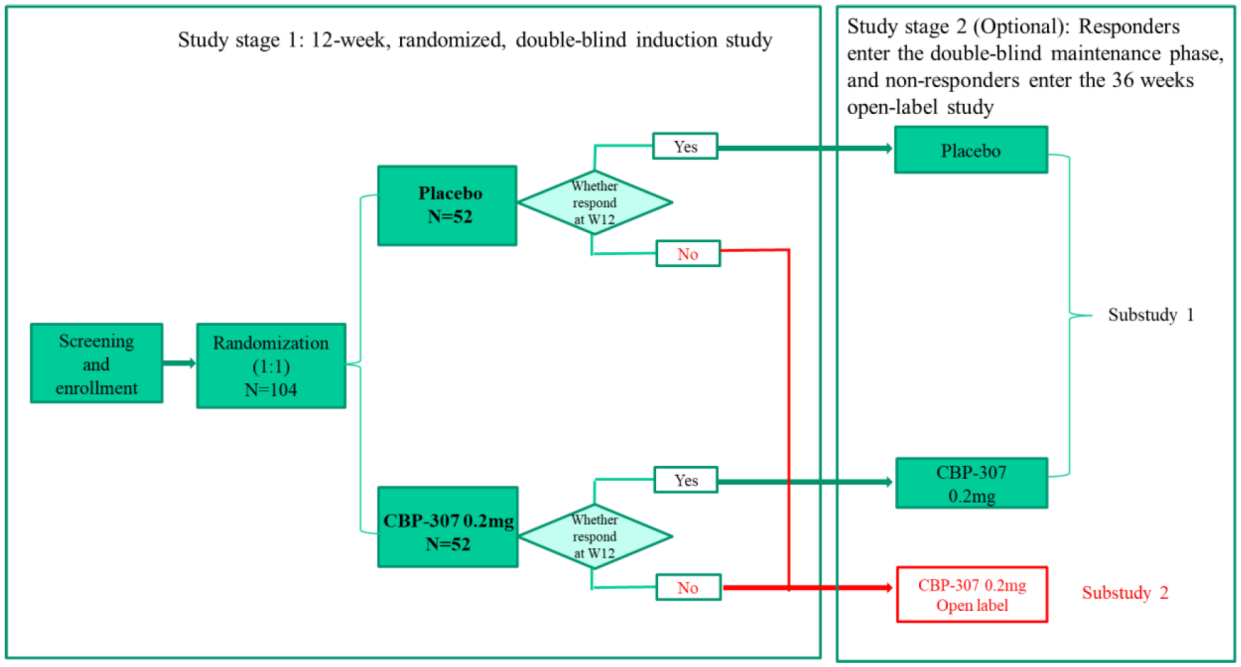
Note: Patients previously enrolled by protocol 4.0/5.0 would have the chance to receive 0.1mg, then they will receive open-label 0.2 mg treatment in stage 2 sub-study 2. But there is no 0.1 mg group in protocol version 6.0 now.

Figure 1 Overall design of the clinical trial

For protocol version 5.0 or earlier:



For protocol version 6.0:



3.2. SCHEDULE OF EVENTS

Schedule of events can be found in table 2 (study flow chart), table 3 (Sub-study 1 of stage 2) and table 4 (Sub-study 2 of stage 2) of the protocol.

3.3. CHANGES FROM PROTOCOL

1. Add modified full analysis set (mFAS) for efficacy endpoints in stage 1 to exclude impact of COVID-19 on week 12 adapted mayo score. For CBP-307CN002 Phase II UC study, approximately 20% missing data is anticipated for the adapted mayo score at Week 12. One major reason is that subjects could not come to site due to COVID-19. mFAS is added to reduce the bias due to those subjects.
2. A Phase II UC study does not have as strict criteria as a pivotal Phase III study. In recent years regulators have been critical of last observation carried forward (LOCF) and similar

approaches for handling missing data and have advocated using more scientifically justifiable (e.g. multiple imputation methods) in primary analyses of Phase III studies alongside testing assumptions. Recommendation of The Prevention and Treatment of Missing Data in Clinical Trials states, “Single imputation methods like last observation carried forward and baseline observation carried forward should not be used as the primary approach to the treatment of missing data unless the assumptions that underlie them are scientifically justified”. The European Medicines Agency (EMA) Guideline on Missing Data in Confirmatory Clinical Trials states, “The risk of underestimating the variance of treatment effect when imputing can be reduced by proper implementation of techniques such as multiple imputation.”

For CBP-307CN002 Phase II UC study, approximately 20% missing data is anticipated for the adapted mayo score at Week 12. With 20% missing data, the balance in the original FAS population could be lost which could result in biased estimates. Multiple Imputation (MI) can reduce bias arising from missing data.

Therefore, multiple imputation will be used to handle missing data in the analysis of the primary efficacy endpoints at Week 12 for CBP-307CN002 study. The original planned efficacy analysis in the protocol therefore becomes a sensitivity analysis in support of the new primary efficacy analysis, as well as LOCF imputed efficacy analysis.

3. Exploratory clinical remission rate by adapted mayo score is added for clinical discussion as exploratory efficacy endpoint. Exploratory clinical remission rate by adapted mayo score is defined as a rectal bleeding subscore <= 1 and a stool frequency subscore <= 1, with an Endoscopy subscore <= 1 [excluding friability].
4. 0.2 mg (all stages) analysis is added for a new population to analyse those patients who received 0.2 mg from initial - administration until end of treatment in the study.

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Analyses for Data Monitoring Committee (DMC) meetings
- Interim Analysis
- Final Analysis

4.1. DATA MONITORING COMMITTEE (DMC)

A DMC SAP, describing the methodology and presentation of results and access to results will be provided by IQVIA as a separate document.

4.2. INTERIM ANALYSIS (PRIMARY ANALYSIS)

One interim analysis (also primary analysis for this study) will take place for this study once all the subjects have completed week 12 (visit 11, last dose/early discontinue visit) in stage 1, the unblind study team will produce the analysis on primary endpoint after database lock. The primary endpoint is to compare clinical efficacy of CBP-307 vs placebo by evaluating the change of adapted Mayo score after 12 consecutive weeks treatment in subjects with moderate to severe UC. Interim analysis will only analyze stage 1 part (including 4-week safety follow-up for early withdrawal subjects). All analysis is used at interim analysis, or week 12.

The interim analysis focuses on efficacy analysis, including change from baseline of adapted Mayo score, complete Mayo score, and IBDQ, and clinical response rate, clinical remission rate, and mucosal healing rate.

The following will be performed in interim analysis:

- Disposition part: patient disposition (details in section 8), major protocol deviation (details in section 8), and analysis sets (details in section 5) summary table in Stage 1 and reference listings.

- Baseline Characteristics: demographics (details in section 9), medical history (details in section 10), prior medications and procedures (details in section 11) summary table in Stage 1 and reference listings.
- Study Exposure: exposure (details in section 12) and compliance (details in section 13) summary table in Stage 1 and reference listings.
- Efficacy: clinical response rate by adapted mayo score and complete mayo score at week 12; clinical remission rate by adapted mayo score and complete mayo score at week 12; analysis of change in adapted mayo score and complete mayo score from baseline at week 12; mucosal healing rate at week 12; analysis of change in IBDQ score from baseline at week 12 (details in section 14).
- Adverse Events: overall summary table in Stage 1; treatment emergent adverse events (TEAEs), drug-related TEAEs, grade>=3 TEAEs, serious TEAEs, TEAEs leading to drug withdrawal, TEAEs leading to death, and TEAEs of special interest by system organ class (SOC) and preferred term (PT) in Stage 1; TEAEs by maximum CTCAE grade, SOC and PT in Stage 1; death details in Stage 1.
- Laboratory: absolute value and change from baseline by visit of hematology, biochemistry, fasting lipids, coagulation, and urinalysis; shift from baseline to worst post-baseline common terminology criteria for adverse events (CTCAE) grade for hematology, biochemistry, fasting lipids, and coagulation; abnormalities in hematology and liver function test. The above summary tables are in Stage 1 as well as their reference listings.
- 12-Lead ECG: absolute value and change from baseline by visit of ECG; shift from baseline to worst post-baseline ECG overall assessment; abnormalities in QT internal and QTcF; shift from baseline to maximum post baseline value and maximum increase from baseline in Stage 1
- Other safety findings: vital signs (VS) part, including absolute value and change from baseline by visit and incidence of markedly abnormal values, and shift from baseline to worst post-baseline overall assessment; pulmonary function test data's absolute value and change

from baseline; ophthalmologic examination part, including overall assessment by visit and change from baseline; optical coherence tomography part, including overall assessment by visit and change from baseline; dermatologic examination part, including overall assessment by visit and change from baseline in Stage 1.

- Concomitant medications and procedures (details in section 11) in Stage 1.

If a decision is made to perform the primary or main analysis, in order to maintain study integrity with respect to the follow-up visits, safety visits and analyses, a Blind Maintenance Plan will be written. This plan will clearly identify the team (including the statistician) that will perform the primary or main analysis and all related activities, restrict other clinical team members and other Sponsor personnel from access to individual subject treatment allocation and site level analysis results, and ensure that the dedicated team will not participate in the data decisions for the following analyses. However, the dedicated team can participate in the analysis following the final database lock.

4.3. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following final analysis database lock (all subjects have completed the study, outstanding data queries have been resolved and the database has been cleaned and finalized.). The PK/PD analysis will be conducted by the PK group, a separate analysis plan will be provided by PK group.

5. ANALYSIS POPULATION

5.1. STAGE 1 POPULATION

Screened Set (Screened) in stage 1

The screened set will contain all subjects who signed informed consent for stage 1.

All Randomized Set (Randomized) in stage 1

The randomized set will contain all subjects who are randomized into stage 1, no matter treated or not.

Full Analysis Set (FAS) in stage 1

The full analysis population (FAS) will contain all randomized subjects who receive at least one dose of study medication or placebo in stage 1. FAS will be based on the planned drug taken.

Modified Full Analysis Set (mFAS) in stage 1

The modified full analysis population (mFAS) will contain all randomized subjects who receive at least one dose of study medication or placebo in stage 1 except subjects without week 12 adapted mayo score due to COVID-19. mFAS will be based on the planned drug taken.

Per Protocol Set (PPS) in stage 1

The per-protocol set (PPS) will contain a subset of FAS subjects who do not have major protocol deviation in stage 1.

Definition of major protocol deviation in stage 1:

1. Any Major clinical protocol deviation of Randomization Criteria
2. Any Major clinical protocol deviation of Eligibility and Entry Criteria
3. Any prohibited concomitant medication in clinical protocol deviation
4. IP compliance below 80% or over 120%
5. Have no baseline Adapted Mayo score
6. Have no Week12 Adapted Mayo score
7. Week 12 Adapted Mayo Score is out of visit window
8. Any unblinding during stage 1
9. Any other critical clinical protocol deviations in stage 1

Definition of minor protocol deviation in stage 1:

Clinical protocol deviation except major protocol deviation happened in stage 1.

Safety Set (SS) in stage 1

The safety set (SS) will contain all randomized subjects who receive at least one dose of study medication or placebo. SS will be based on the actual drug taken.

5.2. STAGE 2 POPULATION

All Subjects Screened (Screened) in stage 2

The all subjects screened will contain all subjects who signed informed consent for stage 2.

Full Analysis Set (FAS) in stage 2

The full analysis set (FAS) will contain all screened subjects who receive at least one dose of study medication or placebo in stage 2. FAS will be based on the planned drug taken.

Per-Protocol Analysis Set (PPS) in Stage 2

The per-protocol set (PPS) will contain a subset of FAS subjects who do not have major protocol deviation in stage 2.

Definition of major protocol deviation in stage 2 sub-study 1:

1. Any Major clinical protocol deviation of Randomization Criteria
2. Any Major clinical protocol deviation of Eligibility and Entry Criteria
3. Any prohibited concomitant medication in clinical protocol deviation
4. IP compliance below 80% or over 120%
5. Have no baseline Adapted Mayo score
6. Have no Week48 Adapted Mayo score
7. Week48 Adapted Mayo Score is out of visit window
8. Any unblinding during stage 2
9. Any other critical clinical protocol deviations in stage 2

Definition of minor protocol deviation in stage 2:

Clinical protocol deviation except major protocol deviation happened in stage 2.

Safety Set (SS) in stage 2

The safety set (SS) will contain all randomized subjects who receive at least one dose of study medication or placebo in stage 2. SS will be based on the actual drug taken.

5.3. ALL STAGES (0.2MG ONLY) POPULATION

All Subjects Screened (Screened)

The Screened Set includes all subjects who signed informed consent for stage 1 and stage 2 in 0.2mg treatment group.

Full Analysis Set (FAS)

The full analysis set includes all randomized subjects who receive at least one dose of 0.2 mg study medication in stage 1 and stage 2, either sub-study 1 or sub-study 2.

6. GENERAL CONSIDERATIONS

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented; for continuous variables, the number of subjects [n], mean, standard deviation [SD] or standard error [SE], median, minimum, and maximum will be presented. Statistical comparisons will be tested at two-sided alpha of 0.05 significance level, unless otherwise specified. Data collected in the study will be presented in by-subject listings for all subjects in the full analysis set (efficacy analysis) and safety analysis set

(safety analysis), unless otherwise specified. All by subject listings will be presented by treatment group, subject identification number in ascending order, unless otherwise specified.

For stage 1 analysis, the analysis period for subjects who enroll stage 2 will be from screening (baseline visit) in stage 1 until before the first dose of stage 2. And for subjects who will not enroll stage 2 (including screen failed subjects before randomization, randomized subjects but not treated, and subjects early discontinued in stage 1), the analysis period will be from screening (baseline visit) in stage 1 until end of study in stage 1. For stage 2 sub-study 1 analysis, the full/safety analysis population will be the randomized subjects who receive at least one dose of study medication or placebo in stage 2, but the analysis period will be from screening (baseline visit) in stage 1 until the end of study in stage 2. But for subjects who will enroll stage 2 sub-study 2, the analysis period will be the date of first dose of the open-label CBP307 0.2mg in stage 2 until the end of study in stage 2 since treatment is changed to open-label CBP307 0.2 mg QD.

For 0.2mg (all stages) group, the analysis period will be the date of first dose of initial administration until the end of stage 2 study, including stage 2 sub-study 1 and stage 2 sub-stage 2.

6.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show start/ stop day of assessments and events.

Reference start date is defined as the day of the first dose of study medication, (Day 1 is the day of the first dose of study medication) and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date, then:

Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date, then:

Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, the date will be imputed based on the imputation rules specified in section 11. The original value will be listed in the listings. The study day and any corresponding durations for this record will be calculated based on the imputed date.

6.2. BASELINE

For stage 1: Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to the first treatment date (including unscheduled assessments) in stage 1. In the case where the last non-missing measurement and the reference start date coincide, and no time collected, that measurement will be considered pre-dose, except that the protocol specifies the measurement is post-dose.

For subject randomized but not treated, baseline is defined as the last non-missing measurement on or before randomization date.

For subjects entered into stage 2 sub-study 1: the baseline will be the same as in stage 1.

For subjects entered into stage 2 sub-study 2: the baseline is defined as the last non-missing measurement taken prior to the first treatment date (including unscheduled assessments) in stage 2 sub-study 2.

For all stages (0.2mg only) analysis, baseline will be the same as in stage 1.

6.3. RETESTS, UNSCHEDULED VISITS

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries but will contribute to the minimum, maximum, best or worst case value where required (e.g. shift table).

Unless otherwise specified, in the case there are more than one records in the same visit, the latest available measurement for that visit will be used for by-visit summaries.

Listings will include scheduled, unscheduled, retest data.

6.4. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Change from baseline =Value at Week X – Baseline Value

Percentage change from baseline will be calculated as:

- Percentage change from Baseline= (Value at Week X – Baseline Value) / Baseline Value × 100%

6.5. SOFTWARE VERSION

All analyses will be conducted using SAS 9.4 or higher version.

7. STATISTICAL CONSIDERATIONS

7.1. MULTICENTER STUDIES

Center pooling will not be carried out for use in analyses for this study.

7.2. MISSING DATA

Missing safety data will be handled as described in separated section (concomitant medication missing data rule in section 11, and adverse event missing data rule in section 15.1).
Missing efficacy data will be handled as described in section 14.1.2 of this analysis plan.

7.3. SUBGROUP ANALYSES

No planned subgroup analyses will be performed for this study.

7.4. SAMPLE SIZE

Approximately 134 subjects with moderate to severe UC will be randomized in the study. Among them, there are approximately 30 subjects in the CBP-307 0.1 mg once daily group. In protocol version 5.0 or earlier, 195 patients with moderate to severe UC were planned to be randomized at 1:1:1 into any of the following 3 groups: CBP-307 0.1 mg once daily, CBP-307 0.2 mg once daily, placebo. Approximately 65 subjects were planned to be in each group. However, protocol amendment happens during the treatment period. The primary endpoint analysis is based on the comparison between the 0.2 mg CBP-307 group and the placebo group, and protocol version 6.0 keeps only these two groups, and sample size is re-calculated. The 0.1 mg group is not applicable in protocol version 6.0, and there will be no further subjects enrolled in the 0.1 mg group. The nearly 30 subjects already randomized with protocol version 5.0 or earlier are kept and analyzed for exploratory purpose.

The sample size re-calculation is based on the comparison between CBP-307 0.2 mg once daily group and placebo group on the primary efficacy endpoint, namely the change in adapted Mayo score from baseline at week 12 after treatment. Assuming that the difference between the 0.2 mg group and the placebo group of the change from baseline at week 12 after treatment in adapted Mayo score is 1.2, and the common standard deviation is 2.0, a significance level of α=0.05 (two-sided), and a dropout rate is 15%, then each group needs to enroll at least 52 subjects (104 subjects in two groups) to provide a power of 80% to detect the difference between the 0.2 mg group and the placebo group on the primary efficacy endpoint. Based on this estimation, the eligible subjects with moderate to severe UC will be randomized at 1:1 into CBP-307 0.2 mg once daily group or placebo group until 52 subjects are enrolled into each group.

8. DISPOSITION AND WITHDRAWALS

Disposition of all screened subjects, Screen failure, screened but not randomized will be

summarized by count and percentage.

Disposition of all randomized subjects will be tabulated by randomized treatment. The categories will include:

Stage 1:

- All subjects screened
- Screen Failed
- Screen success but not randomized
- All randomized subjects
- Subjects who were randomized but not treated with study medication
- Status of study treatment
  - completed
  - Ongoing
  - Discontinued
- Primary reason for treatment discontinuation
- Entered stage 2

- Study Status
  - Early discontinued in stage 1
  - Stage 1 treatment ongoing
  - Stage 1 post treatment follow-up
  - Completed stage 1 but not entered stage 2
  - Entered stage 2
- Primary reason for study discontinuation

Stage 2:

- Subjects archived clinical response by adapted mayo score (for sub-study 1)/ Subjects not archived clinical response by adapted mayo score (for sub-study 2)

- All subjects screened
- Status of study treatment
  - Completed
  - Ongoing
  - Discontinued
- Primary reason for treatment discontinuation
- Study Status
  - Early Discontinued in Stage 2
  - Stage 2 Treatment Ongoing
  - Stage 2 Post Treatment Follow-Up
  - Completed
- Primary reason for study discontinuation

Primary reasons for treatment discontinuation, as entered on the eCRF, will be tabulated; the reasons include adverse event, significant protocol deviation, death, non-compliance problems, lost to follow-up, withdrawal by subject, study terminated by sponsor, pregnancy, lack of efficacy or disease progression, or other. COVID-19 will be presented separately after selected from other reasons in 'Other, Specify' category.

Primary reasons for study discontinuation, as entered on the eCRF, will be tabulated; the reasons include subject didn't meet eligibility criteria(s), adverse event, significant protocol deviation, death, non-compliance problems, lost to follow-up, withdrawal by subject, study terminated by sponsor, pregnancy, lack of efficacy or disease progression, or other. COVID-19 will be presented separately after selected from other reasons in 'Other, Specify' category.

0.2mg only for all stages will present both stage 1 and stage 2 disposition.

Completed or discontinued from study, duration of study, and the reason for study withdrawal will be listed for each safety subject in the listings.

Major protocol deviation leading to subject being excluded from FAS in PPS and summary of all analysis sets will be presented for the safety set and be listed in the listings. Listing of

inclusion/exclusion criteria responses by subject will also be provided.

9. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for randomized population. The following demographic and other baseline characteristics will be reported for this study:

- Age (years) - calculated relative to date of consent
- Sex, including childbearing potential for female subjects
- Race
- Ethnicity
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Alcohol use
- Drug abuse
- Tobacco use
- If Treatment with a Tumor Necrosis Factor (TNF)-α Antagonist Failed?
- Ulcerative colitis history
    - Years since UC diagnosis (years)
    - Stool frequency (times/day)
    - Rectal bleeding
    - Endoscopy score - investigator
    - Endoscopy score - central
    - Physician's global assessment
    - Location and extent of subject's UC
- Family history of colon cancer

- Family history of premature coronary heart disease
- Chest imaging examination results at baseline

BMI (kg/ m^2) = weight (kg)/ height (m^2)

Age (Years) = (date of informed consent – date of birth+1)/365.25

Years since UC diagnosis = (date of informed consent-date of diagnosis+1)/365.25

10. MEDICAL HISTORY

Medical History/ Ulcerative Colitis Medical History will be presented for the FAS.

Medical history collected at screening will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) V21.1 or higher.

Medical history will be summarized by system organ system (SOC) and preferred term (PT) for each treatment group and overall. The tables will be sorted in descending order by SOC and in decreasing frequency based on the total number of subjects by PT (sorted in alphabetic order in case the frequency coincident) in each SOC. The number and percentage of subjects with any medical history will be summarized for each SOC and PT. The denominator used for calculating the percentages will be the total number of subjects included in each treatment group. For the tables, if a subject report the same PT multiple times, then that PT will be counted only once for that subject. Similarly, if a subject reports multiple conditions within the same SOC, then that SOC will be counted only once for that subject in the tables.

No inferential statistics will be generated.

Medical history will be listed by treatment group, study center and subject number. A by-subject listing of ulcerative colitis medical history will be provided by subject number (in ascending order) and medical history of abnormalities (in chronological order).

11. MEDICATIONS AND PROCEDURES

Medications will be presented for the FAS and coded using World Health Organization Drug Dictionary Global (Enhanced WHO Herbal Dictionary) 01Sep2018 or higher. Medications will be presented by Preferred name. Procedures recorded will be coded using MedDRA Version 21.1 or higher. All procedures will be presented by SOC and PT.

All medications and procedures will be presented in a listing.

The following rule is used for handling of partial dates for medications, in the case where it is not possible to define a medication as prior, concomitant, or post treatment, the medication will be classified by the worst case; i.e. concomitant. For concomitant medications, incomplete (i.e., partial missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, consider imputing the start date first.

Missing day and month

- If the year of the incomplete start date is the same as the year of the date of the treatment start date, then the day and month of the treatment start date will be assigned to the missing fields.
- If the year of the incomplete start date is before the year of the date of the treatment start date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the date of the treatment start date, then January 1 will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of

the treatment start date, then the treatment start date will be assigned to the missing day.

- If either the year is before the year of the treatment start date or if both years are the same, but the month is before the month of the treatment start date, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the date of the treatment start date or if both years are the same, but the month is after the month of the treatment start date, then the first day of the month will be assigned to the missing day.

If the stop date is not missing and the start date is after the stop date after missing value calculation, the stop date will be used for the start date.

Incomplete Stop Date

Missing day and month

- If the year of the incomplete stop date is the same as the last treatment date, then the day and month of the last treatment date will be assigned to the missing fields.
- If the year of the incomplete stop date is before the year of the last treatment date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is after the year of the last treatment date, then January 1 will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the last treatment date, then the day of the last treatment date will be assigned to the missing day.

- If either the year is before the year of the last treatment date or if both years are the same, but the month is before the month of the last treatment date, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the date of the last treatment date or if both years are the same, but the month is after the month of the last treatment date, then the first day of the month will be assigned to the missing day.

If the start date is not missing and the stop date is before the start date after missing value calculation, the start date will be used for the stop date.

'Prior' medications are medications which started and stopped prior to the first dose of study medication.

'Concomitant' medications are medications which:

- started prior to, on or after the first dose of study medication and started no later than end of study medication,
- AND ended on or after the date of first dose of study medication or were ongoing at the end of the study.

12. STUDY MEDICATION EXPOSURE

Exposure to study medication in days will be presented for the FAS.

The extent of exposure to study medication will be presented for the following summaries by treatment group and overall:

- Duration of exposure (days) during regular treatment period:
  Duration of exposure (days) during regular treatment = date of last dose during the regular treatment period – date of first dose during the regular treatment period +1;
- Actual duration of exposure (days) is defined as the total number of days on the study drug during the treatment phase (excluding the periods of dose break or dose interruptions).
- Planned cumulative dose (mg) during the regular treatment period:

Planned cumulative dose (mg) is defined as the sum of the total planned dosage that the subject should take during the regular treatment period. (subjects are planned to take drug after coming to site).

Stage 1 and Stage 2 Sub-study 1

Treatment Group	Target Visit Day	Planned Daily Dose (mg)	Target Duration	Target Dose Level in the Target Visit (mg)	Planned Cumulative Dose (mg)
0.2 mg QD	W1D5	0.05	4	0.2	0.2
	W2D8	0.1	3	0.3	0.5
	W4D28	0.2	21	4.2	4.7
	W8D56	0.2	28	5.6	10.3
	W12D84	0.2	28	5.6	15.9
	W18D126	0.2	42	8.4	24.3
	W24D168	0.2	42	8.4	32.7
	W32D224	0.2	56	11.2	43.9
	W40D280	0.2	56	11.2	55.1
	W48D336	0.2	56	11.2	66.3
0.1 mg QD (for protocol version 5.0 or earlier)	W1D5	0.05	4	0.2	0.2
	W2D8	0.1	3	0.3	0.5
	W4D28	0.1	21	2.1	2.6
	W8D56	0.1	28	2.8	5.4
	W12D84	0.1	28	2.8	8.2
	W18D126	0.1	42	4.2	12.4
	W24D168	0.1	42	4.2	16.6
	W32D224	0.1	56	5.6	22.2
	W40D280	0.1	56	5.6	27.8
	W48D336	0.1	56	5.6	33.4
Placebo	W1D5	1 tablet	4	4 tablets	4 tablets
	W2D8	2 tablets	3	6 tablets	10 tablets
	W4D28	2 tablets	21	42 tablets	52 tablets
	W8D56	2 tablets	28	56 tablets	108 tablets
	W12D84	2 tablets	28	56 tablets	164 tablets
	W18D126	2 tablets	42	84 tablets	248 tablets
	W24D168	2 tablets	42	84 tablets	332 tablets
	W32D224	2 tablets	56	112 tablets	444 tablets

	W40D280	2 tablets	56	112 tablets	556 tablets
	W48D336	2 tablets	56	112 tablets	668 tablets

Stage 2 Sub-stage 2

Treatment Group	Target Visit Day	Mapped Visit Day	Planned Daily Dose (mg)	Target Duration	Target Dose Level in the Target Visit (mg)	Planned Cumulative Dose (mg)
0.2 mg QD	W13D5	5	0.05	4	0.2	0.2
	W14D8	8	0.1	3	0.3	0.5
	W16D112	28	0.2	21	4.2	4.7
	W24D168	84	0.2	56	11.2	15.9
	W32D224	140	0.2	56	11.2	27.1
	W40D280	196	0.2	56	11.2	38.3
	W48D336	252	0.2	56	11.2	49.5

- Actual cumulative dose (mg) during the regular treatment period:

Actual cumulative dose (mg) is defined as the sum of the total dosage that the subject taken during the regular treatment period.

- Planned dose Intensity (mg/day) during the regular treatment period:

Planned dose intensity (mg/day) during the regular treatment period = planned cumulative dose (mg) during the regular treatment period/duration of exposure (days) during regular treatment period*100.

- Dose intensity (mg/day) during the regular treatment period:

Dose intensity (mg/day) during the regular treatment period = actual cumulative dose (mg) during the regular treatment period/duration of exposure (days) during regular treatment*100.

- Relative dose intensity (mg/day) during the regular treatment period:

Relative dose intensity (mg/day) during the regular treatment period=dose intensity during the regular treatment period/planned dose intensity during the regular treatment period*100.

Duration of exposure during the regular treatment period, total duration of exposure, planned cumulative dose during the regular treatment period, planned cumulative dose, actual cumulative

dose during the regular treatment period, total actual cumulative dose, planned dose intensity during the regular treatment period, dose intensity during the regular treatment period, relative dose intensity (mg/day) during the regular treatment period will be summarized using descriptive statistics, i.e., number of subjects (n), mean, median, standard deviation (SD), 25th and 75th percentiles (Q1, Q3), minimum and maximum.

In addition, the exposure data for the SS will be included in a listing.

13. STUDY MEDICATION COMPLIANCE

Compliance during the regular treatment period will be assessed using relative dose intensity during the regular treatment period.

Compliance during the regular treatment period will be summarized using descriptive statistics, i.e., number of subjects (n), mean, median, standard deviation (SD), 25th and 75th percentiles (Q1, Q3), minimum and maximum.

The compliance will also be summarized by the number of subjects in each of following categories:

- <80%
- 80% to 120% (including the 80% and 120%)
- >120%

The compliance categories will be summarized by count(s) and percentages (%).

Subjects with missing compliance information will be presented in a separate category, if applicable.

14. EFFICACY OUTCOMES

14.1. EFFICACY ASSESSMENT

Complete Mayo Score

The Mayo score is a standard, widely accepted, digital assessment of UC severity in subjects. The Mayo scores range from 0 to 12 and consist of 4 sub-items, each with the score range from 0 to 3. The higher the score is, the more severe the disease is:

1. Stool frequency [a]

   0 = Normal numbers of stools for this patient

   1 = 1-2 stools more than normal

   2 = 3-4 stools more than normal

   3 = 5 or more stools than normal

2. Rectal bleeding [b]

   0 = No blood seen

   1 = Streaks of blood with stool less than half the time

   2 = Obvious blood with stool most of the time

   3 = Blood alone passes

3. Endoscope findings

   0 = Normal or inactive disease

   1 = Mild disease (erythema, decreased vascular pattern, mild friability)

   2 = Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)

   3 = Severe disease (spontaneous bleeding, ulceration)

4. Physician's global assessment [c]

   0 = Normal

   1 = Mild disease

   2 = Moderate disease

   3 = Severe disease

Notes:

a. Each patient serves as his or her own control to establish the degree of abnormality of the stool

frequency.

b. The daily bleeding score represents the most severe bleeding of the day.

c. The physician's global assessment acknowledges the 3 other criteria, the patient's daily recollection of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.

Complete Mayo scores at baseline and at week 12 are calculated based on the results in the above items 1, 2, 3, and 4 (stool frequency, rectal bleeding, endoscopic findings, and physician's global assessment).

Adapted Mayo score

Adapted Mayo score is calculated based on the above assessment 1, 2 and 3 (Stool frequency, Rectal bleeding and Endoscopic findings). The Adapted Mayo score will be calculated at the visit at screening and week 12 (or early termination visit) during stage 1 study as well as at week 24 (only sub-study 2) and week 48 (or early termination visit) during stage 2 study.

Partial Mayo scores

Partial Mayo scores will be calculated at weeks 2, 4, 8 and 12 (i.e., Mayo score without colonoscopy findings) in study stage 1. In sub-study 1 of study stage 2, partial Mayo scores will be calculated at weeks 18, 24, 32 and 40. In sub-study 2 of study stage 2, partial Mayo scores will be calculated at weeks 16, 32 and 40.

Partial Mayo scores will be calculated based on assessment in the items 1, 2, and 4 of section 14.1.1 (Stool frequency, Rectal bleeding and Physician's global assessment).

14.2. PRIMARY EFFICACY

14.2.1. PRIMARY EFFICACY ENDPOINT

The primary efficacy analysis is based on the primary efficacy endpoint: change in adapted Mayo

score from baseline at week 12 compared between CBP-307 0.2 mg and placebo.

14.2.2. PRIMARY ANALYSIS OF PRIMARY EFFICACY ENDPOINT

The primary efficacy analysis will be based on FAS, mFAS, and PPS.

The covariance (ANCOVA) model with baseline as covariate will be used to analyze the changes in adapted Mayo score from baseline at week 12 between the CBP-307 0.2 mg group and the placebo group stratified by whether the previous treatment with a tumor necrosis factor (TNF)-α antagonist failed (Yes or No). The superiority of the CBP-307 0.2 mg group to placebo on change in adapted Mayo score from baseline at week 12 after treatment will be tested at a significance level of 0.025 with one-sided. If the significance level is reached, then superiority of the CBP-307 0.2 mg will be statistically significant. For subjects enrolled in protocol version 5.0 or earlier in 0.1 mg group, they will be compared with placebo group with same method as 0.2mg QD group, but only results of 0.1 mg group will be presented as supportive results.

The least square mean (LSMEANS), together with the p values and the 95% confidence intervals, between 0.2 mg vs. placebo will be reported using the ANCOVA model (SAS PROC MIXED), with the stratification factor as the confounding factor in the ANCOVA model and the baseline values as covariate.

The change from baseline over time on the Adapted Mayo score will also be plotted by each treatment group for exploratory purpose.

14.2.3. MISSING IMPUTATION FOR PRIMARY EFFICACY

Multiple Imputation

Multiple imputation has 3 distinct phases: Imputation, Analysis and Combining. During the Imputation Phase, the missing data values are filled-in to form a complete dataset. This is done ‘m’ times. For the Analysis Phase, each of the ‘m’ complete datasets are analysed by a statistical

model (as specified in Section 14.2.2). The Combining Phase pools the parameter estimates with their standard errors across the 'm' complete datasets and produces an average estimate with a standard error calculated using Rubin's formula this allows for the uncertainty between imputations as well as the variability within each analysis.

Multiple imputation assumes that the data are missing at random (MAR). MAR assumes that the missingness does not depend on the actual missing values, but that the missing data can be completely explained by the observed data. To test the robustness of the multiple imputation strategy a tipping point analysis may be implemented.

In the case of mayo scores, a multiple imputation approach is implemented for the missing individual adapted mayo score.

Each individual mayo score is imputed and then the composite endpoint measures are created (see list of endpoints in APPENDIX 2).

There are 4 steps to this process:

1. Create a dataset with one record per subject, containing all values of each mayo score for all visits (baseline and week 12 on one record) in stage 1. These variables are included because they are correlated with the endpoint and/or missingness. The multiple imputation process creates complete datasets using PROC MI in SAS 9.4. During post-processing, the endpoints are derived in each of the complete datasets. The endpoints and analysis model in APPENDIX 2.
2. Run 'm' times Markov Chain Monte Carlo (MCMC) imputations to make the missing values in the dataset have a full missingness pattern. This will produce a dataset with an index variable _imputation_ and otherwise the same variables as the input dataset. It will have one record per imputation per subject.
3. Run analysis of covariance model (the method in section 14.2.2) with imputation on each imputed dataset from Step 2. This will generate a dataset with the same structure as the input dataset, but will have the missing values filled in.
4. Combine all estimated statistics into one using PROC MIANALYZE.

14.2.4. SENSITIVITY ANALYSIS OF PRIMARY EFFICACY

The primary efficacy analysis will be performed after all subjects complete (or possibly complete) the treatment with the investigational product. Baseline adapted Mayo score is required. For missing primary efficacy endpoint (changes in the Adapted Mayo score at week 12), the latest post-baseline changes before week 12 will be carried forward if the Mayo score is missing. Imputed week 12 adapted mayo score with last observation carried forward (LOCF) method will be used in sensitivity analysis for FAS and mFAS subjects. The format on the summary statistics will keep the same as primary analysis. Complete case analysis without any imputation will be also summarized with same method in primary analysis for FAS mFAS subjects.

14.3. SECONDARY EFFICACY

The secondary efficacy analyses will be performed in the FAS, mFAS, and PPS. The same analyses as primary endpoints will be performed on the secondary quantitative efficacy endpoints.

14.3.1. SECONDARY ANALYSES ON EFFICACY ENDPOINTS

- Change in adapted Mayo score at week 12 from baseline: 0.1 mg vs placebo (only 0.1 mg group presented)
- Change in complete Mayo score at week 12 from baseline: 0.2 mg vs placebo
- Change in complete Mayo score at week 12 from baseline: 0.1 mg vs placebo (only 0.1 mg group presented)
- Clinical response rate by Adapted Mayo Score at week 12: 0.2 mg vs placebo (defined as a decrease of >= 2 points and at least 30% from baseline, accompanied with a decrease of >= 1 point from baseline in the rectal bleeding subscore or an absolute rectal bleeding

subscore of <= 1 point)

- Clinical response rate by Adapted Mayo Score at week 12: 0.1 mg vs placebo
- Clinical response rate by Complete Mayo Score at week 12: 0.2 mg vs placebo (defined as a decrease of >= 3 points and at least 30% from baseline, accompanied with a decrease of >= 1 point from baseline in the rectal bleeding subscore or an absolute rectal bleeding subscore of <= 1 point)
- Clinical response rate by Complete Mayo Score at week 12: 0.1 mg vs placebo
- Clinical remission rate by Adapted Mayo score at week 12: 0.2 mg vs placebo (defined as a rectal bleeding subscore = 0 and stool frequency sub score <= 1, with an Endoscopy subscore <=1 [excluding friability])
- Clinical remission rate by Adapted Mayo score at week 12: 0.1 mg vs placebo
- Clinical remission rate by Complete Mayo score at week 12: 0.2 mg vs placebo (defined as a total Mayo score of <= 2 points with no individual subscore > 1 point)
- Clinical remission rate by Complete Mayo score at week 12: 0.1 mg vs placebo
- Mucosal healing rate at week 12: 0.2 mg vs placebo (defined as Mayo endoscopic subscore <= 1)
- Mucosal healing rate at week 12: 0.1 mg vs placebo

14.3.2. MISSING DATA METHODS FOR SECONDARY EFFICACY VARIABLES

For the quantitative efficacy endpoint (changes in the Mayo score at week 12), the MI, LOCF, and complete case analysis will be presented if the Mayo score is missing in FAS and mFAS population.

For the qualitative efficacy analyses, subjects with any missing individual rating at week 12 will be considered as non-responders.

Endoscopy video will be obtained during each endoscopy and will be sent to Bioclinica for

central reading and determination of the Mayo endoscopy score. The result of the central reading of the endoscopy will be used to ensure subject eligibility prior to randomization and to calculate the Mayo score at analysis time points specified in the SAP. The Mayo score used for clinical endpoints in the study will utilize the Mayo endoscopy score derived from the central reader. The Mayo endoscopic score read by the investigator will be used as the Mayo score for clinical endpoints in case central reading endoscope data is missing.

14.3.3. ANALYSIS OF SECONDARY EFFICACY VARIABLES

Unless otherwise specified, all secondary efficacy analyses will be performed between treatment group and placebo and based on FAS and PPS. All results of these comparative analyses are used for exploratory purpose.

The clinical response rate at week 12, clinical remission rate at week 12, and mucosal healing rate at week 12 will be analysed

Summary statistics of qualitative statistic will be provided by each treatment group. Statistical comparison between the 0.2 mg CBP-307 group versus the placebo group and between 0.1 mg versus placebo group will be conducted using the Cochran Mantel Haenszel (CMH) test, stratified by whether treatment with a tumor necrosis factor (TNF)-α antagonist failed (Yes or No). The p-value on the rate difference and the 95% Newcombe confidence interval (CI) will be provided.

For example:

The null hypothesis to be tested is that the clinical response rate at week 12 is not different between the 0.2 mg treatment group and the placebo treatment group; i.e.,

H_0: clinical response rate at week $12_{0.2\ mg}$ = clinical response rate at week $12_{placebo}$

The alternative hypothesis is that clinical response rate at week 12 in the 0.2 mg treatment group is higher than that of the placebo treatment group, i.e.,

H_A: clinical response rate at week $12_{0.2\ mg} \neq$ clinical response rate at week $12_{placebo}$

for quantitative summary statistics, the least square mean (LSMEANS), together with the p values and the 95% confidence intervals, between 0.2 mg vs. placebo and between 0.1 mg vs. placebo will be reported using the ANCOVA model (SAS PROC MIXED), with the stratification factor as the confounding factor in the ANCOVA model and the baseline values as covariate.

14.4. EXPLORATORY EFFICACY

14.4.1. EXPLORATORY EFFICACY VARIABLE & DERIVATIONS

14.4.1.1 IBDQ Score

The Inflammatory Bowel Disease Questionnaire (IBDQ) (see Appendix 1 in protocol) is a psychometrically validated subject self-assessment scale used to measure the disease-specific quality of life in subjects with inflammatory bowel diseases including UC. IBDQ contains 32 items related to four aspects: intestinal function, emotional status, systemic symptoms, and social ability. The four aspects are scored as follows:

- Intestinal symptoms (10-70): question 1, 5, 9, 13, 17, 20, 22, 24, 26, 29
- Systemic symptoms (5-35): question 2, 6, 10, 14, 18
- Emotional function (12-84): question 3, 7, 11, 15, 19, 21, 23, 25, 27, 30, 31, 32
- Social ability (5-35): question 4, 8, 12, 16, 28

For each aspect, the higher the score is, the better the quality of life is. IBDQ is used as an endpoint indicator of the study and will be completed by the subjects themselves at baseline and at week 12 (or early termination visit).

The exploratory efficacy variable regarding to IBDQ is:

- Change from baseline at week 12 (stage 1) in IBDQ total and subscale scores (Bowel Systems, Emotion Health, Systemic Systems, and Social Function): 0.2 mg vs placebo
- Change from baseline at week 12 (stage 1) in IBDQ total and subscale scores: 0.1 mg vs

placebo

- Change from baseline at week 24 (stage 2) in IBDQ total and subscale scores: 0.2 mg vs placebo
- Change from baseline at week 24 (stage 2) in IBDQ total and subscale scores: 0.1 mg vs placebo
- Change from baseline at week 48 (stage 2) in IBDQ total and subscale scores: 0.2 mg vs placebo
- Change from baseline at week 48 (stage 2) in IBDQ total and subscale scores: 0.1 mg vs placebo

Other efficacy endpoints in stage 1

- Exploratory cinical remission rate at week 12 by adapted Mayo score: 0.2 mg vs placebo (defined as a rectal bleeding subscore <= 1 and a stool frequency subscore <= 1, with an Endoscopy subscore <= 1 [excluding friability].
- Exploratory cinical remission rate at week 12 by adapted Mayo score: 0.1 mg vs placebo

Efficacy endpoint in stage 2 sub-study 1

- Percentage of subjects who maintain clinical response at week 48: 0.2 mg vs placebo
- Percentage of subjects who maintain clinical response at week 48: 0.1 mg vs placebo
- Percentage of subjects who achieve clinical remission at week 48: 0.2 mg vs placebo
- Percentage of subjects who achieve clinical remission at week 48: 0.1 mg vs placebo
- Percentage of subjects who achieve mucosal healing under endoscope at week 48: 0.2 mg vs placebo
- Percentage of subjects who achieve mucosal healing under endoscope at week 48: 0.1 mg vs placebo

- Percentage of subjects who take oral corticosteroids at baseline, has discontinued treatment with corticosteroids at week 48 and achieved clinical remission: 0.2 mg vs placebo
- Percentage of subjects who take oral corticosteroids at baseline, has discontinued treatment with corticosteroids at week 48 and achieved clinical remission: 0.1 mg vs placebo
- Change in the complete Mayo score at week 48 from baseline: 0.2 mg vs placebo
- Change in the complete Mayo score at week 48 from baseline: 0.1 mg vs placebo
- Change in the adapted Mayo score at week 48 from baseline: 0.2 mg vs placebo
- Change in the adapted Mayo score at week 48 from baseline: 0.1 mg vs placebo
- Percentage of Subjects Who Take Oral Corticosteroids at Baseline, Has Discontinued Treatment with Corticosteroids at Week 48 and Achieved Clinical Remission

Efficacy endpoint in stage 2 sub-study 2

- Percentage of subjects who achieve clinical response at week 24 (at week 12 after treatment in sub-study 2)
- Percentage of subjects who achieve clinical remission at week 24 (at week 12 after treatment in sub-study 2)
- Percentage of subjects who achieve mucosal healing under endoscope at week 24 (at week 12 after treatment in sub-study 2)
- Change in the adapted Mayo score at week 24 (at week 12 after treatment in sub-study 2) from week 12
- Change in the complete Mayo score at week 24 (at week 12 after treatment in sub-study 2) from week 12
- Percentage of subjects who maintain clinical response at week 48 (at week 36 after treatment in sub-study 2) (i.e., have clinical response at both week 24 and week 48)

- Percentage of subjects who achieve clinical remission at week 48 (at week 36 after treatment in sub-study 2)
- Percentage of subjects who achieve mucosal healing under endoscope at week 48 (at week 36 after treatment in sub-study 2)
- Change in the complete Mayo score at week 48 (at week 36 of treatment in sub-study 2) from week 12:
- Change in the adapted Mayo score at week 48 (at week 36 after treatment in sub-study 2) from week 12
- Percentage of Subjects Who Take Oral Corticosteroids at Baseline, Has Discontinued Treatment with Corticosteroids at Week 48 and Achieved Clinical Remission

Efficacy endpoint in all stages for 0.2mg only:

- Change in the adapted Mayo score from baseline
- Change in the complete Mayo score from baseline
- Percentage of subjects who achieve clinical response at week 12 and week 48
- Percentage of subjects who achieve clinical remission at week 12 and week 48
- Percentage of subjects who achieve mucosal healing under endoscope at week 12 and week 48

Change from Baseline by Visit in IBDQ Total and Subscale Scores by VisitSummary of Percentage of Subjects Who Take Oral Corticosteroids at Baseline, Has Discontinued Treatment with Corticosteroids at Week 48 and Achieved Clinical Remission

14.4.2. ANALYSIS OF EXPLORATORY EFFICACY VARIABLES

Unless otherwise specified, exploratory efficacy analyses will be performed between treatment group and placebo and based on FAS, mFAS (only for stage 1), and PPS. All results of these comparative analyses are used for exploratory purpose.

The change in IBDQ total and subscale scores at week 12 will be summarized by treatment group. The least square mean (LSMEANS), together with the p values and the 95% confidence intervals, between 0.2 mg vs. placebo and between 0.1 mg vs. placebo will be reported using the ANCOVA model (SAS PROC MIXED), with the stratification factor as the confounding factor in the ANCOVA model. The change from baseline over time on the IBDQ total and subscale scores will also be plotted by each treatment group for exploratory purpose. If the individual score is missing at week 12 or week 12 is out of visit window, the latest observation carried forward (LOCF) method will be applied. The latest record before week 12 will be used for imputation.

For the endpoint clinical response rate, clinical remission rate, mucosal healing rate, change in complete Mayo score and change in adapted Mayo score of stage 2 sub-study 1 will be same as secondary endpoint in stage 1. But for stage 2 sub-study 2 and 0.2mg only analysis, only descriptive statistics will be presented for single arm.

15. SAFETY ANALYSES

All safety analyses will be based on the SS by treatment group. Only the descriptive statistics will be reported on the safety endpoints and no statistical comparisons will be conducted on safety data, unless otherwise specified.

15.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.1 or higher.

Treatment emergent adverse events (TEAEs) are defined as AEs that started, or worsened in severity, on or after the date of the first dose to the last dose date plus 28 days; it does not necessarily need to have a causal relationship with this treatment.

Missing date will be imputed following the blow rule:

When the AE start date is incomplete (i.e., partially missing), then the following rules will be applied:

Missing day and month

- If the year is the same as the year of the date of the treatment start date, then the day and month of the date of the treatment start date will be assigned to the missing fields.
- If the year is before the year of the treatment start date then December 31 will be assigned to the missing fields.
- If the year is after the year of the date of the treatment start date, then January 1 will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year are the same as the month and year of the treatment start date, then the day of the treatment start date will be assigned to the missing day.
- If either the year is before the year of the date of the treatment start date or if both years are the same, but the month is before the month of the treatment start date, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the date of the treatment start date or if both years are the same, but the month is after the month of the treatment start date, then the first day of the month will be assigned to the missing day.

If the stop date is not missing and the start date is after the stop date after missing value calculation, the stop date will be used for the start date.

An overall summary table for all AEs will be provided by the count and percentage. An overall summary of number of subjects within each of the categories described in the sub-section below,

will be provided as specified in the templates.

Listings will include TEAEs and Non-TEAEs. TEAEs (Y/N) will be flagged in the listings.

15.1.1. ALL TEAEs

Incidence of TEAEs will be presented by SOC and PT and broken down further by maximum severity and relationship to study medication.

15.1.1.1. Severity

Severity is classed per CTCAE grade. If a subject report a TEAE more than once within that SOC/ PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

15.1.1.2. Relationship to Study Medication

Relationship, as indicated by the Investigator, is classed as “Related”, “Possibly Related”, “Unlikely Related”, “Not Related”, A” Related” TEAE is defined as a TEAE with a relationship to study medication as “Related”, “Possibly Related” to study medication. TEAEs with a missing relationship to study medication will be regarded as “Related” to study medication. If a subject report the same AE more than once within that SOC/ PT, the AE with the worst-case relationship to study medication will be used in the corresponding relationship summaries.

15.1.2. TEAEs LEADING TO DISCONTINUATION OF STUDY MEDICATION

TEAEs leading to permanent discontinuation of study medication will be identified by using the “Drug Withdrawal” to the item “Action Taken with Study Drug/ Placebo ” on the “Adverse Events” form of eCRF.

For TEAEs leading to discontinuation of study medication, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

15.1.3. SERIOUS ADVERSE EVENTS

Serious adverse events (SAEs) are those events recorded as” Yes” to the item “Serious Event?” on

the adverse events page of the (e)CRF. A summary of serious TEAEs by SOC and PT will be presented.

15.1.4. ADVERSE EVENTS LEADING TO DEATH

TEAEs leading to Death are those events which are recorded as" Fatal" to the item "Outcome" on the Adverse Events page of the (e)CRF. A summary of TEAEs leading to death by SOC and PT will be presented.

15.1.5. ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest are those events which are recorded as "Yes" to the item "Is This an Adverse Event of Special Interest?" on the Adverse Events page of the eCRF. The adverse event of special interest will include the following:

- Bradycardia and cardiac conduction abnormalities
- Pulmonary toxicity
- Hepatotoxicity
- Macular Edema
- Opportunistic or serious infections
- Malignant neoplasm of skin
- Posterior reversible encephalopathy syndrome
- Progressive multifocal leukoencephalopathy.

A summary of adverse event of special interest by SOC and PT will be presented.

15.2. DEATHS

If any subjects die during the study as recorded on the "death" page of the eCRF, the information will be presented in a summary table and a data listing.

15.3. LABORATORY EVALUATIONS

Laboratory tests include the following: **Laboratory test item**	**Parameter**
Hematology	Red blood cell (RBC) count, HGB, hematocrit (HCT), white blood cell count, blood platelet count, leukocyte differential count (lymphocyte count, neutrophil count, monocyte count, eosinophil count, basophil count)
Blood biochemistry	
Liver function test	Total bilirubin, conjugated bilirubin, ALT, AST, γ-GT, alkaline phosphatase, albumin, total protein, lactate dehydrogenase
Kidney function test	Urea, creatinine, uric acid, Na, K, Cl, Ca, P, amylase [1]
Blood glucose examination	Fasting blood glucose (FBG)
Fasting blood fat [2]	Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides
Coagulation	Prothrombin time activated partial thromboplastin time, and international normalized ratio
Urinalysis/microscopy [3]	Specific gravity, pH, nitrite, protein, glucose, ketone bodies, urobilinogen, bilirubin, occult blood, esterase leukocyte/erythrocyte, and

	white blood cells
Fecal culture/microscopy [4]	Fecal culture, C.difficile, eggs and parasites, and fecal calprotectin
Others	
Virological and serological tests	Anti-VZV IgG, HIV antibody, HBsAg, HBsAb, HBcAb and HCVAb
	Syphilis antibody
	HBV DNA, HCV viral loads
Detection of immunoglobulin	Immunoglobulin A, G, M
Detection of C-reactive protein	C-reactive protein
Pregnancy test [5]	Blood β-human chorionic gonadotropin and urine pregnancy test
Quantiferon or Quantiferon Plus test [6]	TB

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; γ-GT=γ-glutamyltransferase; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HCVAb=hepatitis C antibody; HIV=human immunodeficiency virus; IgG=immunoglobulin G; TB=tuberculosis; VZV=varicella zoster virus.

1. Abnormal laboratory parameters or potential medical condition inconsistent with the clinical manifestations of UC should be repeatedly measured. At any follow-up after drug administration, if the amylase level is significantly higher than the clinical reference range (>=300 U/L), the lipase level should be measured to determine the source of elevated amylase (outside the pancreas).
2. Subjects must fast within 9 hours before a laboratory test.
3. If urinalysis show occult blood or abnormal urine protein in subjects' urine samples, a microscopy needs to be performed. A microscopy mainly refers to a blood test that measures

white blood cells and red blood cells. All other tests are tests with test strips.

4. Fecal culture/microscopy (involving fecal culture, C.difficile, eggs and parasites) is required to be performed at screening. During the screening period and any time point during the study if the subject has symptoms including aggravation of the disease condition or disease activity before recovery, stool samples can be collected for fecal culture/microscopy and C.difficile analysis.
5. Women with fertility are required to undergo a pregnancy test (involving blood β-human chorionic gonadotropin and urine pregnancy test). At screening, subjects with amenorrhea for <5 years are required to undergo measurement of follicle stimulating hormone to confirm postmenopausal condition.
6. Subjects can be enrolled in the study if it is evidenced that TB was treated successfully and Quantiferon or Quantiferon Plus test result is negative. If Quantiferon or Quantiferon Plus test result was uncertain at screening, the retest may be carried out during screening period. If Quantiferon or Quantiferon Plus retest result was uncertain, the subject should not participate in the study. If Quantiferon or Quantiferon Plus retest result is negative, the subject can be enrolled in the study.

Hematology, blood chemistry, and coagulation test results will be summarized at each study visit by treatment group.

Subjects with abnormalities in hematology assessments, defined as absolute lymphocyte count (ALC) <200 cells/uL, absolute neutrophil count (ANC) < 500 cells/uL as well as ANC <1000 cells/uL and total WBC >20,000 cells/uL will be summarized for each treatment group.

In addition, the change and percent change from baseline in complete blood count with Differential will be summarized for each treatment group.

The incidence of subjects with abnormalities for ALT/AST/ALP will be summarized overall and at each visit for each treatment group for the following categories:

>= 3 x ULN

>= 5 x ULN

>= 8 x ULN

The incidence of subjects with abnormalities for total bilirubin and conjugated bilirubin will be summarized overall and at each visit for each treatment group for the following categories:

> 1 x upper limit of normal (ULN)

>= 2 x ULN

Shift Tables from Baseline to Worst Post-baseline CTCAE Grade are presented.

15.4. ECG EVALUATIONS

The following ECG parameters will be reported for this study:

- Heart Rate (bpm)
- PR Interval (msec)
- RR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTcF Interval (msec)
- Overall assessment of ECG (Investigator's judgment):
  - Normal
  - Abnormal, Not Clinically Significant (NCS)
  - Abnormal, Clinically Significant (CS)
  - Not Evaluable

The following summaries will be provided for ECG data:

- Actual value and change from baseline by visit
- Shift from baseline to worst post baseline for overall evaluation
- Incidence of subjects with abnormalities for QT Internal/QTcF by visit
- Shift from baseline according to post-baseline maximum value category for QT Interval

and QTcF

- Shift from baseline according to post-baseline maximum increase category for QT Interval and QTcF
- Listing of ECG
- Listing of Holter ECG

15.4.1. ECG MARKEDLY ABNORMAL CRITERIA

Markedly abnormal quantitative ECG measurements will be identified in accordance with the following predefined markedly abnormal criteria:

- Absolute values for QT interval and QTcF will be classified as:
  - > 450 msec
  - > 480 msec
  - > 500 msec
- Change from Baseline for QT interval and QTcF will be classified as:
  - >30 msec increase from baseline
  - >60 msec increase from baseline

15.5. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Systolic Blood Pressure (SBP) (mmHg)
- Diastolic Blood Pressure (DBP) (mmHg)
- Systolic Blood Pressure(mmHg) (SBP) (Upright Position)
- Diastolic Blood Pressure(mmHg) (DBP) (Upright Position)
- Respiratory Rate (RR) (resp/min)
- Heart Rate (HR) (bpm)
- Temperature (^{0}C)

- Weight (kg)
- Height (cm)

The following summaries will be provided for vital signs data:

- Actual and change from baseline by visit
- Incidence Markedly Abnormal Values of vital signs:
  - SBP (mmHg) Low is defined as observed value less or equal to 90 and change from baseline less or equal to -20.
  - SBP (mmHg) High is defined as observed value greater or equal to 180 and change from baseline greater or equal to 20.
  - DBP (mmHg) Low is defined as observed value less or equal to 50 and change from baseline less or equal to -15.
  - DBP (mmHg) High is defined as observed value greater or equal to 105 and change from baseline greater or equal to 15.
  - HR (Bpm) Low is defined as observed value less or equal to 50 and change from baseline less or equal to -15.
  - HR (Bpm) High is defined as observed value greater or equal to 120 and change from baseline greater or equal to 15.
  - Temperature (˚C) High is defined as observed value greater or equal to 38.3 and change from baseline greater or equak to 1.1.
  - Weight (kg) Low is defined as percentage change from baseline less or equal to -7.0%.
  - Weight (kg) High is defined as percentage change from baseline greater or equal to 7.0%.
- Listing of vital signs

15.6. PHYSICAL EXAMINATION

The following summaries will be provided for physical examination results:

- Overall assessment of physical examination
- Listing of physical examination

The following specific assessments will be conducted: neck/thyroid, chest/lung, heart, lymph, nodes, abdomen, nervous system, and other (if applicable). Each measurement will be categorized as normal/abnormal, NCS/abnormal, CS/NE. Nervous System Physical Examination result will be also summarized by symptoms.

15.7. OTHER SAFETY ASSESSMENTS

15.7.1. PULMONARY FUNCTION TEST

The following pulmonary function test measurements will be reported for this study:

- FEV1 Results
- FEV1 Predicted Results
- FEV1% Predicted Results
- FVC Results
- FVC Predicted Results
- FVC % Predicted Results
- DLCO Results
- DLCO Predicted Results
- DLCO % Predicted Results

The following summaries will be provided for pulmonary function test data:

- Actual value, change, percent change and change in percent predicted from baseline by visit
- PFT test results will also be listed.

15.7.2. OPHTHALMOLOGIC EXAMINATION

The following summaries will be provided for ophthalmologic examination data:

- Ophthalmologic examination result by visit
- Shift from baseline to worst post baseline
- Listing of ophthalmologic examination data

15.7.3. OPTICAL COHERENCE TOMOGRAPHY

The following summaries will be provided for optical coherence tomography data:

- Optical coherence tomography result by visit
- Shift from baseline to worst post baseline
- Listing of optical coherence tomography data

15.7.4. DERMATOLOGIC EXAMINATION

The following summaries will be provided for dermatologic examination data:

- Dermatologic examination result by visit
- Shift from baseline to worst post baseline
- Listing of dermatologic examination data

15.7.5. PREGNANCY TEST

Pregnancy test data will only be listed.

15.7.6. CHEST IMAGING EXAMINATION

Chest imaging examination data will only be listed.

16. REFERENCES

Dobson, A. J. (2002). *An introduction to generalized linear models, 2nd ed.* Chapman & Hall/CRC.

EMA. (n.d.). *Guideline on Missing Data in Confirmatory Clinical Trials.* Retrieved December 15, 2011, from European Medicines Agency: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500096793.pdf

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA OUTPUT CONVENTIONS

Outputs will be presented according to the Shells.

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in that order:

Treatment Group	For Tables and Graphs	For Listings (include if different to tables)
0.1 mg	0.1 mg	
0.2 mg	0.2 mg	
Placebo	Placebo	

PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name
Stage 1	
Screening (Visit 1)	Scr (V1)
Baseline (Visit 2)	BL (V2)

Long Name (default)	Short Name
Week 1 day 1 (Visit 3)	W1D1 (V3)
Week 1 day 5 (Visit 4)	W1D5 (V4)
…	…
Week 16 (Visit 12)	W16 (V12)
Stage 2 sub-study 1	
Week 13 (Visit 12)	W13 (V12)
Week 18 (Visit 13)	W18 (V13)
Week 24 (Visit 14)	W24 (V14)
Week 32 (Visit 15)	W32 (V15)
Week 40 (Visit 16)	W40 (V16)
Week 48 (Visit 17)	W48 (V17)
Week 52 (Visit 18)	W52 (V18)
Stage 2 sub-study 2	
Week 13 (Visit 12)	W13 (V12)
Week 13 day 1 (Visit 13)	W13D1 (V13)
Week 13 day 5 (Visit 14)	W13D5 (V14)
Week 14 (Visit 15)	W14(V15)
Week 16 (Visit 16)	W16(V16)
Week 24 (Visit 17)	W24(V17)
Week 32 (Visit 18)	W32 (V18)
Week 40 (Visit 19)	W40 (V19)
Week 48 (Visit 20)	W48 (V20)
Week 52 (Visit 21)	W52 (V21)

LISTINGS WILL BE ORDERED BY THE FOLLOWING (UNLESS OTHERWISE INDICATED IN THE TEMPLATE):

- Randomized treatment group (or treatment received if it's a safety output), first by active dose [by ascending dose group] and then control/ placebo.
- center-subject ID,
- date (where applicable),
- For listings where non-randomized subjects are included, these will appear in a category after the randomized treatment groups labeled 'Not Randomized'.

APPENDIX 2. LISTING OF EFFICACY PARAMETERS AND STUDY POPULATIONS ANALYSED IN STAGE 1

Efficacy Parameters	Response Analyzed	Comparison Groups			Visit	Study Populations Analyzed	Imputation Method
		Group1	Group2	Statistical Method			
Primary Endpoint (Stage 1)							
Adapted Mayo Score	Change from Baseline	0.2mg QD	Placebo	ANCOVA	Week 12	FAS, mFAS, PPS	MCMC MI, LOCF
Secondary Endpoints (Stage 1)							
Adapted Mayo Score	Change from Baseline	0.1mg QD	Placebo	ANCOVA	Week 12	FAS, mFAS, PPS	MCMC MI, LOCF
Complete Mayo Score	Change from Baseline	0.2mg QD	Placebo	ANCOVA	Week 12	FAS, mFAS, PPS	MCMC MI, LOCF
Complete Mayo Score	Change from Baseline	0.1mg QD	Placebo	ANCOVA	Week 12	FAS, mFAS, PPS	MCMC MI, LOCF
Adapted Mayo Score	Clinical Response Rate	0.2mg QD	Placebo	ANCOVA	Week 12	FAS, mFAS, PPS	NRI
Adapted Mayo Score	Clinical Response Rate	0.1mg QD	Placebo	ANCOVA	Week 12	FAS, mFAS, PPS	NRI
Complete Mayo Score	Clinical Response Rate	0.2mg QD	Placebo	ANCOVA	Week 12	FAS, mFAS, PPS	NRI
Complete Mayo Score	Clinical Response Rate	0.1mg QD	Placebo	ANCOVA	Week 12	FAS, mFAS, PPS	NRI
Adapted Mayo Score	Clinical Remission Rate	0.2mg QD	Placebo	ANCOVA	Week 12	FAS, mFAS, PPS	NRI

Adapted Mayo Score	Clinical Remission Rate	0.1mg QD	Placebo	ANCOVA	Week 12	FAS, mFAS, PPS	NRI
Complete Mayo Score	Clinical Remission Rate	0.2mg QD	Placebo	ANCOVA	Week 12	FAS, mFAS, PPS	NRI
Complete Mayo Score	Clinical Remission Rate	0.1mg QD	Placebo	ANCOVA	Week 12	FAS, mFAS, PPS	NRI
Mayo Endoscopic Subscore	Mucosal Healing Rate	0.2mg QD	Placebo	ANCOVA	Week 12	FAS, mFAS, PPS	NRI
Mayo Endoscopic Subscore	Mucosal Healing Rate	0.1mg QD	Placebo	ANCOVA	Week 12	FAS, mFAS, PPS	NRI
Exploratory Endpoints (Stage 1)							
IBDQ	Change from Baseline	0.2mg QD	Placebo	ANCOVA	Week 12	FAS, mFAS	MCMC MI, LOCF
IBDQ	Change from Baseline	0.1mg QD	Placebo	ANCOVA	Week 12	FAS, mFAS	MCMC MI, LOCF