Clinical Study Protocol

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)

Investigational product:	CBP-307
Protocol No.:	CBP-307CN002
Version date:	December 25, 2020/ Final Version 6.0
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Regulatory agency identifying number(s):	To be determined

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Statement of Confidentiality

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Abbreviations

Abbreviation	Meaning
5-ASA	5-aminosalicylic acid
ACLS	Advanced cardiac life support
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
ALK	Alkaline phosphatase
γ-GT	γ-glutamyltransferase
BP	Blood pressure
cAMP	Cyclic adenosine monophosphate
CD	Crohn's disease
C. difficile	Clostridioides difficile
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Drug maximum concentration
CMH	Cochran-Mantel-Haenszel
CRO	Contract research organization
CRP	C-reactive protein
CTCAE	Common terminology criteria for adverse events
DLCO	Diffusing capacity of the lung for carbon monoxide
EC_{50}	Half maximum effect concentration
ECG	Electrocardiogram
eCRF	Electronic case report form
FAS	Full analysis set
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
GD	Gestation day
GLP	Good Laboratory Practice
HBV	Hepatitis B virus
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus

HR	Heart rate
IBD	Inflammatory bowel disease
IBDQ	Inflammatory bowel disease questionnaire
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IFX	Infliximab
Ig	Immunoglobulin
IRB	Institutional Review Board
ISF	Investigator Site File
IWRS	Interactive web response system
LFT	Liver function test
LQTS	Long QT syndrome
MTD	Maximum tolerated dose
NOAEL	No observed adverse effect level
OCT	Optical coherence tomography
PK	Pharmacokinetics
PD	Pharmacodynamics
PPS	Per-protocol set
QTcF	QT interval corrected using Fridericia's formula
RAVE	Electronic data capture system
RBC	Red blood cell
RTSM	Randomization and Trial Supply Management
S1P1	Sphingol-1-phosphate receptor isoform 1
SAE	Serious adverse event
SAP	Statistical analysis plan
SS	Safety set
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum concentration
TNF	Tumor necrosis factor
TPE	Therapeutic plasma exchange
UC	Ulcerative colitis
ULN	Upper limit of normal
WBC	White blood cell

Sponsor Signature Page of Protocol

Sponsor (Suzhou Connect Biopharmaceuticals, Ltd.) will, in accordance with the requirements of the clinical study protocol, strictly follow the guidelines below throughout the study, giving the greatest respect for subjects:

- the Declaration of Helsinki: ethical principles for medical research involving human subjects;
- the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) (E6);
- the local Good Clinical Practice;
- all applicable laws and regulations, including but not limited to Privacy Protection Act as well as laws and regulations governing clinical trial disclosure.

I have read the full text of the protocol and agree to all the contents.

Name of Sponsor's Representative: Ping Li

Signature of Sponsor's Representative: **Signing Date:**

Liping 5-Jan-2021

Title of Sponsor's Representative: Vice President, Clinical Development

Name of Sponsor: Suzhou Connect Biopharmaceuticals, Ltd.

Investigator Signature Page of Protocol

I agree:

I will, in accordance with the requirements of the clinical study protocol, strictly follow the guidelines below throughout the study, giving the greatest respect for subjects:

- the Declaration of Helsinki: ethical principles for medical research involving human subjects;
- the ICH-GCP (E6);
- the local GCP;
- all applicable laws and regulations, including but not limited to Privacy Protection Act as well as laws and regulations governing clinical trial disclosure.

I have read the full text of the protocol and agree to all the contents.

Name of Investigator:

Signature of Investigator: **Signing Date:**

Title of Investigator:

Name of Study Site:

Statistician Signature Page of Protocol

I agree:

- To strictly follow the protocol, GCP and applicable regulations and laws when carrying out the study.
- To keep all materials supplied by Suzhou Connect Biopharmaceuticals, Ltd. confidential according to confidentiality requirements, and must specify these materials are confidential when submitting to the Independent Ethics Committee (IEC)/Institutional Review Board (IRB).

I have read the full text of the protocol and agree to all the contents.

Name of Statistician: Boran Zheng

Signature of Statistician: **Signing Date:**

Title of Statistician: Senior Biostatistician

Name of Statistical Agency: IQVIA

1 STUDY SYNOPSIS

Protocol Title: 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)

Protocol No.: CBP-307CN002

Phase of Clinical Trial: II

Investigators and Study Sites: The clinical trial is planned to be carried out in approximately 77 sites globally in China, Pakistan, Ukraine and the United States.

Planned Duration of Study: March 2018 to September 2022

Study Objectives and Endpoints:

	Study objectives	**Study endpoints**
Primary endpoint	● 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	● Change in adapted Mayo score from baseline at week 12 compared between CBP-307 0.2 mg and placebo
Secondary endpoint	● 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	● Change in adapted Mayo score from baseline at week 12 after treatment compared between CBP-307 0.1 mg and placebo ● Change in complete Mayo score from baseline at week 12 after treatment ● Comparison of clinical response rate at week 12 by adapted Mayo score (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) ● Comparison of clinical response rate at week 12 by complete Mayo score (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) ● Comparison of clinical remission rate at week 12 by adapted Mayo score (defined as a rectal bleeding subscore = 0 and a stool frequency subscore ≤ 1, with an Endoscopy subscore ≤ 1 [excluding friability])

		● Comparison of clinical remission rate at week 12 by complete Mayo score (defined as a total Mayo score of ≤ 2 points with no individual subscore > 1 point) ● Mucosal healing rate at week 12 after treatment (mucosal healing is defined as Mayo endoscopic subscore ≤ 1)
	● 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	● Incidence, type and severity of TEAEs and SAEs as well as their relations with the investigational product, AEs and SAEs that lead to discontinuation of study, and AEs of special interest (cardiac events as well as pulmonary function tests, ophthalmologic examinations skin examinations, and nervous system physical examinations); AEs will be graded according to CTCAE version 5.0 in the study stage 1 ● 12-lead ECG findings, abnormal clinical laboratory tests (the hematology test, blood chemistry test, urinalysis and coagulation test), vital signs and results of physical examination
Exploratory	● To evaluate the PK/PD of CBP-307 orally administered in subjects with moderate to severe UC in study stage 1 ● To evaluate 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	● Plasma concentration of CBP-307 in subjects with moderate to severe UC ● Absolute lymphocyte count ● Total Igs (IgA, IgG and IgM) ● C-reactive protein (CRP) as a biomarker of plasma protein ● Fecal calprotectin as a fecal biomarker to be analyzed ● Change from baseline in IBDQ total score and subscore at week 12 after treatment (in the study stage 1), at week 24, and week 48 (in the study stage 2) ● Incidence, type and severity of TEAEs and SAEs as well as their relations with the investigational product, AEs and SAEs that lead to discontinuation of study, and AEs of special interest (cardiac events as well as pulmonary function tests, ophthalmologic examinations, skin examinations, and nervous system physical examinations); AEs will be graded according to CTCAE version 5.0 in study stage 2 ● Change in 12-lead ECG findings, abnormal clinical laboratory tests (the hematology test, blood chemistry test, urinalysis and coagulation test), vital signs and results of physical examination in the study stage 2 ● To explore the following efficacy endpoints in subjects with moderately to severely active UC

	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.	who achieved clinical response after 12 weeks of induction therapy in study stage 1: ○ Percentage of subjects who maintain clinical response at week 48 ○ Percentage of subjects who achieve clinical remission at week 48 ○ Percentage of subjects who achieve mucosal healing under endoscope at week 48 ○ Percentage of subjects who take oral corticosteroids at baseline but has discontinued treatment of corticosteroids at week 48 and achieved clinical remission ○ Change in the complete Mayo score at week 48 from baseline ○ Change in the adapted Mayo score at week 48 from baseline ● To explore the following efficacy endpoints in subjects with moderately to severely active UC who do not achieve response after 12 weeks of induction therapy in study stage 1: ○ Percentage of subjects who achieve clinical response at week 24 (after 12 weeks of treatment in sub-study 2) ○ Percentage of subjects who achieve clinical remission at week 24 (after 12 weeks of treatment in sub-study 2) ○ Percentage of subjects who achieve mucosal healing under endoscope at week 24 (after 12 weeks of treatment in sub-study 2) ○ Change in the complete Mayo score at week 24 (after 12 weeks of treatment in sub-study 2) from week 12 ○ Change in the adapted Mayo score at week 24 (after 12 weeks of treatment in sub-study 2) from week 12 ○ Percentage of subjects who maintain clinical response at week 48 (after 36 weeks of 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 (after 36 weeks of treatment in sub-study 2) ○ Percentage of subjects who achieve mucosal healing under endoscope at week 48 (after 36 weeks of treatment in sub-study 2) ○ Change in the complete Mayo score at week 48 (after 36 weeks of treatment in sub-study 2) from week 12

		○ Change in the adapted Mayo score at week 48 (after 36 weeks of treatment in sub-study 2) from week 12

AE=adverse events; CRP=C-reactive protein; CTCAE=common terminology criteria for adverse events; IBDQ=inflammatory bowel disease questionnaire; Ig=immunoglobulin; PD=pharmacodynamics; PK=pharmacokinetics; SAE: serious adverse event; TEAE: treatment-emergent adverse event; UC=ulcerative colitis.

Study design:

This is a multicenter, multicountry, 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.

Study stage 1

After screening, subjects will enter the randomized, double-blind, placebo-controlled induction therapy for 12 weeks, i.e., the study stage 1. Subjects will be given CBP-307 capsules 0.2 mg (or placebo) orally once daily for 12 consecutive weeks. The eligible subjects are planned to be enrolled and randomized at a ratio of 1:1 into the 2 groups (approximately 52 subjects in 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.

Subjects randomized to CBP-307 group will undergo dose titration for 1 week, while those in placebo group will undergo simulated titration. Both CBP-307 and placebo will be administered through the oral route. For subjects in the group of CBP-307 0.2 mg once daily, a dose of 0.05 mg CBP-307 will be given from day 1 to day 4; then, a dose of 0.1 mg CBP-307 will be given for later 3 days; from day 8, a target dose (0.2 mg) will be administered. See Table 1 for details on the Stage 1 dose titration.

Table 1 Stage 1 Titration dosing regimen

Target dose	Day 1 to day 4	Day 5 to day 7	From day 8
CBP-307 0.2 mg	0.05 mg	0.1 mg	0.2 mg
Placebo	Placebo capsules	Placebo capsules	Placebo capsules

Note: During the titration period, CBP-307 0.05 mg will be orally administered at doses of 0.05 mg (1 capsule) and 0.1 mg will be orally administered at 0.05 mg (2 capsules); in the placebo group, placebo capsules at the corresponding quantity (completely identical with

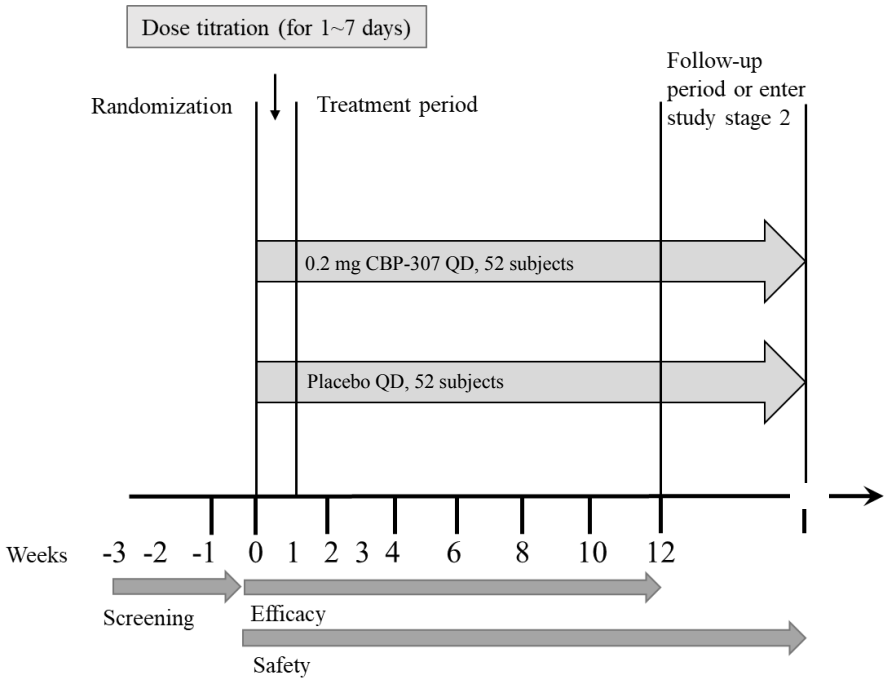
CBP-307 in appearance and weight) are orally administered. From day 8, in the 0.2 mg group, 2 capsules of 0.1 mg will be orally administered; and in the placebo group, 2 capsules of placebo (completely identical with CBP-307 in appearance and weight) will be orally administered. The drugs taken daily are sub-packaged in bottles in a GMP-compliant workshop, the investigational product is independently packaged in boxes based on visit intervals.

For the subjects already enrolled as per the previous approved protocols (version 5.0 or earlier), they will continue the treatment in the stage 1 according to the previous planned schedule.

Administration will be continued for 12 weeks. If subjects who complete 12 weeks of induction therapy of the stage 1 meet the criteria for the study stage 2, they can choose to enter it to further evaluate the safety and efficacy of CBP-307 in medium or long-term administration in subjects with moderate to severe UC. Subjects who early withdraw from the study or complete the study stage 1 but do not enter the stage 2 will enter a 4-week safety follow-up period.

Schematic diagram of design of study stage 1 entering to the stage 2 is shown in Figure 1.

Figure 1 Schematic Diagram of Study Stage 1 Design



Study stage 2

All subjects who complete 12 weeks of induction therapy (with CBP-307 or placebo) in the study stage 1 and complete all examinations (including colonoscopy) at the week 12 visit can choose to enter the study stage 2 of a total of 40 weeks, including 36 weeks of continuous administration and 4 weeks of safety follow-up after the last dose. Subjects who choose to enter the stage 2 will be required to sign an updated informed consent form and will be screened for

eligibility.

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

Sub-study 1 (subjects who have achieved clinical response by adapted Mayo score): Subjects who **have achieved clinical response** shown by efficacy evaluation at week 12 in the study stage 1 and meet the eligibility criteria for stage 2 will enter sub-study 1 of the study stage 2 to receive double-blind maintenance treatment for 36 weeks (weeks 13 to 48), i.e., the therapeutic regimen for them in study stage 1 will be continually maintained (Figure 2). Safety follow-up will be completed at 4 weeks after the last dose. Subjects who present with recurrent UC during maintenance treatment are required to terminate treatment and withdraw from the study.

For the subjects already enrolled as per the previous approved protocols (version 5.0 or earlier), they will follow the previous planned treatment in the sub-study 1 of stage 2 study.

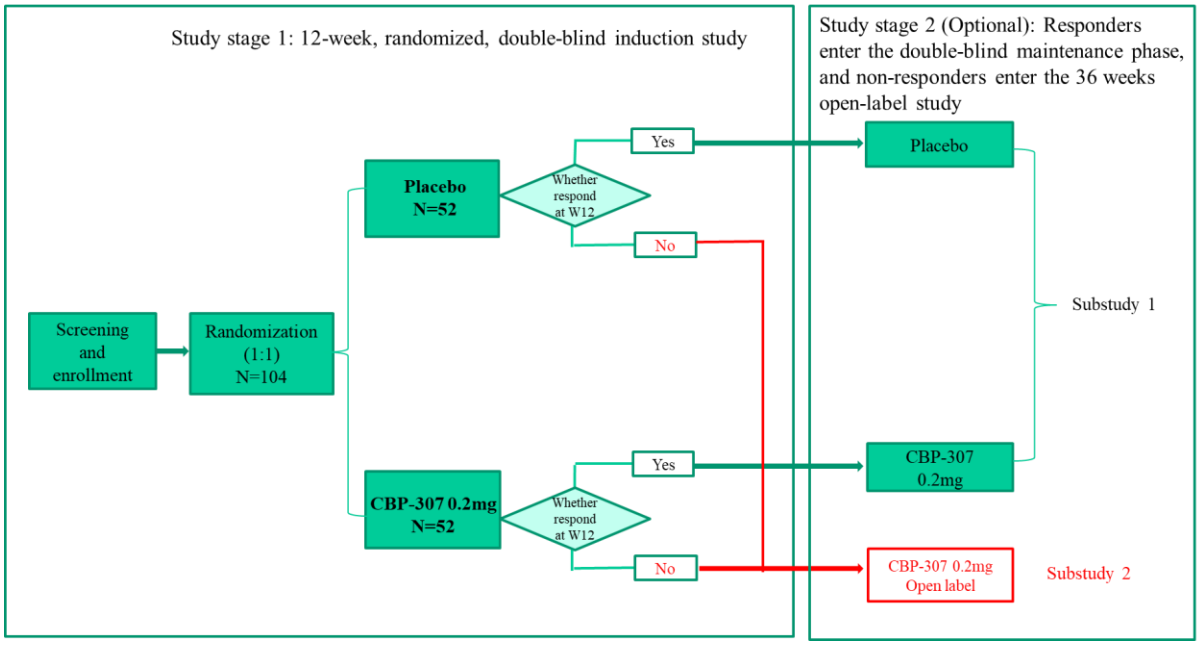
UC disease recurrence i.e., an increased activity of UC, is defined as a repeated (occurring at 2 consecutive visits) partial Mayo score that is at least 5 points and is also ≥3 points higher than the score at week 12 (the end of induction therapy), and where the possibility of increased disease activity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

Sub-study 2 (subjects who have not achieved clinical response by adapted Mayo score): Subjects who **have not achieved clinical response** shown by efficacy evaluation at week 12 in the study stage 1 and meet the eligibility criteria for study stage 2 will enter open-label treatment with CBP-307 0.2 mg (Figure 2). Subjects will receive CBP-307 once daily at an oral dose of 0.2 mg in sub-study 2 regardless of whether they receive CBP-307 0.2 mg or placebo in the study stage 1.

For subjects who enter sub-study 2 of study stage 2, 1-week dose titration will be performed at the first week (week 13). Dose titration will involve 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 will be completed at 4 weeks after the last dose.

At week 24, subjects will undergo efficacy evaluation including colonoscopy. If any subject still has not achieved clinical response, the treatment will be discontinued and the subject will be withdrawn from the study.

Figure 2 Schematic Diagram of Transition from Stage 1 to Stage 2 Substudies



Inclusion and exclusion criteria:

The following criteria are used to select eligible subjects for this study. A subject is eligible to be included in the study only if all of the inclusion criteria apply and none of the exclusion criteria apply.

Inclusion criteria:

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. Male or female subjects aged 18-75 years (inclusive).
2. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements. The subject signs and dates a written informed consent form prior to the initiation of any study procedures.
3. Female subjects of childbearing potential and male subjects who have not undergone vasectomy should use at least one **highly** effective method of contraception during the entire study and 4 weeks after the last dose of investigational products after signing the informed consent form. **The highly effective methods of contraception in this study include:**
    a. Abstinence is acceptable only if it is part of the participant's regularly practiced lifestyle;
    b. Hormone (oral, patch, ring, injection, implant) in combination with a male condom. This must be used for at least 30 days before the first dose of investigational products or an alternative acceptable method must be used;
    c. Intrauterine device (IUD) in combination with a male condom;

   d. Exceptions are: a) women with at least 12 consecutive months amenorrhea in the absence of medications known to induce amenorrhea and have a documented follicle stimulating hormone (FSH) level of greater than 40 mIU/mL or in the postmenopausal range; or b) surgical sterilization (e.g., hysterectomy, bilateral oophorectomy).

4. The subject has a diagnosis of UC established at least 3 months prior to screening by clinical and endoscopic evidence corroborated by a histopathology report. Subjects are confirmed to have moderate to severe active UC within 14 days prior to the first dose of the investigational product, which is based on an adapted Mayo score of 4-9, and an endoscopic subscore of ≥ 2. Endoscopy must be performed during the screening period (day -14 to day -3, allowing centralized reading and evaluation before the first dose at week 0).
5. The subject has evidence of UC extending to the rectum with ≥15 cm involvement on endoscopy.
6. Subjects must be UC patients who are receiving treatment. They can be enrolled if they meet any items below.
   a. Prior to the randomization visit, subjects have received oral 5-ASA (e.g., mesalazine, sulfasalazine, olsalazine, balsalazide) for at least 4 weeks with the dose stable for at least 2 weeks.
   b. Prior to the randomization visit, subjects have received oral or IV corticosteroids e.g. prednisone (daily doses ≤ 30 mg), budesonide (daily doses ≤ 9 mg), methylprednisolone (daily doses ≤ 24 mg), or equivalent dose of corticosteroids for at least 4 weeks, with the dose stable for at least 2 weeks.
7. If oral 5-ASA or corticosteroid for treatment of UC have been recently discontinued, they must have been stopped for at least 2 weeks prior to the screening endoscopy examination which is used for Mayo score assessment.
8. If subjects use non-prohibited concomitant medications, a stable dosing regimen must be used, that is, within 7 days prior to first dose of investigational product or within 5 half-lives of the drug (whichever is longer), there's no new concomitant medications started or changes in the dose of existing non-prohibited concomitant medications.
9. The subject who has extensive colitis or pancolitis of >8 years duration or limited colitis of >12 years duration must have documented evidence that a surveillance colonoscopy was performed within 12 months prior to initial screening visit (can be performed during Screening if not performed in previous 12 months).
10. For subject who has a family history of colorectal cancer, personal history of increased colorectal cancer risk, age >50 years, or other known risk factor, the data of colorectal cancer surveillance within 12 months prior to screening visit must be available (colorectal cancer surveillance can be performed during screening if not in previous 12 months).

Exclusion criteria:

Exclusion criteria are classified into indication-specific exclusion criteria, exclusion criteria for general condition and exclusion criteria for infectious diseases. Patients who meet any of the following criteria will be excluded:

UC-related exclusion criteria:

1. At the screening visit, subjects have evidence of toxic megacolon.
2. The subject has had subtotal or total colectomy.
3. The subject has an existing ileostomy, colostomy (a history of ileostomy or colostomy that has been reversed may be acceptable), or known symptomatic stenosis of the intestine.
4. Investigator judges the subject currently requires or is anticipated to require surgical intervention for UC during the study.
5. The subject has a history or evidence of adenomatous colonic polyps that have not been removed.
6. The subject has a history or evidence of colonic mucosal dysplasia including low or high-grade dysplasia, as well as indeterminate for dysplasia.
7. Subjects have a suspected or confirmed diagnosis of Crohn's enterocolitis, undiagnosed types of colitis, ischemic colitis, or radiation colitis.
8. Subjects were previously exposure to the following treatments:
    - Lymphocyte-depleting therapies (e.g., alemtuzumab, anti-CD4 antibody, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation and daclizumab).
    - Previous treatment with D-penicillamine, leflunomide.
9. The subject has had prior exposure to approved or investigational products that inhibit the lymphocyte trafficking (e.g., natalizumab, fingolimod, ozanimod or etrasimod, etc.) Subjects who were previously exposed to vedolizumab and did not respond to its treatment.
10. Within 60 days prior to the screening visit, the subject has received any of the following for the treatment of UC:
    a. Intravenous immunoglobulin;
    b. Therapeutic plasma exchange (TPE).
11. Within 30 days prior to randomization visit, the subject has received any of the following for the treatment of UC:
    a. Immunosuppressants (such as cyclosporine, tacrolimus, sirolimus or mycophenolate mofetil), thalidomide or traditional Chinese medicine;
    b. Approved non-biologic agents or traditional Chinese medicine treatment.
12. Patients who plan to concurrently use an immunosuppressant (such as azathioprine,

6-mercaptopurine or methotrexate) after randomization. Patients treated with azathioprine, 6-mercaptopurine or methotrexate at screening are required to discontinue it prior to the first dose of the study drug.

13. The subject has received any investigational biologic or non-biologic agent, or approved biologic agent or biosimilars within 60 days or 5 half-lives prior to screening (whichever is longer).
14. The subject has used topical (rectal) treatment with aminosalicylic acid, corticosteroid or traditional Chinese medicine enemas/suppositories or for UC treatment within 2 weeks of the administration of the first dose of study drug.

Exclusion criteria for general conditions:

15. The subject has any unstable or uncontrolled cardiovascular, pulmonary, hepatic, renal, gastrointestinal, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, or other medical disorders that, in the opinion of the investigator, would confound the study results or compromise subject safety.
16. History of uveitis or macular oedema.
17. Clinically relevant cardiovascular conditions, including history or presence of any one of below:
    a. Ischemic heart disease or myocardial infarction; Unstable angina; History of angina pectoris caused by coronary artery spasm, or raynaud's phenomenon (Raynauds);
    b. Congestive heart failure (NYHA class III-IV), cardiac arrest;
    c. Stroke, transient ischemic attack;
    d. History of recurrent syncope or positive result of vasovagal syncope tilt test;
    e. Symptomatic bradycardia, sick sinus syndrome, sinoatrial block, second degree atrioventricular block (e.g., Mobitz type 2 atrioventricular block) or third degree atrioventricular block;
    f. Congenital long QT syndrome (LQTS), or prolonged QT interval corrected using Fridericia's formula (QTcF) in screening ECG (QTcF >450 ms in men, QTcF > 470 ms in women);
    g. Subjects at increased risk for QT prolongation due to hypokalemia or hypomagnesemia; or subjects who are currently taking medications to prolong QT interval (e.g., citalopram, chlorpromazine, haloperidol, methadone, and erythromycin) which result in risk for torsades de pointes;
    h. Under treatment or expected to taking treatment during the study with medications with a known impact on the cardiac conduction system (e.g., beta blockers, calcium channel blockers, Class Ia or Class III anti-arrhythmic drugs. [amiodarone, bromobenzylamine, sotalol, ibutilide, azimilide, dofetilide]);
    i. Hypertension (except well-controlled hypertension after pharmacotherapy); systolic

blood pressure < 95 mm Hg or >140 mm Hg and diastolic blood pressure ≤ 50 mm Hg or ≥ 95 mm Hg at the screening visit;

j. Resting heart rate < 55 times/min or ventricular rate < 55 times/min in 12-lead ECG at screening visit;

k. Investigator deems that the 12-lead ECG at screening visit is clinically significant abnormal, such as, myocardial ischemia, any significant cardiac conduction abnormalities (such as the left bundle branch block), that would put the subject at risk or interfere with the study results;

l. Any other significant heart disease that the investigator judges would put the subject at risk or interfere with the study results.

m. Subjects have a family history of premature coronary heart disease.

18. History of type 1 diabetes, uncontrolled type 2 diabetes (HbA1c > 7%) judged by investigator, patients with diabetes accompanied with significant complications, e.g., retinopathy or kidney disease.
19. The subject has a history of malignancies, including malignant solid tumors and hematological malignancies (Except basal cell carcinomas and in situ squamous carcinomas of the skin that have been excised or cured).
20. The subject has had any surgical procedure requiring general anesthesia within 30 days prior to screening or is planning to undergo major surgery during the study period.
21. The subject has chronic obstructive pulmonary disease, asthma, pulmonary fibrosis or other any significant history of pulmonary diseases, except for mild intermittent asthma that does not require regular maintenance treatment.
22. Pulmonary function test (including examinations of lung ventilation function and pulmonary gas exchange) at the screening visit shows one of the following abnormalities: forced expiratory volume in 1 second (FEV_1) or forced vital capacity (FVC) < 70% of normal expected value.
23. During screening period, any of the following laboratory abnormalities:
    a. Hgb < 8 g/dL;
    b. WBC count < 3.5×10^9/L;
    c. Neutrophils count < 1.5×10^9/L;
    d. Lymphocyte count < 0.8×10^9/L;
    e. Platelet count < 100×10^9/L or >1200×10^9/L;
    f. Serum creatinine > 124 μmol/L for female or > 141 μmol/L for male;

    If the WBC count, neutrophil count or lymphocyte count meets the above criteria during the screening period, a retest can be scheduled during the screening period. It is required that the results of the retest should not meet the above criteria, otherwise subjects do not meet the enrollment criteria.
24. Abnormal liver function test during the screening period, such as abonormalities in

alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (γ-GT), alkaline phosphatase (ALK) or serum total bilirubin, which suggests liver diseases or liver function impairment. The investigator should make a determination according to the following criteria:

a. Subjects with serum total bilirubin > 1.2 times the upper limit of normal (ULN) shown by initial and repeat tests should be excluded from the study;
b. Subjects with any of the other liver function parameters listed above, such as AST, ALT, γ-GT or ALK > 1.5 times the ULN shown by initial and repeat tests, should be excluded from the study;
c. Subjects with increased level of more than 1 parameter in liver function test should be excluded from the study;
d. During the screening period, if a single transaminase level (AST, ALT, γ-GT or ALK) is elevated by more than 1.5 times the ULN, or serum total bilirubin is elevated by more than 1.2 times the ULN, a repeat test can be scheduled as soon as possible before enrollment/randomization to exclude laboratory errors. Only if the results of the repeat test meet the requirements, subjects could be enrolled.

25. Allergic to any component of the study drug (and its excipients).
26. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year prior to Screening.
27. The subject has an active mental disorder that, in the opinion of investigator, may interfere with compliance with study procedures.
28. The subject is unable to participate in all study visits or comply with study procedures.
29. The subject is in a health condition that requires to take prohibited medications listed in Section 6.6.
30. If female, the subject is intending to become pregnant before, during, or within 4 weeks after participating in the study or intending to donate ova during such period.
31. If male, the subject intends to donate sperm during the study or for 4 weeks thereafter.
32. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (e.g., spouse, parent, child, sibling) or may consent under duress.
33. Female subjects who are lactating or have a positive serum pregnancy test during the Screening Period or a positive urine pregnancy test at week 0, prior to study drug administration.

Exclusion criteria for infectious diseases:

34. The subject has evidence of known active infection during the screening period.
35. The subject has evidence of treatment for Clostridioides difficile (C. difficile) infection or other intestinal pathogen with 28 days prior to first dose of study drug.

36. Patients with the histories of following infectious diseases:

    - Treatment with oral anti-infection medication due to acute infection within 2 weeks prior to screening visit or intravenous anti-infection treatment due to acute infection within 4 weeks prior to screening visit;
    - Clinically significant infection (e.g., pneumonia, nephropyelitis and herpes zoster) within 4 weeks prior to screening visit, or ongoing chronic infection;

37. Active or latent tuberculosis (TB) evidenced by the followings:

    - A positive diagnostic TB test within 30 days before screening or during the screening period is defined as:
        - Quantiferon or Quantiferon Plus test positive, or
        - Two consecutive indeterminate Quantiferon tests or Quantiferon Plus tests, or
        - Chest X-ray within 3 months prior to week 0 for which the results are suspicious for pulmonary TB.

    Note: Subjects with documented evidence of previously successfully treated TB, or with a negative Quantiferon or Quantiferon Plus test result, can be enrolled in the study. If Quantiferon or Quantiferon Plus test result is indeterminate at screening, it could be retested during screening period. If Quantiferon or Quantiferon Plus retest result is indeterminate, 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.

38. Chronic hepatitis B virus (HBV) infection* or chronic hepatitis C virus (HCV) infection**.

    *Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb) and hepatitis B core antibody (HBcAb) must be evaluated for all the patients at screening. Patients with positive hepatitis B surface antigen (HBsAg) will be excluded. HBV-DNA test should be carried out at screening if the subject is negative for Hepatitis B surface antigen, negative or positive for hepatitis B surface antibody, and positive for hepatitis B core antibody. The subject should be excluded from the study if HBV-DNA test result is positive, or he/her can be enrolled in the study in case of negative result of HBV-DNA test.

    **An HCV viral load test should be carried out if HCV antibody (HCVAb) is positive. The subject should be excluded from the study in case of positive HCV viral load test result. If the HCV viral load test result is negative, the subject can be enrolled in the study.

39. The subject has any identified congenital or acquired immunodeficiency (e.g., common variable immunodeficiency, human immunodeficiency virus [HIV] infection, organ transplantation).
40. The subject has received any live vaccine within 30 days prior to screening, or subjects are scheduled for immunization with any live vaccine during the study or within 1 month after the last dose of the investigational product.
41. Positive syphilis antibody at screening.

42. Subjects with a history of more than one episode of herpes zoster, or a history of disseminated herpes zoster or disseminated herpes simplex.

Inclusion and exclusion criteria for subjects' entry into the study stage 2 from the stage 1:

Inclusion criteria:

Subjects cannot enter the study stage 2 if any of the following criteria is not satisfied:

1. Subjects must be those with UC who participate in the study of CBP-307CN002 and have completed 12 weeks of treatment with CBP-307 or placebo in the stage 1 and have completed all the assessments (including colonoscopy) at study visit of week 12 in study stage 1.
2. Subjects have good compliance in stage 1, can understand all information about the study stage 2, and are able and willing to comply with the requirements specified in the study protocol.
3. Subjects or their legal representatives voluntarily sign informed consent forms for study stage 2.
4. Female subjects of childbearing potential and male subjects who have not undergone vasectomy should use at least one highly effective method of contraception during the entire study and 4 weeks after the last dose of investigational products after signing the informed consent form. **The highly effective methods of contraception in this study include**:
    a Abstinence is acceptable only if it is part of the participant's regularly practiced lifestyle;
    b Hormone (oral, patch, ring, injection, implant) in combination with a male condom. This must be used for at least 30 days before the first dose of investigational products or an alternative acceptable method must be used;
    c Intrauterine device (IUD) in combination with a male condom;
    d Exceptions are: a) women with at least 12 consecutive months amenorrhea in the absence of medications known to induce amenorrhea and have a documented FSH level of greater than 40 mIU/mL or in the postmenopausal range; or b) surgical sterilization (e.g., hysterectomy, bilateral oophorectomy).

Exclusion criteria:

Subjects who meet any of the following criteria will not be included in study stage 2:

1. The subject has any unstable or uncontrolled cardiovascular, pulmonary, hepatic, renal, GI, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, or other medical disorder that, in the opinion of the investigator, would confound the study results or compromise subject safety.
2. Subjects who are known to be allergic to CBP-307 or its excipients, or subjects experience significant adverse events related to the study drug during the stage 1 of the

CBP-307CN002 study, and the investigator deems that subjects are not appropriate to participate in the stage 2.

3. Subjects currently have evidence of active or untreated latent tuberculosis.
4. Subjects currently have active or chronic recurrent infections, and in the opinion of the investigator subjects are not appropriate to participate in the stage 2 of the study.
5. History of uveitis or macular oedema.
6. Subjects had received any of the following treatments after administration of the first dose in the stage 1 of the study:
   - Biological product;
   - Prednisone>30 mg/day, budesonide>9 mg/day, methylprednisolone>24 mg/day or equivalent dose of steroid treatment;
   - Immunosuppressant (such as azathioprine and 6-mercaptopurine or methotrexate).
7. Investigator deems that the 12-lead ECG results at the study visit of week 12 during study stage 1 is clinically significant abnormal, such as myocardial ischemia, any significant cardiac conduction abnormalities (such as the left bundle branch block), any abnormality that would put the subject at risk or interfere with the study results.
8. Pulmonary function test (including examinations of lung ventilation function and pulmonary gas exchange) of subjects at the study visit of week 12 during the study stage 1 shows 1 of the following abnormalities: forced expiratory volume in 1 second (FEV_1) or forced vital capacity (FVC) < 50% of normal predicted value.
9. Subjects' laboratory measurements at week 12 visit during the study stage 1 meet any of the following criteria:
   - AST or ALT> 3 ULN;
   - Absolute lymphocyte count < 0.2×10^{9}/L;
   - Serum creatinine > 124 μmol/L (in females) or > 141 μmol/L (in males)
10. Any other reason that in the opinion of the investigator may interfere with subject compliance or evaluation of the results of the study.

Study drug, dose and route of administration:

Study drugs in this study include CBP-307 and placebo (both in capsule form). The route of administration will be oral administration. In the study stage 1, subjects with moderate to severe UC will be randomized into one of the following two groups: 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.

In the study stage 2, subjects entering sub-study 1 will continue receiving double-blind maintenance treatment according to their treatment regimen in the stage 1; all subjects entering

sub-study 2 will receive CBP-307 0.2 mg (2 CBP-307 capsules 0.1 mg) once daily.

Study duration:

Study stage 1: The duration for treatment is 12 weeks. Subjects who complete the 12-week treatment of stage 1 but do not enter the stage 2 or early withdraw from the study will undergo safety follow-up for 4 weeks after the last dose.

Study stage 2: All subjects who complete the 12-week study stage 1 treatment (induction therapy with CBP-307 or placebo) and complete all assessments (including colonoscopy) at week 12 visit can choose to enter the study stage 2 for a total of 40 weeks. In the stage 2, subjects will continuously be administered for 36 weeks (week 13-48 of the study), and they will undergo safety follow-up for 4 weeks after the last dose (week 49-52 of the study). Subjects who early withdraw from the study will undergo safety follow-up for 4 weeks after the last dose.

For subjects who complete both stages (stage 1 + stage 2), the study will last for a total of 52 weeks: 48 weeks of administration, and 4 weeks of follow-up.

Study procedures:

The study procedures in the stage 1 are shown in Table 2 Study Flow Chart.

Study procedures in the stage 2 are shown in Table 3 Study Flow Chart (sub-study 1) and Table 4 (sub-study 2).

Sample size:

Approximately 134 subjects with moderate to severe UC will be randomized in the study. Among them, approximately 30 subjects who have already enrolled in CBP-307 0.1 mg group based on protocol version 5.0 or earlier will be analyzed for exploratory purpose. No further subjects will be enrolled in CBP-307 0.1 mg group from protocol version 6.0.

Approximately 104 eligible subjects will be randomized at 1:1 into one of the following 2 groups to undergo induction therapy in the study stage 1: CBP-307 0.2 mg once daily, or placebo (52 subjects in each group) based on protocol amendment and sample size recalculation。

All subjects who complete the 12-week study stage 1 and all tests (including colonoscopy) at visit at week 12 can be selected to enter the study stage 2.

Statistical method:

The primary efficacy endpoint of the study is the change in adapted Mayo score from baseline at week 12 after treatment compared between CBP-307 0.2 mg and placebo at the study stage

1.

The sample size was calculated based on the estimation on primary efficacy endpoint. 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 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.

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. Descriptive statistics will be applied to continuous variables (the number of subjects, mean, standard deviation, minimum, median, and maximum) and categorical variables (the frequency and percentage).

Statistical analysis will be conducted using SAS® 9.4 or higher (SAS Institute Inc., Cary, NC, USA).

Independent Data Monitoring Committee:

The Independent Data Monitoring Committee (IDMC) will be responsible for monitoring data of this study, including the main aspects of the study implementation process.

Table 2 Study Flow Chart of Study Stage 1

Study plan	**Screening**	**Baseline**	**Titration**		**Treatment Period**						**Last dose/early Termination**	**Follow-up[26]**
	First 3 weeks	**Day 0**	**Week 1**		**Week 2**	**Week 3**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 16**
Visit No. [1]	**1**	**2**	**3[1]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11[1]**	**12**
Day	**Day -21 to -1**	**Day 0**	**Day 1**	**Day 5**	**Day 8**	**Day 15±2**	**Day 28±3**	**Day 42±3**	**Day 56±3**	**Day 70±3**	**Day 84±5**	**Day 112±7**
Informed Consent	X											
Inclusion/exclusion criteria	X	X										
Demographic data	X											
Medical history, family history [2]	X	X										
Randomization		X										
Quantiferon or Quantiferon Plus test [3]	X											
Chest imaging examination [4]	X										X[4]	
12-lead ECG [5]	X	X	X	X	X		X		X		X	X
Holter monitoring [6]		X	X	X	X							
Vital signs [7]	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination [8]	X	X	X	X	X		X		X		X	X
Nervous system physical examination [9]	X	X	X	X	X	X	X	X	X	X	X	X
Pulmonary function test [10]	X						X		X		X	
Dermatology examination [11]	X						X		X		X	X

Study plan	**Screening**	**Baseline**	**Titration**		**Treatment Period**						**Last dose/early Termination**	**Follow-up[26]**
	First 3 weeks	**Day 0**	**Week 1**		**Week 2**	**Week 3**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 16**
Visit No. [1]	**1**	**2**	**3[1]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11[1]**	**12**
Day	**Day -21 to -1**	**Day 0**	**Day 1**	**Day 5**	**Day 8**	**Day 15±2**	**Day 28±3**	**Day 42±3**	**Day 56±3**	**Day 70±3**	**Day 84±5**	**Day 112±7**
Ophthalmologic examination [12]	X						X		X		X	X
OCT[13]	X										X	
Laboratory tests												
Hematology [14]	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry	X	X		X	X	X[15]	X	X[15]	X	X[15]	X	X
Lipids (fasting)	X	X					X		X		X	
Blood β-HCG and urine pregnancy test (WOCBP)	X	X			X		X		X		X	X
FSH (only for postmenopausal women)	X											
Coagulation	X	X			X		X		X		X	
Serum virological markers and syphilis antibody [16]	X											
Urinalysis /microscopy [17]	X	X			X		X		X		X	
Fecal culture/microscopy [18]	X											
Colonoscopy [19]	X										X	

Study plan	**Screening**	**Baseline**	**Titration**		**Treatment Period**						**Last dose/early Termination**	**Follow-up[26]**
	First 3 weeks	**Day 0**	**Week 1**		**Week 2**	**Week 3**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 16**
Visit No. [1]	**1**	**2**	**3[1]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11[1]**	**12**
Day	**Day -21 to -1**	**Day 0**	**Day 1**	**Day 5**	**Day 8**	**Day 15±2**	**Day 28±3**	**Day 42±3**	**Day 56±3**	**Day 70±3**	**Day 84±5**	**Day 112±7**
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Investigational product dispensing/return			X	X	X		X		X		X	
Recording the time of IP administration on the day of visit [20]			X	X	X		X		X		X	
Assessment of treatment compliance				X	X		X		X		X	
Adverse event	X	X	X	X	X	X	X	X	X	X	X	X
PK blood sampling [21]			X	X	X		X		X		X	
PD [22]			X	X	X		X		X		X	
Total Igs (IgA, IgG, IgM)	X										X	
Score												
Complete Mayo scores [23]	X										X	
Adapted Mayo scores[23]	X										X	
Partial Mayo scores [23]					X		X		X		X	
Diary dispensing[24]	X											
Diary Review [24]		X	X	X	X	X	X	X	X	X	X	
IBDQ[25]		X									X	
Biomarker analysis												
CRP	X	X					X		X		X	

Study plan	**Screening**	**Baseline**	**Titration**		**Treatment Period**						**Last dose/early Termination**	**Follow-up[26]**
	First 3 weeks	**Day 0**	**Week 1**		**Week 2**	**Week 3**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 16**
Visit No. [1]	**1**	**2**	**3[1]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11[1]**	**12**
Day	**Day -21 to -1**	**Day 0**	**Day 1**	**Day 5**	**Day 8**	**Day 15±2**	**Day 28±3**	**Day 42±3**	**Day 56±3**	**Day 70±3**	**Day 84±5**	**Day 112±7**
Fecal calprotectin	X										X	

Abbreviations: β-HCG=β-human chorionic gonadotropin; CRP=C-reactive protein; ECG=electrocardiogram; FEV_1= Forced Expiratory Volume in 1 second; FSH=follicle stimulating hormone; 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; IBDQ=inflammatory bowel disease questionnaire; Ig=immunoglobulin; OCT=optical coherence tomography; PD=pharmacodynamics; PK=pharmacokinetics; SAE=serious adverse event; TB=tuberculosis.

1. It is recommended that the subjects are admitted to the study center 1 day prior to baseline and stay at the study center until examinations including ECG are completed on day 2 if no further monitoring is required. It is recommended that the scheduled visits should be in the morning. On visit days, subjects are required to take investigational product at site. If time permits, the evaluation time point for subjects should be approximately the same.
   For subjects who cannot continue participating in the study for any reason, the investigator should try to complete evaluation for them during last dose/early termination visit.
2. Medical history survey includes a history of smoking and alcohol drinking and drug abuse. Family history should include a family history of colon cancer and a family history of premature coronary heart disease. The medical history within 3 years before screening is necessarily recorded (the records of history of major diseases and history of surgery are not subject to this limitation.)
3. Patients can be enrolled in the study if it is evidenced that previous TB was treated successfully and Quantiferon or Quantiferon Plus test result at screening is negative. If Quantiferon or Quantiferon Plus test result is indeterminate at screening, it could be retested during screening period. If Quantiferon or Quantiferon Plus retest result is indeterminate, 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.
4. Chest X-ray taken within 3 months prior to screening will be accepted. If no chest X-ray are taken within 3 months before screening, a chest X-ray will be performed at the screening visit. Subjects who prematurely terminated from the study need to undergo chest radiography at the last dose/early termination visit.
5. On Day 1, 2, 5 and 8, 12-lead ECG will be performed within 2 hours before dosing and at 4, 6 hours after dosing. At other follow-up time points, 12-lead ECG tests will be performed at 4 hours after dosing. Time window for 12-lead ECG tests is ±0.5 hours.
6. On Day 0, 1, 5 and 8, 24 ± 0.5 hour continuous Holter monitoring will be performed from 30 min±10 min before dosing (the same time point as day 0).
7. Vital signs include the heart rate, blood pressure, body temperature and respiratory rate. On Day 1, 2, 5 and 8, vital signs are measured before dosing and at 1, 2, 3, 4, 5 and 6 hours (±10 minutes) after dosing. At other scheduled visits, vital signs will be measured before dosing.

8. Physical examination includes height and weight, evaluation of the neck/thyroid, chest/lung, heart, lymph nodes, abdomen, nervous system, etc. Body height is measured only at the screening visit. A complete physical examination (except height measurement) is performed at screening and on Day 1, 28 ±3, 84 ± 5, and 112 ±7. At other visits, only the body weight needs to be measured.
9. Nervous system physical examination is required for each visit, and the investigators should actively query about nervous system symptoms such as cephalgia, convulsions, confusion, vision loss, speech disturbances, facial drooping, weakness, problems with coordination, gait and sensory loss, and mental impairment. If any of the above symptoms appear, a neurology consult would be ordered for further assessment, and extra examinations including CT scanning, MRI examination and other related tests will be conducted by neurologists' judgment.
10. At screening visit, if pulmonary function tests show FEV1 or FVC < 70% of normal predicted value, the subject needs to be excluded.
11. Dermatology examination includes an overall examination of the skin for lesions and examinations of the extremities. It is mainly aimed at excluding suspected lesions of basal cell carcinoma. Dermatology examinations at screening and on day 84 ± 5 (12 weeks) visits need to be performed in the department of dermatology. Dermatology examinations at other visits can be performed by the investigator.
12. Ophthalmologic examination includes checking of visual abnormalities (for example, blurred vision or decreased visual acuity) in subjects and needs to be performed in the department of ophthalmology.
13. In case optical coherence tomography (OCT) shows suspected macular edema, it is required to perform a complete retinal examination including collecting history of eye diseases, visual acuity check, and dilated fundus examination. During the study, if an ophthalmologic examination identifies visual abnormalities (e.g., blurred vision or decreased visual acuity), then, additional OCT can be performed. All subjects diagnosed with macular edema must discontinue the investigational product.
14. On Day 1, 5 and 8, hematology tests need to be performed before administration and at 4-6 hours after administration respectively. At other visits during treatment, only hematology tests prior to administration need to be performed.
15. Blood chemistry tests on Day 15 (visit 6), 42 (visit 8) and 70 (visit 10) only include liver function tests.
16. At screening, serological tests are performed for all subjects to determine the subjects' immune status against the viruses: HIV antibody, HBsAg, HBsAb and HBcAb and anti-HCV. *Subjects with positive HBsAg will be excluded. HBV-DNA test should be carried out at screening if the subject is negative for HBsAg, negative or positive for HBsAb, and positive for HBcAb. The subject should be excluded from the study if HBV-DNA test result is positive, or he/her can be enrolled in the study in case of negative result of HBV-DNA test. **An HCV viral load test should be carried out if HCV antibody is positive in the subject. The subject should be excluded from the study in case of positive HCV viral load test result. If the HCV viral load test result is negative, the subject can be enrolled in the study.
17. If urinalysis show occult blood or abnormal urine protein in subjects' urine samples, a microscopy examination needs to be performed. A microscopy examination mainly focuses on the presence of white blood cells and red blood cells. All other parameters will be tested with test strips.
18. Fecal culture/microscopy (involving fecal culture, C. difficile, parasite ovas and parasites) is required to be performed at screening. During the screening period and at any time point during the study, if the subject has symptoms including aggravation of the disease condition or recurrence of previous disease activity, stool samples can be collected for fecal culture/microscopy and C. difficile analysis.
19. Within 14 days prior to randomization at screening, colonoscopy will be performed to obtain a Mayo endoscopic subscore and a complete Mayo score and then determine subject

eligibility. Colonoscopy will also be performed at week 12 (or early termination from the study visit).

20. On the days of visits during the study treatment period, the investigational product will be taken at the study sites and the time of administration will be recorded according to the study flow chart.
21. Collection of PK blood samples only applies to subjects in the PK subgroup. Time points for the collection of PK blood samples: 15-30 min before administration and 4-6 hours after administration at week 1 (day 1 and day 5), week 2 (day 8), week 4 (day 28), week 8 (day 56), and week 12 (day 84); 1-2h after administration at week 1 (day 1 and day 5) and week 4 (day 28).
22. The subjects in the PK subgroup are required to undergo measurement of lymphocyte counts (used for investigating the PD) at all time points for the collection of PK blood samples. According to the study flow chart, if there are corresponding hematology tests at the time points for the collection of PK blood samples, such as time points before administration and at 4-6 hours after administration on day 1, it is not necessary to collect additional PD blood samples, otherwise it is required to collect PD blood samples simultaneously. For the subjects in the non-PK subgroup, lymphocyte counts used for the PD study are obtained from hematology tests, so it is not necessary to collect additional PD blood samples.
23. Mayo score: The complete Mayo score is calculated from the stool frequency, rectal bleeding, endoscopic findings, and physician overall evaluation. See section 7.2.3. The adapted Mayo score is calculated from stool frequency, rectal bleeding, and endoscopic findings, See Section 7.2. Partial Mayo scores will be calculated based on the data of item 1, 2 and 4 in Section 7.2. (stool frequency, rectal bleeding, endoscopic findings,).
24. Subject diaries are dispensed at screening visits and reviewed at all visits from baseline to last dose/early termination from the study.
25. IBDQ will be completed by subjects at baseline and week 12 visits.
26. Subjects who complete the 12 weeks of study stage 1 but do not enter the study stage 2 or early withdraw from the study will undergo safety follow-up for 4 weeks after the last dose.

Table 3. Sub-study 1 of the Study Stage 2: Study Flow Chart for the Entry of Subjects into Double-Blind Maintenance Treatment After Achieving Clinical Response at Week 12

Study Plan	**Stage 2 Screening[1]**	**Sub-study 1 of the Study Stage 2 Treatment Period**				**Last dose/early Termination**	**Follow-up**
	Week 13	**Week 18**	**Week 24**	**Week 32**	**Week 40**	**Week 48**	**Week 52**
Visit No. [2]	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Day	**Day 90 ±5 [1]**	**Day 126 ±5**	**Day 168 ±5**	**Day 224 ±5**	**Day 280 ±5**	**Day 336 ±5**	**Day364 ±5**
Informed Consent [3]	X						
Inclusion/exclusion criteria	X						
Quantiferon or Quantiferon Plus Test [4]	X						
Chest imaging examination [5]						X	
12-lead ECG [6]	X	X	X	X	X	X	X
Vital signs [7]		X	X	X	X	X	X
Physical examination [8]		X	X	X	X	X	X
Nervous system physical examination [9]	X	X	X	X	X	X	X
Pulmonary function test [10]			X	X		X	
Dermatology examination [11]			X		X	X	X
Ophthalmologic examination[12]			X	X		X	X
OCT [13]			X			X	
Laboratory tests							
Hematology [14]		X	X	X	X	X	X
Blood chemistry [15]		X	X	X	X	X	X
Lipids (fasting)			X			X	
Blood β-HCG and urine pregnancy test (WOCBP)		X	X	X	X	X	X
Coagulation			X			X	
Urinalysis /microscopy [16]		X	X	X	X	X	
Fecal culture/microscopy [17]	X						

Study Plan	**Stage 2 Screening[1]**	**Sub-study 1 of the Study Stage 2 Treatment Period**				**Last dose/early Termination**	**Follow-up**
	Week 13	**Week 18**	**Week 24**	**Week 32**	**Week 40**	**Week 48**	**Week 52**
Visit No. [2]	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Day	**Day 90 ±5 [1]**	**Day 126 ±5**	**Day 168 ±5**	**Day 224 ±5**	**Day 280 ±5**	**Day 336 ±5**	**Day364 ±5**
Colonoscopy [18]						X	
Concomitant medication	X	X	X	X	X	X	X
Investigational product dispensing/return	X	X	X	X	X	X	
Recording the time of IP administration on the day of visit [19]	X	X	X	X	X	X	
Assessment of treatment compliance		X	X	X	X	X	
Adverse event	X	X	X	X	X	X	X
Score							
Complete Mayo scores [20]						X	
Adapted Mayo scores [20]						X	
Partial Mayo scores [20]		X	X	X	X		
Diary Review [21]	X	X	X	X	X	X	
IBDQ[22]			X			X	
Biomarker analysis							
CRP			X			X	
Fecal calprotectin						X	
Total immunoglobulin (IgA, IgG, IgM）						X	

Abbreviation: beta-hcg = beta - human chorionic gonadotropin; CRP= c-reactive protein; ECG = electrocardiogram; FEV1= maximum forced respiration of 1 second; FVC= forced vital capacity; IBDQ= qol questionnaire for ibd; Ig= immunoglobulin; OCT = optical coherence tomography; SAE= severe adverse events; TB= tuberculosis

Notes:

1. Subjects who have completed the 12-week induction therapy in study stage 1 and have completed the evaluation of study visit 11 (see Table 1) and reached the clinical response at visit 11, can choose to enter the maintenance period of sub-study 1 of study stage 2. If the subject is eligible, the study process will follow this flow chart. visit 12 will be the screening visit in study stage 2, and the qualification assessment of visit 12 will be based on the results of the 11th visit in the study. Subjects who meet the study stage 2 eligibility criteria and

have achieved clinical response will enter study stage 2 sub-study 1 (maintenance treatment period) and continue their treatment in study stage 1. The interval between the first administration of sub-study 2 and the last administration of study stage 1 will be less than 1 week.

2. Subjects are recommended to be followed up in the morning. At the indicated visits, subjects will be given medication at the site. If time permits, subjects in the study should be evaluated at roughly the same time. For subjects who cannot continue to participate in the study for any reason, the investigator should make every effort to complete the evaluation during the end of the study/early termination of the follow-up visit.
3. The signing of informed consent can also be done at visit 11 of study stage 1 (week 12).
4. The Quantiferon or Quantiferon Plus of the screening of stage 1 can be used as the basis. However, if the subjects had a history of exposure to TB patients during study stage 1, or suspected TB infection, the Quantiferon or Quantiferon Plus assay should be performed again. If possible, the blood samples of the Quantiferon or Quantiferon Plus assay could be collected at visit 11 (week 12). If the Quantiferon or Quantiferon Plus results are negative, the subject could be included in the study. If the Quantiferon or Quantiferon Plus results are indeterminate, they can be tested again. If the Quantiferon or Quantiferon Plus results are still indeterminate, the patient should not be included. If the Quantiferon or Quantiferon Plus repeat test results are negative, the subject could be enrolled.
5. Only patients who do not have abnormal chest radiographs at visit 11 of study stage 1 are allowed to be included; during the study period, the investigator may review the chest X-ray or chest CT according to the clinical situation.
6. The 12-lead ECG will be examined at 4 hours after administration and 6 hours after administration at visit 12, and will be examined at 4 hours after administration at the remaining visits (except the follow-up visit after treatment ends). The time window for 12-lead ECG is + / - 0.5 hours.
7. Vital signs include heart rate, blood pressure, body temperature and respiratory rate. Vital signs will be checked before administration.
8. Physical examination in sub-study 1 of study stage 2 included measurement of body weight, assessment of neck/thyroid, chest/lung, heart, lymph nodes, abdomen, nervous system, etc. Complete physical examination was required at each visit.
9. Nervous system physical examination is required for each visit, and the investigators should actively query about nervous system symptoms such as cephalgia, convulsions, confusion, vision loss, speech disturbances, facial drooping, weakness, problems with coordination, gait and sensory loss, and mental impairment. If any of the above symptoms appear, a neurology consult would be ordered for further assessment, and extra examinations including CT scanning, MRI examination and other related tests will be conducted by neurologists' judgment.
10. According to the pulmonary function test results of visit 11, subjects with FEV1 or FVC < 50% of the predicted normal value cannot be enrolled. Pulmonary function test will be performed at weeks 24, 32, and 48, and additional pulmonary function tests will be performed during the study, depending on the subject's clinical status.
11. The dermatology examination includes an overall examination of the skin for lesions and examinations of extremities. Dermatology examinations at visits of weeks 24 and 48 need to be performed in the department of dermatology. Dermatology examinations at other visits can be performed by the investigator.
12. Ophthalmologic examination that includes checking of visual abnormalities (for example, blurred vision or decreased visual acuity) are required at weeks 24, 32, 48, and 52 to be examined by an ophthalmologist.
13. In case OCT shows suspected macular edema, it is required to perform a complete retinal examination including collecting history of eye diseases, visual acuity check, and dilated fundus examination. During the study, if an ophthalmologic examination identifies visual abnormalities (e.g., blurred vision or decreased visual acuity), then, additional OCT can

be performed. All subjects diagnosed with macular edema must discontinue the investigational product.

14. Hematology tests will be performed before dosing at weeks 18, 24, 32, 40, and 48. Hematology tests are also required at week 52.
15. Blood chemistry tests will be performed before dosing at weeks 18, 24, 32, 40 and 48. Blood chemistry tests are also required at week 52.
16. If urinalysis show occult blood or abnormal urine protein in subjects' urine samples, a microscopy examination needs to be performed. A microscopy examination mainly focuses on the presence of white blood cells and red blood cells. All other parameters will be tested with test strips.
17. During the study period, fecal culture/microscopic examination (including fecal culture, c. difficile toxin, parasite ovas and parasites) may also be performed if the subject's status requires it.
18. Colonoscopy will be performed at visit 11 in study stage 1 to obtain the individual Mayo endoscopic subscore and complete Mayo score of the subjects and to determine their eligibility. Colonoscopy will also be performed at week 48 (end of the study visits or early termination visit).
19. On the days of visits during the study treatment period, the investigational product will be taken in the study sites and the time of administration will be recorded according to the study flow chart.
20. Mayo score: the complete Mayo score is calculated from the stool frequency, rectal bleeding, endoscopic findings, and physician overall evaluation; The adapted Mayo score is calculated from stool frequency, rectal bleeding and endoscopic findings. Partial Mayo score is calculated from stool frequency, rectal bleeding, and physician overall evaluation.
21. Review of subject diaries: subject diary review is required for all visits from visit 12 to the end of the study/early termination visit.
22. The IBDQ is to be completed by the subjects at week 24 and 48 or early termination visit.

Table 4. Sub-study 2 of the Study Stage 2: Study Flow Chart for The Entry of Subjects into Open-Label Treatment After No Clinical Response Is Achieved at Week 12

Study plan	**Stage2 Screening** [1]	**Titration** [2]		**Sub-study 2 of Study Stage 2 Treatment Period**					**Last dose/early Termination**	**Follow-up**
	Week 13	Week 13		Week 14	Week 16	Week 24	Week 32	Week 40	Week 48	Week 52
Visit No. [3]	12	13	14	15	16	17	18	19	20	21
Day	Day 90 ±5	Titration Day1 [2,#]	Titration Day5 [2]	Titration Day 8	Day 112 ±5	Day 168 ±5	Day 224 ±5	Day 280 ±5	Day 336 ± 5	Day 364 ±5
Informed Consent [4]	X									
Inclusion/exclusion criteria	X									
Quantiferon or Quantiferon Plus Test [5]	X									
Chest imaging examination [6]									X	
12-lead ECG [7]		X	X	X	X	X	X	X	X	X
Holter monitoring [8]		X	X	X						
Vital signs [9]		X	X	X	X	X	X	X	X	X
Physical examination [10]		X	X	X	X	X	X	X	X	X
Nervous system physical examination [11]	X	X	X	X	X	X	X	X	X	X
Pulmonary function test [12]					X		X		X	
Dermatology examination [13]					X		X		X	X
Ophthalmologic examination [14]					X		X		X	X
OCT[15]						X			X	
Laboratory tests										
Hematology [16]				X	X	X	X	X	X	X
Blood chemistry [17]				X	X	X	X	X	X	X
Lipids (fasting)						X			X	
Blood β-HCG and urine pregnancy test (WOCBP)				X	X	X	X	X	X	X
Coagulation						X			X	
Urinalysis /microscopy [18]				X	X	X	X	X	X	
Fecal culture/microscopy [19]	X									

Study plan	**Stage2 Screening** [1]	**Titration** [2]		**Sub-study 2 of Study Stage 2 Treatment Period**					**Last dose/early Termination**	**Follow-up**
	Week 13	Week 13		Week 14	Week 16	Week 24	Week 32	Week 40	Week 48	Week 52
Visit No. [3]	12	13	14	15	16	17	18	19	20	21
Day	Day 90 ±5	Titration Day1 [2,#]	Titration Day5 [2]	Titration Day 8	Day 112 ±5	Day 168 ±5	Day 224 ±5	Day 280 ±5	Day 336 ± 5	Day 364 ±5
Colonoscopy [20]						X			X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X
Investigational product dispensing/return		X	X	X	X	X	X	X	X	
Recording the time of IP administration on the day of visit [21]		X	X	X	X	X	X	X	X	
Assessment of treatment compliance			X	X	X	X	X	X	X	
Adverse event	X	X	X	X	X	X	X	X	X	X
Score										
Complete Mayo scores [22]						X			X	
Adapted Mayo scores[22]						X			X	
Partial Mayo scores [22]					X		X	X		
Diary Review [23]	X	X	X	X	X	X	X	X	X	
IBDQ[24]						X			X	
Biomarker analysis										
CRP						X			X	
Fecal calprotectin						X			X	
Total immunoglobulin (IgA, IgG, IgM)									X	

Abbreviation: beta-hcg = beta - human chorionic gonadotropin; CRP= c-reactive protein; ECG = electrocardiogram; FEV1= maximum forced respiration of 1 second; FVC= forced vital capacity; IBDQ= qol questionnaire for ibd; Ig= immunoglobulin; OCT = optical coherence tomography; SAE= severe adverse events; TB= tuberculosis.

Notes:

#. It is recommended that the subjects are admitted to this study center prior to Day1-dosing of titration and stay at the study center until examinations including ECG are completed on day 2 if no further monitoring is required. It is recommended that the scheduled visits should be in the morning. On visit days, subjects are required to take investigational product at site. If time permits, the evaluation time point for subjects should be approximately the same.

1. Subjects who have completed the 12-week induction therapy of study stage 1 and have completed the evaluation of study visit 11 (see Table 1) while not achieved clinical response at visit 11, can choose the sub-study 2 of study stage 2 to receive open-label treatment of 0.2 mg CBP-307 daily. If the subject is eligible, the study process will follow this flow chart. Visit 12 is the screening visit in study stage 2, and the qualification assessment will be based on the results of visit 11. Subjects who meet the eligibility criteria for stage 2 and have not achieved clinical response will be enrolled in sub-study 2 of stage 2 and treated with 0.2mg CBP-307. The interval between the first administration of sub-study 2 and the last administration of study stage 1 will be less than 1 week.
2. Subjects eligible for inclusion in sub-study 2 of study stage 2 at visit 12 will receive dose titration for one week from visit 13. If the assessment at visit 12 meets the requirements and time permits, the dose titration can be started and the required procedures of visit 13 can be completed on the same day. The dose titration includes 0.05 mg CBP-307 for four consecutive days from the first day, 0.1 mg CBP-307 for the subsequent three days, and target dose of 0.2 mg CBP-307 will be started on the 8th day. Upon completion of the dose titration, subjects will receive oral treatment of 0.2 mg CBP-307 once a day.
3. Subjects are recommended to be followed up in the morning. At the indicated visits, subjects will be given medication at the site. If time permits, subjects in the study should be evaluated at roughly the same time. For subjects who cannot continue to participate in the study for any reason, the investigator should make every effort to complete the evaluation during the end of the study/early termination visit.
4. The signing of informed consent can also be done at visit 11 (week 12).
5. The Quantiferon or Quantiferon Plus of the screening of study stage 1 can be used as the basis. However, if the subjects had a history of exposure to TB patients during study stage 1, or if TB infection was suspected, the Quantiferon or Quantiferon Plus assay should be performed again. If possible, the Quantiferon or Quantiferon Plus blood samples could be collected at visit 11 (week 12). If the Quantiferon or Quantiferon Plus results are negative, the subject could be included in the study. If the Quantiferon or Quantiferon Plus results are indeterminate, they can be tested again. If the results of the Quantiferon or Quantiferon Plus results are still indeterminate, the subject could not be included. If the Quantiferon or Quantiferon Plus repeat test results are negative, the subject could be enrolled.
6. Only patients who do not have abnormal chest radiographs at visit 11 of study stage 1 are allowed to be included; During the study period, the investigator may review chest X-ray or chest CT according to the clinical situation.
7. 12-lead ECG examination will be performed within 2 hours before administration, 4 hours after administration and 6 hours after administration on Day 1, 2, 5 and 8 of treatment titration, and 12-lead ECG were performed at 4 hours after administration for other visits. The ECG time window will be ± 0.5 h.
8. On Titration Day 1, 5 and 8, 24-hour ±0.5 hour continuous Holter monitoring will be performed from 30min ±10 min before dosing .
9. Vital signs include heart rate, blood pressure, body temperature and respiratory rate. Vital signs will be measured before dosing and at 1, 2, 3, 4, 5 and 6 hours (± 10 minutes) after dosing on Day 1, 2, 5 and 8 of treatment titration. At other visits, vital signs will be measured before dosing.
10. Physical examination of stage 2 sub-study 2 will includes measurement of body weight, assessment of neck/thyroid, chest/lung, heart, lymph nodes, abdomen, nervous system, etc. At titration day 1, week 16, week 24, week 32, week 40, week 48, and week 52, complete physical examination will be conducted; at the rest visits, only the body weight will be

measured.

11. Nervous system physical examination is required for each visit, and the investigators should actively query about nervous system symptoms such as cephalgia, convulsions, confusion, vision loss, speech disturbances, facial drooping, weakness, problems with coordination, gait and sensory loss, and mental impairment. If any of the above symptoms appear, a neurology consult would be ordered for further assessment, and extra examinations including CT scanning, MRI examination and other related tests will be conducted by neurologists' judgment.
12. Based on the pulmonary function test results of visit 11, subjects with FEV1 or FVC < 50% of the predicted normal value cannot be enrolled. Pulmonary function test will be performed at weeks 16, 32, and 48, and additional pulmonary function tests can be performed during the study, depending on the subject's clinical status.
13. The dermatology examination includes an overall examination of the skin for lesions and examination of extremities. Dermatology examinations at visits of weeks 32 and 48 need to be performed in the department of dermatology. Dermatology examinations at other visits can be performed by the investigator.
14. Ophthalmologic examination that includes checking of visual abnormalities (for example, blurred vision or decreased visual acuity) are required at weeks 16, 32, 48, and 52 to be examined by an ophthalmologist.
15. In case OCT shows suspected macular edema, it is required to perform a complete retinal examination including collecting history of eye diseases, visual acuity check, and dilated fundus examination. During the study, if an ophthalmologic examination identifies visual abnormalities (e.g., blurred vision or decreased visual acuity), then, additional OCT can be performed. All subjects diagnosed with macular edema must discontinue the investigational product.
16. Hematology tests will be performed before dosing at weeks 14, 16, 24, 32, 40, and 48. Hematology tests are also required at week 52.
17. Blood chemistry tests will be performed before dosing at weeks 14, 16, 24, 32, 40 and 48. Blood chemistry tests are also required at week 52.
18. If urinalysis shows occult blood or abnormal urine protein in subjects' urine samples, a microscopy examination needs to be performed. A microscopy examination mainly focuses on the presence of white blood cells and red blood cells. All other parameters are to be tested with test strips.
19. During sub-study 2 of study stage 2, fecal culture/microscopy (including fecal culture, clostridium difficile toxin, parasites ovas and parasites) may also be performed if the subject's status requires it.
20. Colonoscopy will be performed at visit 11 in study stage 1 to obtain the Mayo endoscopic subscore and complete Mayo score of the subjects and to determine their eligibility. Colonoscopies will also be performed at week 24 and week 48 (end of the study visit or early termination visit).
21. On the days of visits during the study treatment period, the investigational product will be taken at the study sites and the time of administration will be recorded according to the study flow chart.
22. Mayo score: the complete Mayo score is calculated from the stool frequency, rectal bleeding, endoscopic findings, and physician overall evaluation; The adapted Mayo score is calculated from stool frequency, rectal bleeding and endoscopic findings. Partial Mayo score is calculated from stool frequency, rectal bleeding, and physician overall evaluation.
23. Review of subject diaries: subject diary review is required for all visits from visit 12 to the end of the study/early termination visit.
24. The IBDQ is to be completed by the subjects at week 24 and 48 or early termination visit.

2 ETHICAL CONSIDERATIONS

2.1. Regulatory and Ethical considerations

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

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

Before the study starts, the investigator is required to submit the Protocol, Protocol Amendment, Investigator's Brochure, Informed Consent Form (ICF) and other relevant documents such as recruitment advertisements (if applicable) to the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) for approval. All correspondence with the IEC/IRB needs to be kept in the Investigator Site File (ISF). A copy of the approval letter issued by the IEC/IRB approval needs to be submitted to sponsor. The study can only be started after approved by the IEC/IRB.

If the protocol needs to be amended during the study, the revised protocol should be submitted to the IEC/IRB for approval before the implementation of the protocol amendment. If new important information involving investigational product is obtained, ICF must be revised and then submitted to the IEC/IRB in written form for review and approval. The subjects must be informed of the update and re-consented to the most current, approved ICF version.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the study center and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

After reading the protocol, each investigator will sign the protocol signature page and send a

copy of the signed page to the sponsor or representative. The study will not start at any study center at which the investigator has not signed the protocol.

2.2. Subject information and the Informed Consent Form

Sponsor will not obtain the name of the subjects. The subject's number will be recorded in the electronic case report form (eCRF). If the subject's name appears in any document (such as a laboratory test report), the name must be erased from the copy of the document to be submitted to sponsor. The study data must be stored in computers in accordance with local regulations for data protection. It is required that subjects be informed that clinical quality assurance auditors, the IEC/IRB, the regulatory authority, or other authorized personnel appointed by the sponsor may review their medical records to verify the collected data and that all personal information for review will be kept strictly confidential in accordance with local regulations for data protection.

The investigator will keep a subject identification code list (containing the subject's number and corresponding name), so that subject records can be identified.

Informed consent must be obtained from a subject before the start of any study procedures. Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center. The medical record must include a statement that written informed consent was obtained before the subject was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF. Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study. A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

Subjects are required to sign an updated ICF before entering the study stage 2.

3 STUDY BACKGROUND

3.1. Overview of ulcerative colitis

Inflammatory bowel disease (IBD) is a type of intestinal inflammatory disease that includes ulcerative colitis (UC) and Crohn's disease (CD). The cause of IBD is unknown. UC is a chronic non-specific inflammatory disease of the rectum and colon. The lesion is characterized by diffuse and superficial inflammation of the colonic mucosa. It is located mostly in the rectosigmoid colon, but can extend to the entire colon.

The clinical manifestations of UC include diarrhea, bloody purulent stool, and abdominal pain.

Systemic features of UC, such as fever, weight loss, weakness, and hypoproteinemia, mostly appear in patients with moderate to severe UC. Extra-intestinal manifestations such as uveitis, arthritis, ankylosing spondylitis, or primary sclerosing cholangitis may also be seen in association with UC. Most of the patients show a chronic course of recurrent episodes, alternating with remission, and the symptoms of some patients are persistent and gradually worsening. Patients with IBD are at a higher risk of colorectal cancer.

In recent decades, the incidence of UC in Asia and the world has tended to increase persistently. The prevalence of UC in the United States, Western Europe, and Japan is approximately 200/100,000, 150/100,000 and 63.6/100,000, respectively. It is estimated that the prevalence of UC in China has reached 11.6 cases per 100,000 person-years. Although the prevalence in China is lower than in Western countries, it increases rapidly: an analysis of 10218 UC cases in China suggests that the prevalence of UC increased by 3.08 times from 2506 cases in 1980s to 7512 cases in 1990s.

3.2. Drug overview, structure and physicochemical properties

CBP-307 is a novel sphingosine-1-phosphate receptor subtype 1 (S1P1) modulator. It works by blocking the egress of T cells out from lymph nodes and thereby reducing their entry into intestinal tissues to exacerbate inflammation.

The active pharmaceutical ingredient (API) of CBP-307 is a white or off-white crystalline powder.

Name of the compound: CBP-307

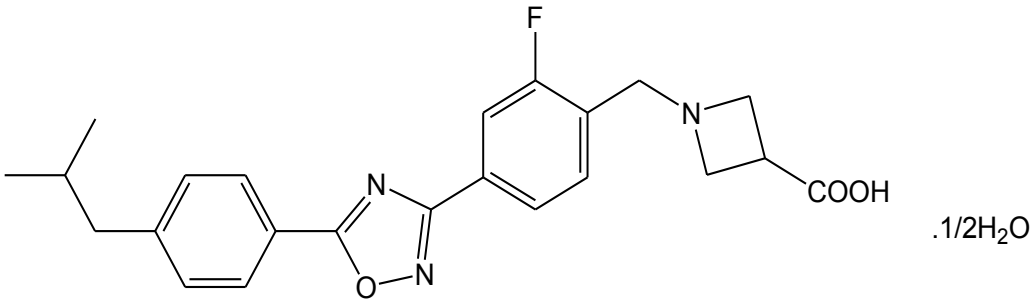
Chemical formula: $C_{23}H_{24}FN_3O_3 \bullet 1/2\ H_2O$

Molecular weight: 418.46

Chemical name: 1-(2-fuoro-4-(5-(4-isobutylphenyl)-1, 2, 4-oxadiazol-3-yl) benzyl) azetidine-3-carboxylic acid 1/2 hydrate

Chemical structure:

Figure 3. Chemical structure of CBP-307



3.3. Nonclinical pharmacology, pharmacokinetics and toxicology

3.3.1. Nonclinical pharmacology

In vitro and in vivo pharmacology

CBP-307 is a highly potent and specific second-generation S1P1 agonist. The sponsor has conducted a series of in vitro cell-based assays (i.e., compound-induced changes in the levels of intracellular cyclic adenosine monophosphate (cAMP) and β-arrestin, and S1P receptor internalization) to verify the activity and selectivity of CBP-307. The test results showed that CBP-307 increased the levels of cAMP and β-arrestin in S1P1-expressing cells with half maximal effective concentrations (EC_{50}) of 0.09 nM and 0.67 nM, respectively, whereas it had no effect on S1P3, a S1P receptor subtype known to induce fibrosis in human and animal tissues. The sponsor also evaluated the effect of CBP-307 in the induction of internalization of S1P receptors expressed in Chinese hamster ovary (CHO). Data show that CBP-307 effectively induced the internalization of S1P1 with an EC_{50} of 7.05 nM and S1P5 with an EC_{50} of 22.21 nM.

CBP-307 activates and induces S1P1 internalization, thereby inhibiting the migration of lymphocytes from lymph nodes in animals and humans and thus reducing the number of lymphocytes in the peripheral blood. When CBP-307 0.1 mg/kg, 0.1 mg/kg and 0.3 mg/kg was orally administered to rats, mice and beagle dogs, respectively, it reduced the number of lymphocytes in the peripheral blood of these animals by more than 50%. This effect was dose-dependent and reversible. The numbers of lymphocytes in the peripheral blood of animals typically returned to the pre-dose level 12-48 hours after a single dose.

Safety pharmacology

The results of safety pharmacology studies that meet the requirements of Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies showed that oral administration of CBP-307 50 mg/kg has no effect on the respiratory function of beagle dogs, and CBP-307 100 mg/kg has no effect on central nervous system (CNS) functions in SD rats. Cardiovascular safety studies showed that CBP-307 50 mg/kg caused a slight increase in diastolic blood pressure in

female beagle dogs within 1 to 3 hours after administration, and it had no effect on ECG parameters, including heart rate, RR interval, PR interval, QRS duration, QRS voltage, QT interval, QTcF interval, Tp-e interval, ST voltage and systolic blood pressure.

CBP-307 30 μM does not inhibit the activity of any major human cytochrome P450 enzymes including 1A2, 2C9, 2C19, 2D6, 3A4, 2B6 and 2C8, thus CBP-307 is unlikely to interact with other drugs metabolized by the P450 enzymes. Besides, it was found that CBP-307 10 μM had only 12% inhibitory effect on astemizole, which was able to bind to the hERG potassium channel (expressed on the surface of HEK cells). Such finding indicates that the potential of CBP-307 to cause QT prolongation in human is very low.

3.3.2. Pharmacokinetics and metabolism

Preclinical pharmacokinetics studies showed that the bioavailability of CBP-307 1 mg/kg in rats and beagle dogs were 62% and 37%, respectively. Therefore, the apparent clearance of CBP-307 was relatively low in rats (approximately 11% of hepatic blood flow), while slightly higher in beagle dogs (approximately equal to hepatic blood flow); and the half-lives of CBP-307 in rats and beagle dogs after a single oral dose were 5.3 and 2.7 hours, respectively.

The half-life of CBP-307 in Cynomolgus monkeys ranged from 1.91 hours to 2.34 hours (mean: 2.13 hours) after a single oral dose; the maximum concentration (C_{max}) ranged from 112.25 ng/mL to 183.25 ng/mL (mean: 146.62 ng/mL); AUC_{last} ranged from 405.22 ng*h/mL to 639.96 ng*h/mL (mean: 523.18 ng*h/mL). The bioavailability of CBP-307 was between 15.75%-30.99% with an average of 21.64%.

Toxicokinetic analysis showed that, with CBP-307 administered orally in rats and dogs, exposure increased with increasing doses. Exposure increases in rats were dose proportional at 1 to 10 mg/kg and less than dose-proportional at 100 mg/kg. Exposure in dogs was dose proportional at 1 to 80 mg/kg. No sex-associated differences were seen in exposure in rats or beagle dogs. Exposure accumulation was observed after 28 days of repeat dosing in rats, but no accumulation after repeat dosing was seen in dogs.

After 13 weeks of repeat dosing in Cynomolgus monkeys, no significant accumulation of CBP-307 was observed.

A recent open-label study to evaluate the absorption, distribution, metabolism and elimination of a single oral dose of [^{14}C]-labeled CBP-307 in SD rats showed that the overall mean recovery of radiation was 97.94% within 0-168 h after a single dose of 3 mg/100 μCi/kg in male and female SD rats. CBP-307 was mainly excreted through the feces, and its excreted amount accounted for 78.24% of its dose. It was partly excreted through the urine, and its excreted amount accounted for 13.48% of its dose. Excretion mainly occurred within 72 hours after

administration, and the total excreted amount accounted for 86.90% of the dose.

Preliminary in vitro metabolism studies in liver microsomes identified 5 main metabolites of CBP-307. No metabolite was present in amount > 10% of the parent compound. Metabolite profiles were similar between mice, rats, dogs, monkeys, and humans.

Preliminary studies of protein binding showed that CBP-307 had high plasma protein binding rates: >99% in humans and approximately 98-99% in animals.

Studies of the permeability and transport properties in the Caco-2 cell model showed that CBP-307 exhibited high permeability in the Caco-2 cell model: no significantly inhibited efflux of CBP-307 (1-20 μM) by P-gp, suggesting that CBP-307 is not a potential substrate of P-gp.

3.3.3. Toxicology

A series of GLP toxicological studies in preclinical species including SD rats and Cynomolgus monkeys were carried out to determine the side effects, target organs, maximum tolerated dose (MTD) and no-observed-adverse-effect level (NOAEL).

No death occurred in rats treated with a single dose of ≤ 1000 mg/kg CBP-307, or 4-week repeat doses of ≤ 100 mg/kg; similarly, no deaths were seen in dogs treated with a single dose of ≤ 500 mg/kg, or 4-week repeat doses of 80 mg/kg. A 4-week multiple-dose study showed that the MTD for rats was >100 mg/kg, whereas the MTD for beagle dogs was ≥80 mg/kg/day. AUC_{0-24} corresponding to the MTD for rats was 154584.94 h ng/mL (in males) and 224954.18 h ng/mL (in females); while AUC_{0-24} corresponding to the MTD for beagle dogs was 28547.40 h ng/mL. The NOAEL for rats was 1 mg/kg with corresponding AUC_{0-24} of 1472.37 h ng/mL in males and 1507.79 h ng/mL in females. The NOAEL for beagle dogs was 1 mg/kg with corresponding AUC_{0-24} of 479.90 h ng/mL.

A 13-week repeated dose toxicity study showed that in all groups of SD rats that were given oral doses of 0.1, 1, and 10 mg/kg once daily for 13 consecutive weeks, there were visible decreases in the white blood cell (WBC) count and the number of lymphocytes. These changes were considered to be related to the expected pharmacology action of CBP-307. Under the test conditions above, the NOAEL of CBP-307 was 10 mg/kg. The mean C_{max} and AUC_{0-24} under this dose for 13 weeks are 3416.57 ng/mL and 30913.66 h ng/mL, respectively. In Cynomolgus monkeys that were intragastrically given repeated doses of 0.1, 1, and 10 mg/kg, respectively, once daily for 13 consecutive weeks, there were visible increases in the number of neutrophils and decreases in the numbers of WBCs and lymphocytes. All these changes were related to the expected pharmacological action (immunosuppressive effect) of CBP-307. During the study, 2 animals in the 1 mg/kg dose group presented with moribund condition and were then euthanized. The cause of moribund condition was related to the aggravation of infection after

drug administration. Excluding these 2 animals, other animals had a mean C_{max} of 477.08 ng/mL and a mean AUC_{0-24} of 2005.64 h·ng/mL, respectively, at NOAEL of 10 mg/kg for 13 weeks.

In a phase I reproductive toxicity test, rats were intragastrically given CBP-307 with repeated doses of 1, 10, 80 mg/kg/day, respectively, once daily. At doses of 1, 10, and 80 mg/kg/day, there were decreases in body weight, slowdown of weight gain, and decreases in food consumption in female and male rats. At a dose of 80 mg/kg/day, there was a decrease in the fertility of female and male rats, and the NOAEL for the fertility of female and male rats was 10 mg/kg/day. At a dose of 80 mg/kg/day, there were increases in the number of stillbirths and fetal loss after implantation, and the NOAEL for early embryo development was 10 mg/kg/day. At a dose of 10 mg/kg/day, the exposure (AUC_{0-t}) after administration on day 29 in male rats was 28812.62 h·ng/mL, and the exposure (AUC_{0-t}) on embryo implantation (Gestation day 6, GD6) in female rats was 21966.31 h·ng/mL.

In a phase II reproductive toxicity test, rats were intragastrically given repeated doses of CBP-307 0.03, 0.3 and 3 mg/kg/day, respectively, once daily for 10 consecutive days from GD6 to hard palate closure (GD15). The test results showed that at doses of 0.3 and 3 mg/kg/day, CBP-307 caused a decrease in food consumption in pregnant female rats. At a dose of 3 mg/kg/day, CBP-307 caused decreases in the live birth rate and the body weight and decreases in the body length and tail length in fetal rats. At doses of 0.3 and 3 mg/kg/day, CBP-307 caused increases in incidence rates of visceral and skeletal abnormalities and variations in fetal rats. The NOAEL for embryo-fetal development was 0.03 mg/kg/day. At a dose of 0.03 mg/kg/day, the maternal exposure (AUC_{0-24}) after last administration was 32.31 h•ng/mL.

In a phase II reproductive toxicity test, New Zealand rabbits were orally administered once daily doses of 0.1, 0.5, or 2.5 mg/kg/day for 13 consecutive days from GD6 to hard palate closure (GD18). The test showed that at a dose of 2.5 mg/kg/day, CBP-307 caused an increase in the fetal loss rate after implantation, a decrease in the live birth rate and increases in the number and percentage of absorbed fetuses in early fetal period. The NOAEL for embryo-fetal development was 0.5 mg/kg/day. At all doses of 0.1, 0.5 and 2.5 mg/kg/day, no fetal teratogenicity was observed. At a dose of 0.5 mg/kg/day, the maternal exposure (AUC_{0-24}) to CBP-307 after last administration was 210.89 h•ng/mL.

GLP-compliant genetic toxicology studies have shown that CBP-307 may not induce mutations.

The preclinical study data of CBP-307 are detailed in the Investigator's Brochure[14].

3.4. Clinical study data

3.4.1 Overview of the clinical study

Between November 2014 and September 2015, sponsor conducted and completed a phase I clinical study on CBP-307 in Australia (Study Protocol No.: CBP-307AU001). This study was a randomized, double-blind, placebo-controlled, parallel-group clinical trial in healthy subjects, which included a single-dose escalation part and a multiple-dose escalation part. The primary objective of the trial was to evaluate the safety and tolerability of CBP-307 following oral single- and multiple-dose administration. The secondary objectives were to characterize the pharmacokinetics and pharmacodynamics of CBP 307 following oral single- and multiple-dose administration and to determine the effect of foods on the pharmacokinetics and pharmacodynamics of the drug.

In the single-dose escalation part, 8 subjects in each cohort were randomized to investigational product (administered in 6 subjects) or placebo (administered in 2 subjects). Four CBP 307 doses were evaluated: 0.1, 0.25, 0.5, and 2.5 mg. A total of 28 subjects took the drug, and 8 of them participated in a test on the effect of foods.

CBP-307 was also studied in subjects at doses of 0.15 or 0.25 mg in the 28 days multiple-dose regimen. In each dose cohort, 6 study participants were given CBP 307 and 2 were given placebo.

The clinical trial showed that at a single dose of 0.1, 0.25 and 0.5 mg, CBP-307 had a good safety profile, good tolerability, good pharmacokinetic characteristics and a half-life of approximately 25 hours which allows once daily oral administration. Results of the 4-week repeat dose part showed that a dose of 0.1 mg and 0.25 mg once daily was able to effectively reduce the number of peripheral blood lymphocytes and had good tolerability. After continuous administration for 4 weeks, at 7 days after the dosing ended, peripheral blood lymphocyte counts in subjects receiving the multiple-dose regimen had returned to predose levels for the 0.15 and 0.25 mg cohorts.

3.4.2. Pharmacodynamics

CBP-307 can effectively reduce the number of human peripheral lymphocytes. The effect of the reduction in the number of lymphocytes was dose-dependent at the doses studied. The maximal peripheral blood lymphocyte count reduction for subjects receiving the single-dose regimen was observed at approximately 6 hours postdosing. The mean counts of peripheral lymphocytes in the 0.1 mg, 0.25 mg, 0.5 mg and 2.5 mg cohorts decreased by approximately 11%, 40%, 71% and 77% from baseline, respectively, which indicates that CBP-307 has potent effect on regulating the number of peripheral lymphocytes. The 4-week daily multiple-dose part showed that both 0.15 mg and 0.25 mg could significantly reduce the number of peripheral

lymphocytes in human. After the continuous administration of 0.25 mg once daily, the lymphocyte count decreased by more than 75% from baseline.

3.4.3. Pharmacokinetics

At 1-2 hours after a single oral dose of CBP-307, it was detectable in the blood; and the time to maximum concentration (T_{max}) was 4-6 hours after administration. Subjects taking CBP-307 while eating a standard high-fat breakfast had higher blood concentrations than those who took CBP-307 under fasting conditions. The drug exposure (AUC_{last} and C_{max}) was positively correlated with the dose within the range of 0.1 mg to 2.5 mg.

After a single oral dose of 0.25 mg, 0.5 mg and 2.5 mg, the elimination of CBP-307 followed the single exponential decay, and CBP-307 was still detectable in plasma at 72 hours after administration. The 4-week multiple-dose part showed that in both the 0.15 mg group and the 0.25 mg group, the plasma concentrations gradually increased in the first 10 days and then reached a steady state. The plasma concentrations at 0-24 hours after administration on day 28 was higher than that at 0-24 hours after administration on day 1, which indicated that the drug was accumulated after repeated administration. After a daily dose of 0.15 mg for 28 consecutive days, the accumulation ratios of AUC_{0-24} and C_{max} were 2.8 and 3.3, respectively.

3.4.4. Safety

The side effects of S1P1 agonists include bradycardia, sinus arrest and second-degree atrioventricular block. Currently the commonly accepted mechanism of these side effects is due to the activation of S1P1 in atrial myocytes causing bradycardia. Most of these side effects have no clinical manifestations/symptoms, and they appear mainly within a few hours after oral administration on day 1. Fingolimod and all second-generation S1P1 regulators (including ozanimod [Celgene], Siponimod [Novartis] and Ponesimod [Actelion]) were reported to have the same side effects, whose severity was positively correlated with the dose.

Observations showed that CBP-307 had side effects consistent with the reported ones above: a moderate decrease of the heart rate within 2-4 hours after administration and its severity was dose-dependent. At doses of 0.1 mg, 0.25 mg and 0.5 mg, no cardiac adverse events (AEs) occurred after a single dose; and at these doses, the most common AEs caused by CBP-307 and placebo were headache and dizziness, and no serious adverse events (SAEs) occurred. At an ultra-high dose (i.e., 2.5 mg, approximately 10 times of the target clinical dose), one subject experienced bradycardia and transient cardiac arrest for 9 seconds after administration, which resolved spontaneously on the same day without specific treatment. This subject had a relatively low baseline heart rate (55 beats/minute) and a lower heart rate of 33 beats/minute after dosing, which was the only SAE in the phase I clinical trial. As a comparison, it was also reported that the first dose of fingolimod 0.5 mg caused transient cardiac arrest in a subject,

which resolved within 24 hours.

The 4-week multiple-dose part showed that at doses of 0.15 mg and 0.25 mg once daily, CBP-307 had a good safety profile. The most common AEs were headache, dizziness and lymphopenia. In individual subjects, the alanine aminotransferase (ALT) levels slightly increased but were all lower than 3 times the upper limit of normal and were not accompanied by changes in levels of other liver enzymes or total bilirubin and returned to normal after the last dose of CBP-307. Elevated ALT has also been reported associated with both fingolimod and second-generation drugs.

No apparent effect of CBP-307 on pulmonary function, blood pressure, ophthalmic parameters or blood chemistry parameters were observed.

The clinical study data of CBP-307 are detailed in the Investigator's Brochure.

3.5. Study rationale and benefit/risk assessment

In clinical practice, treatment protocol for UC are mainly developed according to the severity of UC and the extent of its involvement. Although the incidence of UC is increasing rapidly globally, for patients with moderate to severe UC, there are still many limitations to current available treatment options.

5-aminosalicylic acid (5-ASA) is the main drug for induction and maintenance of remission in patients with mild to moderate UC, but it is less effective in patients with severe UC. It is still controversial whether patients with moderately to severely active UC can benefit from the administration of 5-ASA. For UC patients who fail the treatment with 5-ASA, especially those with extensive lesions, systemic glucocorticoid therapy is generally required. Although systemic glucocorticoid can induce UC remission quickly and effectively, they are not recommended for maintenance treatment due to its significant side effects, including osteoporosis, impaired glucose tolerance, and increased risk of infection.

Immunomodulators (including 6-mercaptopurine, azathioprine) can maintain the remission of patients with moderate to severe UC. Due to their relatively slow onset of action (azathioprine does not achieve the maximum efficacy before 12-16 weeks following administration), they cannot be used for rapid induction of remission during flares of UC. Adverse reactions related to the use of immunomodulators include myelosuppression, leukopenia, liver function impairment and infection etc. In addition, aminosalicylic acid preparations are often combined with thiopurine drugs for clinical treatment of UC, but 5-ASA preparations may increase the risk of myelosuppression. It was reported that these immunomodulators might increase the potential risk for lymphoma in patients with inflammatory bowel disease.

Monoclonal antibodies targeting TNF-α have been approved for the treatment of UC in several

countries around the world. They include infliximab (IFX), a chimeric murine-human monoclonal IgG 1 antibody, adalimumab (ADA), a fully human monoclonal antibody, and certolizumab pegol (CZP), a pegylated (polyethylene glycol) antigen-binding fragment (Fab). Monoclonal antibodies targeting TNF-α can induce and maintain remission, and are indicated for patients with severely active UC that is resistant to corticosteroid administered intravenously, and patients with corticosteroid-dependent active UC who fail immunomodulators treatment or are intolerant to them (due to the presence of contraindications or serious adverse reactions). Although TNF-α antagonists represent an important addition to the UC therapeutic medications, they are effective in only a subset of UC patients. IFX can only induce remission in 31%-39% of UC patients and maintain long-term (1-year observation period) clinical remission in 26% of UC patients. In addition, secondary failure associated with the immunogenicity of monoclonal antibodies to TNF-α is also common. Although patients have initial responses, it will gradually lose response over time. The TNF-α antagonists are also associated with a number of serious safety concerns based on their suppression of systemic immunity, including reactivation of tuberculosis (TB); bacterial, viral, fungal and opportunistic infections, and malignancies. Infusion reactions to TNF-α antagonists are not rare, e.g., the incidence of infusion reactions to IFX can reach to 3%-10%.

In summary, although pharmacotherapy for UC has made great progress in recent years, the current treatment options, especially oral medications, still cannot meet the medical needs of patients with moderate to severe UC. CBP-307 currently being developed is a novel, potent S1P1 modulator in oral form, and has shown to induce rapid and reversible lymphopenia in rodents and dogs. It is predicted that CBP307 may be effective and well-tolerated for UC treatment as shown by the completed preclinical pharmacology and toxicology studies on CBP-307, the phase I clinical study in healthy subjects, and the published results of a clinical study on the treatment of ozanimod (also known as RPC1036), a S1P1 modulator, for patients with moderate to severe UC. Similar to other S1P1 class members, its proposed mechanism for the treatment of UC is to inhibit the transfer of inflammatory T cells from lymph nodes and reduce their entry into intestinal tissues, thereby relieving intestinal inflammation. However, given its reduced effect on S1P3, it may confer a safety advantage over other S1P1 products.

A good safety profile of CBP-307 was demonstrated in available clinical data. Headache, dizziness and lymphopenia were the most common AEs observed. CBP-307 showed no impact on pulmonary function, blood pressure, ophthalmic parameters or blood chemistry parameters. Similar to other S1P1 regulators, CBP-307 showed side effect of dose-dependent moderate heart rate slowdown within 2-4 hours after administration; however, at single doses of 0.1 mg, 0.25 mg and 0.5 mg, no adverse cardiac events were reported.

This study is aimed at evaluating the effectiveness, safety and pharmacokinetic characteristics

of CBP-307 when orally administered in patients with moderate to severe UC, thereby providing a basis for a further clinical study and determining the dose to be administered in the phase III clinical study. The study includes two stages. In stage 1, subjects will be randomized at a ratio of 1:1 to receive double-blind therapy with CBP-307 0.2 mg or placebo for 12 weeks. Study stage 1 is aimed at evaluating the efficacy, safety and pharmacokinetic characteristics of different doses of CBP-307 when orally administered. Stage 2 of the study will further evaluate the safety and efficacy of CBP-307 in medium and long-term oral administration (for 36 weeks).

In this study, to protect patients from potential cardiac risk, dose titration will be performed before the patient is administered with the target dose. During the period of titration, 12-lead electrocardiogram (ECG) and 24-hour Holter will be applied for cardiac monitoring. Bradycardia and cardiac conduction abnormalities are defined as adverse events of special interest (AESI) of this study which will be given special attention and prompt reporting. Other potential safety risks including pulmonary toxicity, hepatotoxicity, macular edema, severe and opportunistic infections, skin tumors, posterior reversible encephalopathy syndrome, and progressive multifocal leukoencephalopathy, though not observed with CBP-307 in prior clinical trials, have been reported with other S1P1 agonist; therefore, these AEs are also defined as AESI of this study. Based on these benefit/risk assessments above, the conduct of this study is considered justifiable.

4 STUDY OBJECTIVES AND ENDPOINTS

	Study objectives	**Study endpoints**
Primary	● 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	● Change in adapted Mayo score from baseline at week 12 compared between CBP-307 0.2 mg and placebo
Secondary	● 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	● Change in adapted Mayo score from baseline at week 12 compared between CBP-307 0.1 mg and placebo ● Change in complete Mayo score from baseline at week 12 after treatment ● Comparison of clinical response rate at week 12 by adapted Mayo score (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) ● Comparison of clinical response rate at week 12 by complete Mayo score (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) ● Comparison of clinical remission rate at week 12 by adapted Mayo score (defined as a rectal bleeding subscore = 0 and stool frequency subscore ≤ 1, with an Endoscopy subscore ≤ 1 [excluding friability]) ● Comparison of clinical remission rate at week 12 by complete Mayo score (defined as a total Mayo score of ≤ 2 points with no individual subscore > 1 point) ● Mucosal healing rate at week 12 after treatment (mucosal healing is defined as Mayo endoscopic subscore ≤ 1)
	● 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	● Incidence, type and severity of TEAEs and SAEs as well as their relations with the investigational product, AEs and SAEs that lead to discontinuation of study, and AEs of special interest (cardiac events as well as abnormal pulmonary function tests, ophthalmologic examinations, skin examinations, and nervous system physical examinations); AEs will be graded according to CTCAE version 5.0 in study stage 1 ● 12-lead ECG findings, abnormal clinical laboratory tests (the hematology test, blood chemistry test, urinalysis and Coagulation test), vital signs and results of physical examination
Exploratory	• To evaluate the PK/PD of CBP-307 orally administered in subjects with moderate to severe UC in the study stage 1 • To evaluate 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	● Plasma concentrations of CBP 307 in subjects with moderate to severe UC ● Absolute lymphocyte count ● Total Igs (IgA, IgG and IgM) ● C-reactive protein (CRP) as a biomarker of plasma protein ● Fecal calprotectin as a fecal biomarker to be analyzed ● Change in the total IBDQ score and subscore from baseline at week 12 after treatment (in study stage 1), at week 24, and week 48 (in study stage 2) ● Incidence, type and severity of TEAEs and SAEs as well as their relations with the investigational product, AEs and SAEs that lead to discontinuation of study, and AEs of special interest (cardiac events as well as pulmonary function tests, ophthalmologic examinations, skin examinations, and nervous system physical

	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 sub-study 2 of the study stage 2.	examinations); AEs will be graded according to CTCAE version 5.0 in study stage 2 ● Change in 12-lead ECG findings, abnormal clinical laboratory tests (the hematology test, blood chemistry test, urinalysis and coagulation test), vital signs and results of physical examination in the study stage 2 ● To explore the following efficacy endpoints in subjects with moderately to severely active UC who achieved clinical response after 12 weeks of induction therapy in study stage 1: o Percentage of subjects who maintain clinical response at week 48 o Percentage of subjects who achieve clinical remission at week 48 o Percentage of subjects who achieve mucosal healing under endoscope at week 48 o Percentage of subjects who take oral corticosteroids at baseline but has discontinued treatment of corticosteroids at week 48 and achieved clinical remission o Change in the complete Mayo score at week 48 from baseline o Change in the adapted Mayo score at week 48 from baseline ● To explore the following efficacy endpoints in subjects with moderately to severely active UC who do not achieve response after 12 weeks of induction therapy in study stage 1: o Percentage of subjects who achieve clinical response at week 24 (after 12 weeks of treatment in sub-study 2) o Percentage of subjects who achieve clinical remission at week 24 (after 12 weeks of treatment in sub-study 2) o Percentage of subjects who achieve mucosal healing under endoscope at week 24 (after 12 weeks of treatment in sub-study 2) o Change in the complete Mayo score at week 24 (after 12 weeks of treatment in sub-study 2) from week 12 o Change in the adapted Mayo score at week 24 (after week 12 of treatment in sub-study 2) from week 12 o Percentage of subjects who maintain clinical response at week 48 (after 36 weeks of treatment in sub-study 2) (i.e., achieve clinical response at both week 24 and week 48)

		○ Percentage of subjects who achieve clinical remission at week 48 (after 36 weeks of treatment in sub-study 2) ○ Percentage of subjects who achieve mucosal healing under endoscope at week 48 (after 36 weeks of treatment in sub-study 2) ○ Change in the complete Mayo score at week 48 (after 36 weeks of treatment in sub-study 2) from week 12 ○ Change in the adapted Mayo score at week 48 (after 36 weeks of treatment in sub-study 2) from week 12

AE=adverse events; CRP=C-reactive protein; CTCAE=common terminology criteria for adverse events; IBDQ=inflammatory bowel disease questionnaire; Ig=immunoglobulin; PD=pharmacodynamics; PK=pharmacokinetics; SAE: serious adverse event; TEAE: treatment-emergent adverse event; UC=ulcerative colitis.

5 STUDY PLAN

5.1. Study design and study procedures

This study is a multicenter, multicountry, phase II clinical trial to evaluate the efficacy and safety of CBP-307 in subjects with moderate to severe ulcerative colitis (UC). This study is scheduled to be carried out approximately between March 2018 and September 2022 in approximately 77 sites globally in China, Pakistan, Ukraine and the United States.

This study includes stage 1 and stage 2.

Study stage 1

After screening, subjects will enter the randomized, double-blind, placebo-controlled induction therapy for 12 weeks, i.e., the study 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.

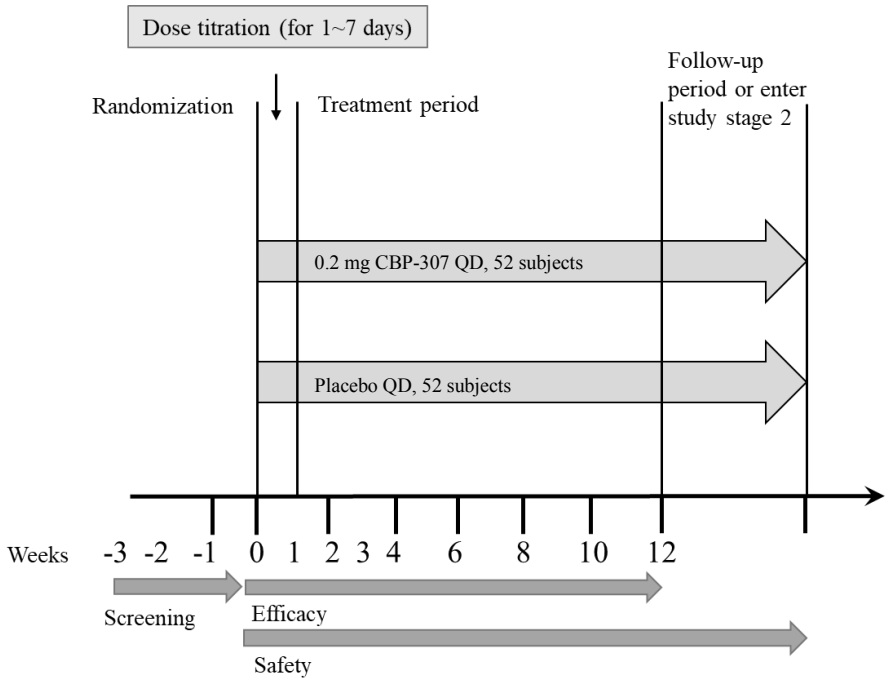
In study stage 1, subjects randomized to the CBP-307 group will undergo dose titration for 1 week while those in placebo group will undergo simulated titration (Figure 4). Both CBP-307 and placebo will be administered through the oral route. For subjects in the group of dose titration of CBP-307 0.2 mg once daily, a dose of 0.05 mg CBP-307 will be given from day 1

to day 4; then, a dose of 0.1 mg CBP-307 will be given for later 3 days; from day 8, a target dose (0.2 mg) will be administered. The titration dosing regimen is detailed in Section 6.2.

For the subjects already enrolled as per the previous approved protocols (version 5.0 or earlier), they will continue the treatment in the stage 1 according to the previous planned schedule.

Administration will be continued for 12 weeks. If subjects who complete 12 weeks of induction therapy of the stage 1 meet the criteria for the study stage 2, they can choose to enter it to further evaluate the safety and efficacy of CBP-307 in medium or long-term administration in subjects with moderate to severe UC. Subjects who early withdraw from the study or complete the study stage 1 but do not enter the stage 2 will enter a 4-week safety follow-up period.

Figure 4. Study design of the stage 1



Study stage 2

All subjects who complete 12 weeks of induction therapy (with CBP-307 or placebo) in the study stage 1 and complete all examinations (including colonoscopy) at the week 12 visit can choose to enter the study stage 2 of a total length of 40 weeks, including 36 weeks of continuous treatment and 4 weeks of safety follow-up after the last dose. Subjects who choose to enter the stage 2 will be required to sign an updated informed consent form and will be screened for eligibility.

The study stage 2 contains two sub-studies: sub-study 1 and sub-study 2. Subjects entering the study stage 2 will enter one of sub-studies based on their results of efficacy evaluation in the study stage 1 (Figure 5).

Sub-study 1 (subjects who have achieved clinical response by adapted Mayo score): Subjects who have **clinical response** shown by efficacy evaluation at week 12 in the study stage 1 and meet the eligibility criteria for stage 2 will enter sub-study 1 of the study stage 2 to receive double-blind maintenance treatment for 36 weeks (weeks 13 to 48), i.e., the therapeutic regimen for them in stage 1 will be continually maintained. Safety follow-up will be completed at 4 weeks after the last dose. Subjects who present with recurrent UC during maintenance treatment are required to terminate treatment and withdraw from the study.

For the subjects already enrolled as per the previous approved protocols (version 5.0 or earlier), they will follow the previous planned treatment in the sub-study 1 of stage 2 study.

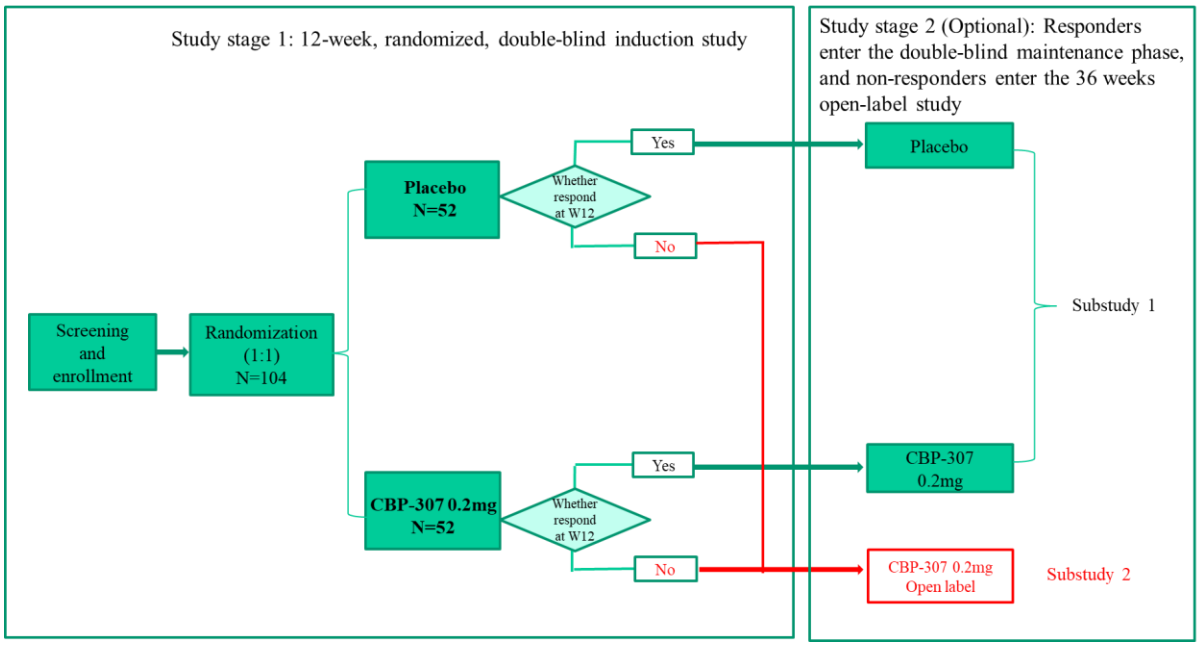
UC disease recurrence i.e., an increased activity of UC, is defined as a repeated (occurring at 2 consecutive visits) partial Mayo score that is at least 5 points and is also ≥3 points higher than the score at week 12 (the end of induction therapy), and where the possibility of increased disease activity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

Sub-study 2 (subjects who have not achieved clinical response by adapted Mayo score): Subjects who **have not achieved clinical response** shown by efficacy evaluation at week 12 in the study stage 1 and meet the eligibility criteria for stage 2 will enter open-label treatment with CBP-307 0.2 mg. Subjects will receive CBP-307 once daily at an oral dose of 0.2 mg in sub-study 2 regardless of whether they receive CBP-307 0.2 mg or placebo in the study stage 1.

For subjects who enter sub-study 2 of study stage 2, 1-week dose titration will be performed at the first week (week 13). Dose titration will involve 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 will be completed at 4 weeks after the last dose.

At week 24, subjects will undergo efficacy evaluation including colonoscopy. If the subjects have not achieved clinical response, the treatment will be discontinued and the subjects will be withdrawn from the study.

Figure 5. Study design of stages 1 and 2



5.2. Rationale for study design and dose selection

5.2.1. Rationale for study design

The design of the study stage 1 allows for a double-blind, placebo-controlled comparison of efficacy and safety parameters of CBP-307 vs. placebo during the induction period of 12 weeks in subjects with moderately to severely active UC.

The study stage 2 is designed to evaluate the efficacy and safety of CBP-307 in its medium and long-term treatment. Sub-study 1 of the study stage 2 will include subjects who have achieved clinical response during the induction period and will continue the blinded maintenance treatment for 36 weeks with the regimen used during the induction period. Such study design could avoid the re-assignment of responded subjects, and blinding maintenance could reduce bias in efficacy and safety evaluation. Sub-study 2 of the study stage 2 is an open-label treatment with CBP-307 at dose of 0.2 mg/day to evaluate the clinical response of subjects (who do not respond during the induction period) at a daily dose of 0.2 mg, as well as its efficacy and safety in medium and long-term maintenance treatment.

5.2.2. Rationale for dose selection

The dose selection for this study has taken into account the results of previous non-clinical pharmacological & toxicological studies and clinical studies. The doses of CBP-307 for humans have been screened based on fingolimod and other similar S1P1 agonists administered in non-clinical and clinical studies.

The decrease in the number of lymphocytes in peripheral blood is a typical PD response to (or

a PD marker for) S1P1 agonists. fingolimod (FTY720), a first-generation S1P1 agonist, second-generation S1P1 agonists under development, such as ozanimod and etrasimod, and CBP-307 belong to the same class of drugs. In all clinical studies of S1P1 agonists including fingolimod, ozanimod and etrasimod, the decrease in the number of lymphocytes in peripheral blood was used as a PD marker for S1P1 agonists, the doses administered in phase II clinical studies were selected based on a decrease by 50%-70% in the lymphocyte count in peripheral blood from the baseline. A lot of clinical data on fingolimod have demonstrated that after a decrease by approximately 70% in the lymphocyte count, an increased dose may fail to further improve the therapeutic effect on multiple sclerosis. Among these studies in different compounds, more therapeutically potential was observed in patients treated with higher doses when safety risks were comparable in different dosages. Thus, in this phase II UC study, the clinical data on similar S1P1 agonists are fully referred to, and the doses are determined based on the PD data of CBP-307 derived from the phase I clinical studies and the efficacy data from the phase II Crohn's disease study.

An Australian study of the safety, pharmacokinetics and efficacy of repeated doses of CBP-307 administered once daily for 28 days showed that the pre-dose lymphocyte counts in the 0.15-mg and 0.25 mg groups decreased by 48.5% and 75%, respectively, after the pharmacokinetics (PK) reached steady state. The phase I clinical study of CBP-307 (administered once daily for 14 days) in Chinese healthy subjects, found that the pre-dose lymphocyte counts in the 0.1-mg and 0.2 mg groups decreased by approximately 50% and 70%, respectively, after steady state was reached. This observation is consistent to pharmacodynamic (PD) requirement for the selection of a low dose and a high dose to be administered in a phase II clinical study. From the experience in a CBP-307 phase II Crohn's disease study, 0.1 mg or 0.2mg orally administered once daily is selected. Obvious therapeutic effects could be observed only in patients treated by 0.2 mg once daily, including the clinical improvement as well as the biomarker changes in parallel. Additionally, safety data from all these different CBP-307 phase I and II studies showed that both 0.1 mg and 0.2 mg once daily administration had comparably overall safety profile.

Thus, in order to achieve the PD requirement (the reduction in lymphocyte), and meanwhile to reduce the exposure to the less effective / ineffective dose, 0.2 mg orally administered once daily is selected as an appropriate dose in this study.

5.3. Study duration

Study stage 1: The duration for treatment is 12 weeks. Subjects who complete the 12-week treatment of stage 1 but do not enter the stage 2 or early withdraw from the study will undergo safety follow-up for 4 weeks after the last dose.

Study stage 2: All subjects who complete the 12-week study stage 1 treatment (induction therapy with CBP-307 or placebo) and complete all assessments (including colonoscopy) at week 12 visit can choose to enter the study stage 2 for a total of 40 weeks. In the stage 2, subjects will continuously be administered for 36 weeks (week 13-48 of the study), and they will undergo safety follow-up for 4 weeks after the last dose (week 49-52 of the study). Subjects who early withdraw from the study will undergo safety follow-up for 4 weeks after the last dose.

For subjects who complete both stages (stage 1 + stage 2), the study will last for a total of 52 weeks: 48 weeks of administration, and 4 weeks of follow-up.

5.4. Study population

Subjects aged 18-75 years (inclusive), regardless of sex, who are diagnosed with moderate to severe UC (adapted Mayo score ≥ 4).

5.4.1. Inclusion criteria and Exclusion criteria for study stage 1

Inclusion criteria:

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. Male or female subjects aged 18-75 years (inclusive).
2. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements. The subject signs and dates a written informed consent form prior to the initiation of any study procedures.
3. Female subjects of childbearing potential and male subjects who have not undergone vasectomy should use at least one highly effective method of contraception during the entire study and 4 weeks after the last dose of investigational products after signing the informed consent form. **The highly effective methods of contraception in this study include**:
    a. Abstinence is acceptable only if it is part of the participant's regularly practiced lifestyle;
    b. Hormone (oral, patch, ring, injection, implant) in combination with a male condom. This must be used for at least 30 days before the first dose of investigational products or an alternative acceptable method must be used;
    c. Intrauterine device (IUD) in combination with a male condom;
    d. Exceptions are: a) women with at least 12 consecutive months amenorrhea in the absence of medications known to induce amenorrhea and have a documented follicle stimulating hormone (FSH) level of greater than 40 mIU/mL or in the postmenopausal range; or b) surgical sterilization (e.g., hysterectomy, bilateral oophorectomy).
4. The subject has a diagnosis of UC established at least 3 months prior to screening by

clinical and endoscopic evidence corroborated by a histopathology report. Subjects are confirmed to have moderate to severe active UC within 14 days prior to the first dose of the investigational product, which is based on an adapted Mayo score of 4-9, and an endoscopic subscore of ≥ 2. Endoscopy must be performed during the screening period (day -14 to day -3, allowing centralized reading and evaluation before the first dose at week 0).

5. The subject has evidence of UC extending to the rectum with ≥15 cm involvement on endoscopy.
6. Subjects must be UC patients who are receiving treatment. They can be enrolled if they meet any items below.
    a. Prior to the randomization visit, subjects have received oral 5-ASA (e.g., mesalazine, sulfasalazine, olsalazine, balsalazide) for at least 4 weeks with the dose stable for at least 2 weeks
    b. Prior to the randomization visit, subjects have received oral or IV corticosteroids e.g. prednisone (daily doses ≤ 30 mg), budesonide (daily doses ≤ 9 mg), methylprednisolone (daily doses ≤ 24 mg), or equivalent dose of corticosteroids for at least 4 weeks, with the dose stable for at least 2 weeks.
7. If oral 5-ASA or corticosteroid for treatment of UC have been recently discontinued, they must have been stopped for at least 2 weeks prior to the screening endoscopy examination which is used for Mayo score assessment.
8. If subjects use non-prohibited concomitant medications, a stable dosing regimen must be used, that is, within 7 days prior to first dose of investigational product or within 5 half-lives of the drug (whichever is longer), there's no new concomitant medications started or changes in the dose of existing non-prohibited concomitant medications.
9. The subject who has extensive colitis or pancolitis of >8 years duration or limited colitis of >12 years duration must have documented evidence that a surveillance colonoscopy was performed within 12 months prior to initial screening (can be performed during Screening if not performed in previous 12 months).
10. For subject who has a family history of colorectal cancer, personal history of increased colorectal cancer risk, age >50 years, or other known risk factor, the data of colorectal cancer surveillance within 12 months prior to screening visit must be available (colorectal cancer surveillance can be performed during screening if not in previous 12 months).

Exclusion criteria

Exclusion criteria are classified into indication-specific exclusion criteria, exclusion criteria for general condition and exclusion criteria for infectious diseases. Patients who meet any of the following criteria will be excluded:

UC-related exclusion criteria:

1. At the screening visit, subjects have evidence of toxic megacolon.
2. The subject has had subtotal or total colectomy.
3. The subject has an existing ileostomy, colostomy (a history of ileostomy or colostomy that has been reversed may be acceptable), or known symptomatic stenosis of the intestine.
4. Investigator judges the subject currently requires or is anticipated to require surgical intervention for UC during the study.
5. The subject has a history or evidence of adenomatous colonic polyps that have not been removed.
6. The subject has a history or evidence of colonic mucosal dysplasia including low or high-grade dysplasia, as well as indeterminate for dysplasia.
7. Subjects have a suspected or confirmed diagnosis of Crohn's enterocolitis, undiagnosed types of colitis, ischemic colitis, or radiation colitis.
8. Previous exposure to the following treatments:
    - Lymphocyte-depleting therapies (e.g., alemtuzumab, anti-CD4 antibody, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation and daclizumab).
    - Previous treatment with D-penicillamine, leflunomide.
9. The subject has had prior exposure to approved or investigational products that inhibit the lymphocyte trafficking (e.g., natalizumab, fingolimod, ozanimod or etrasimod, etc.) Subjects who were previously exposed to vedolizumab and did not respond to its treatment.
10. Within 60 days prior to the screening visit, the subject has received any of the following for the treatment of UC:
    a. Intravenous immunoglobulin (IVIG);
    b. Therapeutic plasma exchange (TPE).
11. Within 30 days prior to randomization visit, the subject has received any of the following for the treatment of UC:
    a. Immunosuppressants (such as cyclosporine, tacrolimus, sirolimus or mycophenolate mofetil), thalidomide or traditional Chinese medicine;
    b. Approved non-biologic agents or traditional Chinese medicine treatment.
12. Patients who plan to concurrently use an immunosuppressant (such as azathioprine, 6-mercaptopurine or methotrexate) after randomization. Patients treated with azathioprine, 6-mercaptopurine or methotrexate at screening are required to discontinue it prior to the first dose of the study drug.
13. The subject has received any investigational biologic or non-biologic agent, or approved biologic agent or biosimilars within 60 days or 5 half-lives prior to screening (whichever is longer).
14. The subject has used topical (rectal) treatment with aminosalicylic acid, corticosteroid or traditional Chinese medicine enemas/suppositories or for UC treatment within 2 weeks of

the administration of the first dose of study drug.

***Exclusion criteria for general conditions**:*

15. The subject has any unstable or uncontrolled cardiovascular, pulmonary, hepatic, renal, gastrointestinal, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, or other medical disorders that, in the opinion of the investigator, would confound the study results or compromise subject safety.
16. History of uveitis or macular oedema.
17. Clinically relevant cardiovascular conditions, including history or presence of any one of below:
    a. Ischemic heart disease or myocardial infarction; Unstable angina; History of angina pectoris caused by coronary artery spasm or raynaud's phenomenon (Raynauds);
    b. Congestive heart failure (NYHA class III-IV), cardiac arrest;
    c. Stroke, transient ischemic attack;
    d. History of recurrent syncope or positive result of vasovagal syncope tilt test;
    e. Symptomatic bradycardia, sick sinus syndrome, sinoatrial block, second degree atrioventricular block (e.g., Mobitz type 2 atrioventricular block) or third degree atrioventricular block;
    f. Congenital long QT syndrome (LQTS) or prolonged QT interval corrected using Fridericia's formula (QTcF) in screening ECG (QTcF >450 ms in men, QTcF > 470 ms in women) ;
    g. Subjects at increased risk for QT prolongation due to hypokalemia or hypomagnesemia; or subjects who are currently taking medications to prolong QT interval (e.g., citalopram, chlorpromazine, haloperidol, methadone, and erythromycin) which result in risk for torsades de pointes;
    h. Under treatment or expected to taking treatment during the study with medications with a known impact on the cardiac conduction system (e.g., beta blockers, calcium channel blockers, Class Ia or Class III anti-arrhythmic drugs [amiodarone, bromobenzylamine, sotalol, ibutilide, azimilide, dofetilide]);
    i. Hypertension (except well-controlled hypertension after pharmacotherapy); systolic blood pressure < 95 mm Hg or >140 mm Hg and diastolic blood pressure ≤ 50 mm Hg or ≥ 95 mm Hg at the screening visit;
    j. Resting heart rate < 55 times/min or ventricular rate < 55 times/min in 12-lead ECG at screening visit;
    k. Investigator deems that the 12-lead ECG at screening visit is clinically significant abnormal, such as myocardial ischemia, any significant cardiac conduction abnormalities (such as the left bundle branch block), that would put the subject at risk or interfere with the study results;

l. Any other significant heart disease that the investigator judges would put the subject at risk or interfere with the study results.
m. Subjects have a family history of premature coronary heart disease.

18. History of type 1 diabetes, uncontrolled type 2 diabetes judged (HbA1c > 7%) by investigator, patients with diabetes accompanied with significant complications, e.g., retinopathy or kidney disease.
19. The subject has a history of malignancies, including malignant solid tumors and hematological malignancies (Except basal cell carcinomas and in situ squamous carcinomas of the skin that have been resected or cured).
20. The subject has had any surgical procedure requiring general anesthesia within 30 days prior to screening or is planning to undergo major surgery during the study period.
21. The subject has chronic obstructive pulmonary disease, asthma, pulmonary fibrosis or any other significant history of pulmonary diseases except for mild intermittent asthma that does not require regular maintenance treatment.
22. Pulmonary function test (including examinations of lung ventilation function and pulmonary gas exchange) at the screening visit shows one of the following abnormalities: forced expiratory volume in 1 second (FEV1) or forced vital capacity (FVC) < 70% of normal expected value.
23. During screening period, any of the following laboratory abnormalities:
    a. Hgb < 8 g/dL;
    b. WBC count < 3.5×10^9/L;
    c. Neutrophils count < 1.5×10^9/L;
    d. Lymphocyte count < 0.8×10^9/L;
    e. Platelet count < 100×10^9/L or >1200×10^9/L;
    f. Serum creatinine > 124 μmol/L for female or > 141 μmol/L for male;

    If the WBC count, neutrophil count or lymphocyte count meets the above criteria during the screening period, a retest can be scheduled during the screening period. It is required that the results of the retest should not meet the above criteria, otherwise subjects do not meet the enrollment criteria.

24. Abnormal liver function test during the screening period, such as abnormalities in alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (γ-GT), alkaline phosphatase (ALK) or serum total bilirubin, which suggest liver disease or liver function impairment. The investigator should make a determination according to the following criteria:
    a. Subjects with serum total bilirubin > 1.2 times the upper limit of normal (ULN) shown by initial and repeat tests should be excluded from the study;
    b. Subjects with any of the other liver function parameters listed above, such as AST,

ALT, γ-GT or ALK > 1.5 times the ULN shown by initial and repeat tests, should be excluded from the study;

c. Subjects with increased level of more than 1 parameter in liver function test should be excluded from the study;

d. During the screening period, if a single transaminase level (AST, ALT, γ-GT or ALK) is elevated by more than 1.5 times the ULN, or serum total bilirubin is elevated by more than 1.2 times the ULN, a repeat test can be scheduled as soon as possible before enrollment/randomization to exclude laboratory errors. Only if the results of the repeat test meet the requirements, subjects could be enrolled.

25. Allergic to any component of the study drug (and its excipients).
26. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year prior to Screening.
27. The subject has an active mental disorder that, in the opinion of investigator's opinion, may interfere with compliance with study procedures.
28. The subject is unable to participate in all study visits or comply with study procedures.
29. The subject is in a health condition that requires to take prohibited medications listed in Section 6.6.
30. If female, the subject is intending to become pregnant before, during, or within 4 weeks after participating in the study or intending to donate ova during such period.
31. If male, the subject intends to donate sperm during the study or for 4 weeks thereafter.
32. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (e.g., spouse, parent, child, sibling) or may consent under duress.
33. Female subjects who are lactating or have a positive serum pregnancy test during the Screening Period or a positive urine pregnancy test at week 0, prior to study drug administration.

Exclusion criteria for infectious diseases:

34. The subject has evidence of known active infection during the screening period.
35. The subject has evidence of treatment for Clostridioides difficile (C. difficile) infection or other intestinal pathogen with 28 days prior to first dose of study drug.
36. Patients with the histories of following infectious diseases:

- Treatment with oral anti-infection medication due to acute infection within 2 weeks prior to screening visit or intravenous anti-infection treatment due to acute infection within 4 weeks prior to screening visit;
- Clinically significant infection (e.g., pneumonia, nephropyelitis and herpes zoster) within 4 weeks prior to screening visit, or ongoing chronic infection;

37. Active or latent tuberculosis (TB) evidenced by the followings:

- A positive diagnostic TB test within 30 days before screening or during the screening period is defined as:
  - Quantiferon or Quantiferon Plus test positive, or
  - Two consecutive indeterminate Quantiferon tests or Quantiferon Plus tests, or
  - Chest X-ray within 3 months prior to week 0 for which the results are suspicious for pulmonary TB.

Note: Subjects with documented evidence of previously successfully treated TB, or with a negative Quantiferon or Quantiferon Plus test result, can be enrolled in the study. If Quantiferon or Quantiferon Plus test result is indeterminate at screening, it could be retested during screening period. If Quantiferon or Quantiferon Plus retest result is indeterminate, 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.

38. Chronic hepatitis B virus (HBV) infection* or chronic hepatitis C virus (HCV) infection**.

*Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb) and hepatitis B core antibody (HBcAb) must be evaluated for all the patients at screening. Patients with positive hepatitis B surface antigen (HBsAg) will be excluded. HBV-DNA test should be carried out at screening if the subject is negative for Hepatitis B surface antigen, negative or positive for hepatitis B surface antibody, and positive for hepatitis B core antibody. The subject should be excluded from the study if HBV-DNA test result is positive, or he/her can be enrolled in the study in case of negative result of HBV-DNA test.

**An HCV viral load test should be carried out if HCV antibody (HCVAb) is positive. The subject should be excluded from the study in case of positive HCV viral load test result. If the HCV viral load test result is negative, the subject can be enrolled in the study.

39. The subject has any identified congenital or acquired immunodeficiency (e.g., common variable immunodeficiency, human immunodeficiency virus [HIV] infection, organ transplantation).
40. The subject has received any live vaccine within 30 days prior to screening. Or subjects are scheduled for immunization with any live vaccine during the study or within 1 month after the last dose of the investigational product.
41. Positive syphilis antibody at screening.
42. Subjects with a history of more than one episode of herpes zoster, or a history of disseminated herpes zoster or disseminated herpes simplex.

5.4.2. Inclusion and exclusion criteria for subjects' entry into the study stage 2 from the stage 1:

Inclusion criteria:

Subjects cannot enter the study stage 2 if any of the following criteria is not satisfied:

1. Subjects must be those with UC who participate in the study of CBP-307CN002 and have completed 12 weeks of treatment with CBP-307 or placebo in the stage 1 and have completed all the assessments (including colonoscopy) at study visit of week 12 in study stage 1.
2. Subjects have good compliance in stage 1, can understand all information about the study stage 2, and are able and willing to comply with the requirements specified in the study protocol.
3. Subjects or their legal representatives voluntarily sign informed consent forms for study stage 2.
4. Female subjects of childbearing potential and male subjects who have not undergone vasectomy should use at least one highly effective method of contraception during the entire study and 4 weeks after the last dose of investigational products after signing the informed consent form. **The highly effective methods of contraception in this study include**:

    a. Abstinence is acceptable only if it is part of the participant's regularly practiced lifestyle;

    b. Hormone (oral, patch, ring, injection, implant) in combination with a male condom. This must be used for at least 30 days before the first dose of investigational products or an alternative acceptable method must be used;

    c. Intrauterine device (IUD) in combination with a male condom;

    d. Exceptions are: a) women with at least 12 consecutive months amenorrhea in the absence of medications known to induce amenorrhea and have a documented FSH level of greater than 40 mIU/mL or in the postmenopausal range; or b) surgical sterilization (e.g., hysterectomy, bilateral oophorectomy).

Exclusion criteria:

Subjects who meet any of the following criteria will not be included in study stage 2:

1. The subject has any unstable or uncontrolled cardiovascular, pulmonary, hepatic, renal, GI, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, or other medical disorder that, in the opinion of the investigator, would confound the study results or compromise subject safety.
2. Subjects who are known to be allergic to CBP-307 or its excipients, or subjects experience significant adverse events related to the study drug during the stage 1 of the CBP-307CN002 study, and the investigator deems that subjects are not appropriate to participate in the stage 2.
3. Subjects currently have evidence of active or untreated latent tuberculosis.

4. Subjects currently have active or chronic recurrent infections, and in the opinion of the investigator subjects are not appropriate to participate in stage 2 of the study.
5. History of uveitis or macular oedema.
6. Subjects had received any of the following treatments after administration of the first dose in stage 1 of the study:
   a) Biological product;
   b) Prednisone>30 mg/day, budesonide>9 mg/day, methylprednisolone>24 mg/day or equivalent dose of steroid treatment;
   c) Immunosuppressant (such as azathioprine and 6-mercaptopurine or methotrexate).
7. Investigator deems that the 12-lead ECG results at the study visit of week 12 during study stage 1 is clinically significant abnormal, such as myocardial ischemia, any significant cardiac conduction abnormalities (such as the left bundle branch block), any abnormality that would put the subject at risk or interfere with the study results.
8. Pulmonary function test (including examinations of lung ventilation function and pulmonary gas exchange) of subjects at the study visit of week 12 during the study stage 1 shows 1 of the following abnormalities: forced expiratory volume in 1 second (FEV_1) or forced vital capacity (FVC) < 50% of normal predicted value.
9. Subjects' laboratory measurements at week 12 visit during the study stage 1 meet any of the following criteria:
   - AST or ALT> 3 ULN;
   - Absolute lymphocyte count < 0.2×10^{9}/L;
   - Serum creatinine > 124 μmol/L (in females) or > 141 μmol/L (in males).
10. Any other reason that in the opinion of the investigator may interfere with subject compliance or evaluation of the results of the study.

5.4.3. Re-screening after the failure of screening

The numbers of all subjects who fail the screening will not be used again. Whether a subject who fails the screening is allowed to undergo re-screening will be evaluated by the sponsor's medical monitor based on individual case. Subjects receiving re-screening will be required to complete all laboratory tests and procedures during the screening period, including colonoscopy (except that recent colonoscopy videos are available for the centralized reading at the site and the ilecolonoscopy is performed within 30 days prior to the first dose). In case the results of the pulmonary function test, ophthalmologic examination (including OCT) or dermatology examination during initial screening period at the study site are within 30 days

prior to the first dose, the results could be re-used after the investigators' evaluation based on individual case. Subject is allowed to be re-screened only once.

5.4.4. Criteria for termination of treatment or early withdrawal of subjects

Subjects should be encouraged to complete the study, but they are allowed to voluntarily withdraw from the study at any time during its conduct. The investigator should provide written statements of the withdrawal of subjects from the study. Primary reasons why subjects terminate or withdraw from the study or discontinue the investigational product should be recorded in the eCRF according to the following classifications.

1) Adverse events (AEs)

The Subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.

- Liver function test (LFT) abnormalities

The investigational product should be discontinued immediately, and appropriate clinical follow-up should be performed (including repeated laboratory tests until the subject's laboratory measurements returns to normal or baseline, please refer to Section 7.5), if the following circumstances occur at any time during study medication treatment:

  - ALT or AST > 8 ×ULN, or
  - ALT or AST > 5 ×ULN and a re test > 5 ×ULN, or
  - ALT or AST > 3 ×ULN and elevated total bilirubin > 2 ×ULN, or international normalized ratio (INR) > 1.5, or
  - ALT or AST > 3 ×ULN with fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever and rashes.

- Decrease in pulmonary function

If the subject's pulmonary function test results (FEV_1 and/or FVC) fall below 50% of the predicted values, treatment should be discontinued immediately, and appropriate clinical follow-up should be performed (please refer to Section 7.5).

- Macular edema

All subjects diagnosed with macular edema must discontinue the investigational product (see Section 7.5).

2) Significant protocol deviation at the time of enrollment or during the study

The discovery post randomization that the subject fails to meet protocol entry criteria or does not adhere to protocol requirements, and continued participation in the study may poses unacceptable risk to the subject's health.

3) Lost to follow-up

The subject does not return to the study site, and the investigator makes multiple attempts to contact the subject but fails. If a subject is lost to follow-up, the investigator should make every effort to contact the subject and record each attempt to contact the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods).

4) Subject non-compliance with the protocol

If a subject is in significant non-compliance with the protocol, the subject could be early terminated after discussion/consultation by the investigator, the medical monitor of the contract research organization (CRO), and sponsor.

5) Withdrawal of informed consent by the subject

The subject voluntary withdraws from the study. The subject (or their legal representatives) wishes to withdraw from the study. The reason for withdrawal, if provided should be recorded in the eCRF.

6) Termination of study

Sponsor, Ethics Committee or regulatory body terminates the study.

7) Pregnancy

Subject pregnancy.

Note: If a subject is found to be pregnant, the subject must withdraw from the study immediately. The procedure for withdrawal from the study is detailed in Section 8.8.

8) Treatment failure or disease progression

Study stage 1: The investigator considers that subject is not benefiting from investigational treatment, and present with disease progression during the study: e.g., in the opinion of the investigator, continued participation would pose an unacceptable risk to the subject or need for surgical intervention for treatment of UC.

Study stage 2: In sub-study 1, if the subject present with UC recurrence during maintenance treatment, the subject is required to terminate the treatment and withdraw from the study.

UC disease recurrence i.e., an increased activity of UC, is defined as a repeated (occurring at 2 consecutive visits) partial Mayo score that is at least 5 points and is also $\geqslant$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).

In sub-study 2, if subjects have not achieved clinical response yet at week 24, they will be required to terminate treatment and withdraw from the study. In addition, for all subjects who enter the study stage 2, if the investigator judges that they are not benefiting from the study treatment, or present with disease progression during the study period, or need for surgical intervention for UC treatment, the investigational treatment should also be terminated.

9) Others

Note: Specific reasons should be recorded in the eCRF. The investigator should do their utmost to determine the primary reason of withdrawal, and if possible, document it (e.g., withdrawal due to AEs or treatment failure).

5.4.5. Criteria for termination of the clinical study.

The study may be terminated prematurely in case of the following:

- The principal investigator and sponsor believe that the number and severity of AEs indicate that the study must be terminated.
- Newly obtained data raise concerns about the safety of the investigational product: continuation of the study may pose a risk to subjects.
- The principal investigator and sponsor believe that a flawed study design or unplanned unblinding has impaired the integrity of the study, thereby making it impossible to evaluate the efficacy and safety of the investigational product.

The premature termination of the study must be determined and recorded by the principal investigator in consultation with sponsor. Study results must be reported as far as possible according to the protocol requirements.

5.4.6. Procedure for termination of or withdrawal from the study

If possible, perform a complete follow-up visit for subject who withdraws from the study, including a physical examination, vital signs, an ECG test and a laboratory test (Refer to Study Flow Chart Table 1, 2 and 3). To evaluate AEs or laboratory abnormalities and ensure that they are reversible or stable, follow-up visits will be conducted at an appropriate time for all subjects who withdraw after the last dose of the investigational product. Results will be recorded in the original medical record and eCRF. The reasons for withdrawal will also be recorded in the original medical record and eCRF.

6 TREATMENT REGIMEN

6.1. Randomization and blinding method

6.1.1. Randomization method

Subjects meeting all eligibility criteria of study stage 1 will be randomized into the study and stratified according to whether the subject had previous failure of a tumor necrosis factor (TNF)-α antagonist therapy.

Sub-study 1 of the study stage 2 will include subjects who have achieved clinical response by adapted Mayo score in the 12-week induction therapy in study stage 1 as shown by efficacy evaluation and who meet eligibility criteria for entering study stage 2: they will receive blinded maintenance treatment with the regimen used during study stage 1. Sub-study 2 of the study stage 2 will include subjects who have not achieved clinical response by adapted Mayo score in the induction therapy in study stage 1 and who meet eligibility criteria for stage 2: they will receive open-label treatment with CBP-307 0.2 mg/day.

6.1.2. Allocation of subjects

In study stage 1, subjects will be randomly assigned to one of the following 2 groups in a 1:1 ratio:

- CBP-307 0.2 mg, once daily
- Placebo, once daily

In study stage 2, subjects included in sub-study 1 will continue treatment with the regimen used during stage 1. Subjects included in sub-study 2 will receive oral treatment with CBP-307 0.2 mg once daily after dose titration.

6.1.3. Blinding and blinding process

The study stage 1 is a randomized, double-blind, placebo-controlled clinical study, and sub-study 1 of the study stage 2 will aim at investigating the long-term safety and efficacy in subjects who have achieved clinical response in study stage 1 by continuing with the double-blind treatment. Sponsor, the clinical team entrusted by the CRO, the investigator, the clinical center's personnel involved in the study and the subjects do not know to which group subjects are randomly assigned throughout the study.

In case of an emergency, the investigator has the responsibility for determining if unblinding of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. Generally, sponsor must be informed of unblinding in advance, unless in urgent cases where unblinding is necessary for the medical treatment of the subject, sponsor must be notified within 48 hours after unblinding. The date and reason for unblinding must be entered into the clinical trial management database.

The investigator should not perform unblinding recklessly. If unblinding occurs, the subject's participation in the trial will be discontinued, but they should remain in the study for 4-week safety follow-up.

Sub-study 2 of the study stage 2 will be open-label treatment with a dose of 0.2 mg/day of CBP-307, so blinding process is not applicable.

6.2. Treatment regimen

Oral administration within half an hour after meal at 7:00~10:00 am every day. If possible, subjects should try to keep taking the drug at a similar time point every day.

Dose regimen of the dose titration period in the study stage 1

Subjects in CBP-307 group will undergo dose titration for 1 week while those in placebo group will undergo simulated titration. Both CBP-307 and placebo will be administered through the oral route. For subjects in the group of CBP-307 0.2 mg once daily, a dose of 0.05 mg CBP-307 will be given from day 1 to day 4; then, a dose of 0.1 mg CBP-307 will be given for later 3 days; from day 8, a target dose (0.2 mg) will be administered.

Detailed steps for dose titration are in Table 5.

Table 5. Titration dosing regimen

Target dose	Day 1 to day 4	Day 5 to day 7	From day 8
CBP-307 0.2 mg	0.05 mg	0.1 mg	0.2 mg
Placebo	Placebo capsules	Placebo capsules	Placebo capsules

Note: During the titration period, CBP-307 0.05 mg will be orally administered at doses of 0.05 mg (1 capsule) and 0.1 mg will be orally administered at 0.05mg (2 capsules); in the placebo group, placebo capsules at the corresponding quantity (completely identical with CBP-307 in appearance and weight) will also be orally taken. From day 8, in the 0.2 mg group, 2 capsules of 0.1 mg will be orally administered; and in the placebo group, 2 capsules of placebo (completely identical with CBP-307 in appearance and weight) will also be orally taken. The drugs taken daily will be sub-packaged in bottles in a GMP-compliant workshop, the investigational product will be independently packaged in boxes based on visit intervals.

Dose regimen of the dose titration in study stage 2

Subjects included in sub-study 1 of study stage 2 are no longer required to undergo dose titration. Subjects included in sub-study 2 (open-label treatment) of stage 2 will undergo 1-week dose titration. Dose titration involves administration of CBP-307 0.05 mg initiated on day 1 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.

Dose titration in the sub-study 2 of stage 2 are in Table 6.

Table 6. Administration regimen dose titration in study stage 2

Target dose	Day 1 to day 4	Day 5 to day 7	From day 8
CBP-307 0.2 mg/day	0.05 mg/day	0.1 mg/day	0.2 mg/day

Note: During the titration period, CBP-307 0.05 mg will be achieved with 1 capsule of 0.05 mg strength and 0.1 mg will be achieved with 2 capsules of 0.05mg strength; From day 8, 2 capsules of 0.1 mg will be administered. The drugs taken daily will be sub-packaged in bottles in a GMP-compliant workshop, the investigational product will be independently packaged in boxes based on visit intervals.

6.2.1. Cardiac monitoring during titration

In study stage 1, detailed schedule for cardiac monitoring during titration is provided in Table 7.

In the stage 2 sub-study 2, detailed schedule for cardiac monitoring during titration is provided in Table 8.

Table 7. Stage 1 Cardiac monitoring

	Cardiac monitoring											
	Titration **day 1**				Titration **day 2**				Titration **day 5 and day 8**			
Monitoring method	**Before administration**	**Every hour within the 6 h after administration**	**The 4th hour and 6th hour**	**Continuous monitoring for 24 hours**	**Before administration**	**Every hour within the 6 h after administration**	**The 4th hour and 6th hour**	**Continuous monitoring for 24 hours**	**Before administration**	**Every hour within the 6 h after administration**	**The 4th hour and 6th hour**	**Continuous monitoring for 24 hours**
Vital signs	X	X	X[3]		X	X	X[3]		X	X	X[3]	
12-lead ECG	X		X[3]		X		X[3]		X		X[3]	
Holter monitoring	X[1]			X[2]					X[2]			X[2]

Notes:

1. 24-hour Holter monitoring before day 1 will be initiated 1 day before drug administration (baseline day 0).
2. 24-hour Holter monitoring will be initiated from 30min ±10min before drug administration until 24 ho urs after drug administration.
3. Subjects still need further monitoring in the following cases:
   - at 6 hours after drug administration, the subject's heart rate is still < 45 times/min;
   - at 6 hours after drug administration, the subject's heart rate is still at the lowest level after drug administration;
   - at 6 hours after drug administration, 12-lead ECG shows newly-occurring second degree or higher degree atrioventricular block;
   - at 6 hours after drug administration, the QTcF interval is prolonged (> 450 ms in males; > 470 ms in females);
   - at 6 hours after drug administration, if the subject has symptomatic bradycardia, they will be monitored until it has resolved.

Table 8. Sub-study 2 of Study Stage 2 Cardiac Monitoring

	Cardiac monitoring											
	Titration **day 1**				Titration **day 2**				Titration **day 5 and day 8**			
Monitoring method	**Before administration**	**Every hour within the 6 h after administration**	**The 4th hour and 6th hour**	**Continuous monitoring for 24 hours**	**Before administration**	**Every hour within the 6 h after administration**	**The 4th hour and 6th hour**	**Continuous monitoring for 24 hours**	**Before administration**	**Every hour within the 6 h after administration**	**The 4th hour and 6th hour**	**Continuous monitoring for 24 hours**
Vital signs	X	X	X[3]		X	X	X[3]		X	X	X[3]	
12-lead ECG	X		X[3]		X		X[3]		X		X[3]	
Holter monitoring	X[1]			X[2]					X[2]			X[2]

Notes:

1. 24-hour Holter monitoring before day 1 will be initiated 1 day before drug administration.
2. 24-hour Holter monitoring will be initiated from 30min ±10min before drug administration until 24 hours after drug administration.
3. Subjects still need further monitoring in the following cases:
   - at 6 hours after drug administration, the subject's heart rate is still < 45 times/min;
   - at 6 hours after drug administration, the subject's heart rate is still at the lowest level after drug administration;
   - at 6 hours after drug administration, 12-lead ECG shows newly-occurring second degree or higher degree atrioventricular block;
   - at 6 hours after drug administration, the QTcF interval is prolonged (> 450 ms in males; > 470 ms in females).
   - at 6 hours after drug administration, if the subject has symptomatic bradycardia, they will be monitored until it has resolved.

6.2.2. Missing dose

Subjects should be informed that they can take a missed dose within 4 hours after the normal time for oral administration; otherwise they will need to take the drug of original dose at the normal time on the following day. If subjects experience vomiting after taking the capsules, they do not need to re-take the drug on the same day but need to take the drug at the original dose at the normal time on the following day. If subjects cannot take the drug due to other medical conditions, which leads to dose discontinuation, they are required to contact the investigator in time.

On occasions of missed doses:

- Within the first 2 weeks of treatment, if dose is missed for more than 1 day (2 to7 days interruption), the drug dosing needs to be restarted at the site and the first-dose monitoring procedures need to be repeated for subjects.

- After 2 weeks of treatment, if the dosing is missed no more than 2 days, subjects can take the original dose at the normal time on the following day; if the dosing is interrupted for 3 to 7 consecutive days, the drug will need to be restarted at the site with proper oversight. ECG will be performed before dose administration and at 4 and 6 hours after dose; vital signs will be monitored hourly. However, there will be no 24-hour Holter monitoring.

Subjects, except those who experience dose discontinuation due to a significant decrease in the peripheral lymphocyte count, will be required to withdraw from the study if the dose is discontinued for more than 7 days (see Section 8.6 for details).

6.3. Labeling and packaging of the investigational product

The investigational product will be provided by sponsor: Suzhou Connect Biopharmaceuticals Ltd.

The label of the investigational product will contain the following information:

- Statement that it is used for clinical study only
- Warning “Please keep out of reach of children”
- Sponsor's name and production address
- Drug name (a statement: “CBP-307 or Placebo”)

- Drug number
- Protocol No.
- Dosing instructions
- Storage condition
- Shelf life
- Batch No.

6.4. Distribution of investigational product

In study stage 1, the investigator or his/her designee will register subjects in an electronic data capture system (Medidata RAVE) at screening, complete randomization using the RAVE Randomization and Trial Supply Management (RTSM) system, and obtain random numbers in RAVE and dispense drugs accordingly. Before drug dispensing, a drug identifying number will be provided by the RAVE RTSM system and displayed in real time in RAVE, so that the study site's investigator or his/her designee is accessible to the identifying number. If the drug provided by sponsor is lost or damaged, the study site's investigator or his/her designee will complete drug replacement procedures on RAVE's interface. At visits for drug dispensing, the investigator or his/her designee will access the RAVE as the above to keep a record of drug dispensing and return.

Subjects who complete the study stage 1 and enter sub-study 1 of study stage 2 will receive double-blind maintenance treatment for 36 weeks (weeks 13-48) with the same regimen used in the stage 1. The approach to drug dispensing is the same as that in the stage 1. Subjects who complete study stage 1 and enter sub-study 2 of study stage 2 will enter open-label treatment with CBP-307 0.2 mg/day. Subjects, regardless of whether they receive CBP-307 0.2 mg or placebo in stage 1, will receive CBP-307 at an oral dose of 0.2 mg once daily in sub-study 2 of the study stage 2. Drugs for open-label treatment will be directly distributed by the investigator, and their ID numbers are entered into the RAVE.

Note: For the subjects already enrolled as per the previous approved protocols (version 5.0 or earlier), they will follow the previous planned treatment until they finish the study.

6.5. Accountability of investigational product and treatment compliance

6.5.1. Accountability of investigational product

CBP-307 capsules and placebo should be stored at controlled 2-8℃. The investigational product must be stored in a cabinet according to the storage conditions on the label. The cabinet

will be locked and managed by a specially designated person.

The study site's investigator or his/her authorized representative (such as a pharmacist) will ensure that the investigational product is stored in a safe area in accordance with the recommended storage conditions and regulations.

The investigator must keep a detailed accountability record containing the information on the receipt, use, loss, or other disposal of the investigational product. To maintain a complete record, all drugs will be described in detail in the drug quantity and inventory record, and at each visit, the drugs that are not used yet and returned by the subject will be counted.

After the end of the trial, sponsor will instruct how to dispose of the unused investigational product. If sponsor authorizes the study site to dispose of the drug, the investigator must ensure that the materials are disposed of in accordance with relevant regulatory requirements and the hospital's procedures, and then, disposal will be recorded well. At the end of the study, the subject cannot take the investigational product anymore.

6.5.2. Study treatment compliance

Study stage 1: At each visit (exclusive of visit 6, 8 and 10) from visit 4 (day 5) to the end of treatment (week 12), the study site will evaluate treatment compliance.

Study stage 2: The study site will evaluate treatment compliance at each visit from visit 13 (week 18) to the end of maintenance treatment (week 48) in sub-study 1. At each visit from visit 14 (day 5 of titration) to the end of treatment (week 48) during the study stage 2, the study site will evaluate treatment compliance.

Poor compliance is defined as when actual oral dose is less than 80% of the oral dose specified in the package insert or more than 120% of the specified oral dose. The investigator will decide whether the subject with poor treatment compliance should withdraw from the study. The investigator needs to record the condition of the subject with poor treatment compliance in the original medical record and the corresponding eCRF.

Throughout the study, the study site must strictly manage the investigational product until all drugs are returned to sponsor. Any discrepancies between the drug record and the drug inventory must be reported to sponsor.

6.6. Concomitant medication and treatments

6.6.1. Medications and treatments allowed to be used

Subjects can use the following medications at therapeutic doses:

- Oral 5-ASAs compounds (e.g., mesalazine, sulfasalazine, olsalazine, balsalazide) provided that these medications have been used for at least 6 weeks and with the dose stable for at least 2 weeks prior to randomization visit.

- Oral or IV corticosteroid therapy e.g. prednisone at a stable dose ≤ 30 mg/day, budesonide dose ≤ 9 mg, methylprednisolone dose ≤ 24 mg) or equivalent dose of steroid provided the corticosteroid treatment has been used for at least 4 weeks, with a stable dose for at least 2 weeks prior to randomization visit. The dose of corticosteroid should remain stable throughout the treatment period unless the subject experiences medical conditions causing failure to tolerate the original dose of corticosteroids or continued use of the original dose of steroids will pose significant risk to the subject in the opinion of investigators. After discussing with the medical monitor, the corticosteroid could be tapered according to the subject's condition and the reason should be recorded in detail in the medical document. All subjects included in study stage 2 who meet the criteria of tapering should start corticosteroids tapering. The detailed plan for tapering is shown in below section.

- If the dose of probiotics (such as Bifidobacterium and Saccharomyces boulardii) has been stable for 2 weeks prior to the first dose of the investigational product, then, probiotics can be used.

- Antibiotics used for UC treatment (i.e., ciprofloxacin and metronidazole), provided that their dose has remained stable for 2 weeks prior to the first dose of the investigational product.

Note: The dose of all medications above should be kept stable throughout the study.

Corticosteroids tapering

Sub-study 1 of the study stage 2: After subjects are included in sub-study 1 of the study stage 2, corticosteroids tapering should be initiated. The dose of oral 5-ASA must still be kept stable. The recommended schedule for corticosteroid tapering in the study is as follows:

- If the dose of prednisone is >20 mg/day (or equivalent), it is recommended to reduce the dose at a rate of 5 mg/week until the dose reaches 20 mg/day.
- If the dose of prednisone is ≤20 mg/day (or equivalent) or reduced to 20 mg/day (or equivalent), it is recommended to reduce the dose at a rate of 2.5 mg/week until drug withdrawal.
- The dose of budesonide should be reduced at a rate of 3 mg every 3 weeks

For subjects who cannot tolerate the corticosteroid taper without recurrence of clinical symptoms, corticosteroids may be increased up to the original dose at the beginning of

induction therapy (should not exceed baseline dose). In such cases, the tapering regimen above must be reinitiated within 2 weeks.

Sub-study 2 of the study stage 2: After subjects are included in sub-study 2 of the study stage 2 and complete dose titration, the investigator can decide whether to maintain the original dose or gradually reduce the dose of corticosteroids according to the subjects' treatment course and dose of corticosteroid. If subjects have achieved clinical response at week 24, corticosteroids tapering must be initiated. The recommended plan for such reduction is the same as above.

6.6.2. Prohibited medications and treatments

Precautions to be taken into account throughout the study:

- Subjects should not receive major surgery after participating in the study.
- Subjects should not donate blood, semen or oocyte samples during the study or within 4 weeks after the last dose of the investigational product.

The following drugs are prohibited during the study:

- Any other medications used to treat UC, including those that have been approved or are being developed (5-ASA drugs or glucocorticoids are allowed to be used, but their dose should maintain stable).
- Live vaccines, except the flu vaccine (during the treatment period and within 1 month after the last dose of the investigational product).
- Chronic nonsteroidal anti-inflammatory drug (NSAID) (note: occasional use of NSAID or acetaminophen for headache, arthritis, myalgias, menstrual cramps, etc., or low-dose aspirin [81-162.5 mg] for cardiovascular prophylaxis are permitted).
- The following drugs cannot be used in the study:
  - Treatment with medications with known impact on the cardiac conduction system and QT interval prolongation, and the second degree or higher degree atrioventricular block. A list of examples of prohibited cardiac medications is provided in Table 9.
  - Marketed biologic therapies such as abatacept, infliximab, etanercept, adalimumab, anakinra, rituximab and golimumab.
  - Immunosuppressants (e.g., azathioprine, 6-mercaptopurine or cyclosporine, methotrexate, tacrolimus, sirolimus or mycophenolate mofetil).
  - Any medication administered through the rectum for UC treatment, including enemas

(e.g., 5-ASA and corticosteroids), other than required for endoscopy preparation.

- Treatment with immunoadsorption column.
- Any investigational drug other than the study treatment.
- Intravenous immunoglobulin or therapeutic plasma exchange (TPE).
- D-penicillamine, leflunomide or thalidomide.
- Treatment with lymphocyte inhibitors (natalizumab, vedolizumab, fingolimod, ozanimod or etrasimod).
- Immunosuppressants that deplete lymphocyte (such as alemtuzumab, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone and daclizumab).

Table 9. Examples of Prohibited Cardiac Medications

Drug classification	Example of medication
β -blockers	Acebutolol, atenolol, betaxolol, bisoprolol, carteolol, metoprolol, nadolol, propranolol, sotalol and timolol
Calcium channel blockers	Diltiazem and verapamil
Antiarrhythmic drugs	Amiodarone, bepridil hydrochloride, disopyramide, dofetilide, dronedarone, flecainide, ibutilide, lidocaine, procainamide, propafenone, quinidine and tocainide
Drugs that prolong the QT interval	Citalopram (>20 mg/day), chlorpromazine, haloperidol, methadone and erythromycin

The investigator should record any use of concomitant medications in the original medical record and the corresponding eCRF, including the dose, specification, the route of administration, the date of administration, and the cause of administration. All information of prior medication related to UC treatment must be recorded, and the information of prior medication related to non-UC treatment within 60 days before screening must be recorded. For drugs containing a single active ingredient, their generic names should be recorded as far as possible. For drugs containing multiple ingredients, their brand names should be recorded. In addition, the daily dose should be recorded as far as possible.

6.7. Plan for trial termination

Sponsor has the right to terminate the study prematurely for safety reasons. In addition, sponsor has the right to terminate the study prematurely for management reasons. In any case, safety

follow-up should be ensured for all subjects who have entered the study. Any premature termination of the trial should be notified in writing to the Ethics Committee and relevant regulatory authorities.

7 STUDY ASSESSMENTS

For visit plan details refer to the Study Flow Chart (Study stage 1, sub-study 1 of the study stage 2, and sub-study 2 of the study stage 2 referring to flow chart Table 2, Table 3, Table 4 respectively).

7.1. General information

General information to collect will include demographics, family history, medical history, concomitant disease and treatments, a history of current medication use, and symptoms and signs related to the disease.

7.2. Efficacy assessments

7.2.1. Subject diary

Subject diary information will be collected using an electronic validation system for China and US sites only. For sites in other countries, subject diary information will be collected by paper subject diary instead. The investigator will dispense subject diaries at the screening visit and instruct subjects how to record information appropriately. Subject diaries need to be reviewed at all visits from baseline to last dose/early termination. The investigator should continually give sufficient instructions to subjects for them to properly complete the subject diary.

Subject diary will contain the following information:

- Frequency of "normal" bowel movements (during the improvement of ulcerative colitis or within 24 hours prior to the initial appearance of signs and symptoms of ulcerative colitis)
- Bowel movement frequency/day
- Blood in the stool
- Degree of abdominal discomfort
- General health
- Other discomforts
- Daily medication log

In each study stage, from study start to last dose/early termination, the study site will review the information recorded in the subject diary at each study visit. The most recent 3 consecutive days within the week before the visit should be used to calculate stool frequency and rectal

bleeding subscores for Mayo score calculation; and then, evaluation will be performed by the study site.

Because the colonoscopy preparation can interfere with the assessment, diary entries used to calculate the stool frequency and rectal bleeding subscores should not be taken from the day before (the preparation day), the day of, and the day after the colonoscopy is performed.

7.2.2. Colonoscopy

In study stage 1, colonoscopy will be performed to obtain a Mayo endoscopic subscore and a complete Mayo score and then determine subject eligibility within 14 days prior to randomization during screening period. Colonoscopy will also be performed at week 12 (or early termination). Besides, subjects who enter study stage 2 will undergo colonoscopy at week 24 (only for sub-study 2) and week 48 (or early termination visit).

To ensure data quality and standardization, each study site should examine with the same colonoscope throughout the clinical study wherever possible, and all the colonoscopic results will be centrally read and evaluated. All the colonoscopy examinations should be performed by a properly trained endoscopist to complete colonoscopy at each site, and the same endoscopist should be used for a certain subject throughout the study wherever possible. If impossible, it is required to record the exact name of the endoscopist responsible for each colonoscopy.

For the information on requirements for colonoscopy and evaluation by the central reader, see the relevant operating document.

7.2.3. Mayo score

The Mayo score is a standard, widely accepted, quantitative assessment of UC severity in subjects. The Mayo scores range from 0 to 12 and consist of 4 subscores, each ranging from 0 to 3 (shown below). 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. Findings on Endoscopy

   0 = Normal or inactive disease

   1 = Mild disease (erythema, decreased vascular pattern)

   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 subject 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 will serve to acknowledge the 3 other criteria, and the physician will record the subject's daily abdominal discomfort and general sense of well-being and other observations, such as physical examination findings and the patient's performance status.

7.2.3.1 Complete Mayo scores

Complete Mayo scores will be calculated based on data in the above items 1, 2, 3, and 4 (stool frequency, rectal bleeding, endoscopic findings, and physician's global assessment). Evaluation of the complete Mayo score will be performed at the visit at screening and week 12

(or early termination visit) during study stage 1 as well as at week 24 (only for sub-study 2) and week 48 (or premature withdrawal from study visits) during the study stage 2.

7.2.3.2 Adapted Mayo score

Adapted Mayo score will be calculated based on the above items1, 2 and 3 (stool frequency, rectal bleeding, endoscopic findings). The adapted Mayo score will be calculated at the visit at screening and week 12 (or early termination visit) during study stage 1 as well as at week 24 (only sub-study 2) and week 48 (or early termination visit) during study stage 2.

7.2.3.3 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 data in the items 1, 2, and 4 of section 7.2.3 (stool frequency, rectal bleeding, and physician's global assessment).

7.2.4 Inflammatory bowel disease questionnaire

The Inflammatory Bowel Disease Questionnaire (IBDQ) (see Annex 1) is a psychometrically validated patient self-assessment scale used to measure the disease-specific quality of life in patients with inflammatory bowel diseases including UC. IBDQ contains 32 items related to four aspects: Bowel Systems (10 items), Emotion Health (12 items), Systemic Systems (5 items) and Social Function (5 items). The 4 aspects are scored as follows:

- Bowel Systems (10-70)
- Emotion Health (12-84)
- Systemic Systems (5-35)
- Social Function (5-35)

Subjects will be asked to recall symptoms and quality of life from the last 2 weeks and rate each item on a 7-point Likert scale (higher scores equate to higher quality of life). A total IBDQ score will be calculated by summing the scores from each domain. IBDQ is used as an endpoint of the study and will be completed by the subjects themselves.

7.3. Safety assessments

Safety assessments involves vital signs, physical examination, pulmonary function tests, ophthalmologic examination, OCT, Holter monitor, 12-lead ECG, laboratory tests (hematology test, blood chemistry test, urinalysis, and coagulation test), as well as monitoring of AEs in all

subjects after drug administration.

To ensure the health of subjects, the investigator will review the data from each subject throughout the study.

7.3.1. Chest X-ray examination

Chest X-ray taken within 3 months prior to screening could be accepted. If no chest X-ray has been taken within 3 months before screening, a chest X-ray examination will be performed at the screening visit.

7.3.2. Vital signs

Vital signs include the heart rate (HR), blood pressure (BP, including systolic blood pressure and diastolic blood pressure), body temperature and respiratory rate. Evaluation of vital signs are scheduled to be performed according to Table 2, Table 3 and Table 4 (the study flow chart).

At screening and baseline, HR and BP need to be measured after at least 5 minutes rest in supine position.

During study stage 1 and sub-study 2 of the study stage 2, when obtaining the predose HR and BP on titration day 1, the subject should rest in the supine position for at least 5 minutes before measurement to ensure the accuracy of the baseline measurement. In case the cuff sizes available does not match the subject's upper arm circumference, a sphygmomanometer with an appropriately sized cuff can be used instead. The repeat HR and BP measurements will be made at 2-minute intervals. The lowest predose value of supine HR and BP (based on the systolic BP) should be taken as the baseline measure and used for comparison to postdose values. Orthostatic blood pressure will then be measured once with the subject in the upright position (after standing for 2 minutes). A sudden, significant fall in BP (> 20 mmHg) at 2-5 minutes after standing from the supine position will be considered as orthostatic hypotension and will be documented in the subject chart and eCRF.

Post-baseline HR and BP need to be measured after the subject has been supine for at least 5 minutes. Any clinically significant changes from baseline values should be confirmed by repeated measurement. Post-baseline blood pressure in the upright position will be measured in the same way (at 2 minutes after standing). If there is a significant decrease in blood pressure (> 20 mmHg) at 2-5 minutes after standing from the supine position to the upright position, it is considered as orthostatic hypotension and is to be recorded in the subject's medical record and eCRF.

7.3.3. Physical examination

All abnormal findings during screening must be documented in the original medical record and the eCRF to report the relevant medical history/current condition of disease. Important findings after randomization that meet the definitions of AEs must be documented in the original medical record and the AE of eCRF.

A complete physical examination should involve the evaluation of the neck/thyroid, chest/lung, heart, lymph nodes, abdomen, nervous system, etc., the overall examination of the skin and extremities, and the detection of possible visual abnormalities (e.g., blurred vision or decreased visual acuity) in subjects.

The height and body weight should be measured when the subjects take off its heavy clothes and shoes, the height should be in centimeter and rounded off, and the body weight is in kilogram (kg) and accurate to one decimal place.

Nervous system physical examination

Nervous system physical examination will be performed by the investigators by actively query about nervous system symptoms such as cephalgia, convulsions, confusion, vision loss, speech disturbances, facial drooping, weakness, problems with coordination, gait and sensory loss, and mental impairment. If any of the above symptoms appear, a neurology consult would be ordered for further assessment, and extra examinations including CT scanning, MRI examination and other related tests will be conducted by neurologists' judgment.

7.3.4. Pulmonary function test

Pulmonary function tests include FEV_1, FVC, and diffusing capacity of the lung for carbon monoxide (DLCO). Specialized equipment is required to measure DLCO; therefore, this test will only be conducted at sites that have, or have access to, the right facilities. The pulmonary function tests will be conducted in a qualified pulmonary function laboratory or respiratory department.

7.3.5. Dermatology examination

Dermatology examination includes a thorough examination of skin injuries and limbs. It is mainly aimed at excluding suspected lesions of basal cell carcinoma. Dermatology examinations should be completed in the department of dermatology for following visits: screening visit and day 84 ±3 (12 weeks) visit in study stage 1; weeks 24 and 48 during sub-study 1 of the study stage 2; weeks32 and 48 during sub-study 2 of the study stage 2. Dermatology examinations at other visits can be performed by the investigator: weeks 4, 8 and

16 during study stage 1; weeks 40 and 52 during sub-study 1 of the study stage 2; weeks 16 and 52 during sub-study 2 of the study stage 2.

7.3.6. Ophthalmologic examination

Ophthalmologic examination will check for visual abnormalities (for example, blurred vision or decreased visual acuity) in subjects and needs to be performed in the department of ophthalmology.

When optical coherence tomography (OCT) shows suspected macular edema, it is required to perform a complete retinal examination including collecting history of eye diseases, visual acuity check, and dilated fundus examination. During the study, if an ophthalmologic examination finds visual abnormalities (e.g., blurred vision or decreased visual acuity), then, additional OCT can be performed. All subjects diagnosed with macular edema must discontinue the drug and withdraw from the study.

7.3.7. 12-lead ECG

Subjects cannot undergo 12-lead ECG measurement before having rested in the supine position for at least 10-15 minutes.

7.3.8. Holter monitoring

Holter monitoring will start at least 30 min prior to drug administration and last until at least 24 hours after drug administration. Subjects will remain in a supine position prior to Holter monitoring. Holter analysis parameters will be described in detail in the operating document.

7.3.9. Monitoring of concomitant treatment

The use of concomitant medications and procedures will be monitored throughout the study. Except the investigational product, any other medications used will be regarded as concomitant medication. These medications could be prescription drugs prescribed by doctors or over-the-counter drugs purchased by subjects. At each visit during the period from the subject signs the informed consent form to the end of the study, the investigator will ask the subject whether he/she has used any other medication besides the investigational product. All medications (including vitamin preparations, over-the-counter medicines, and Traditional Chinese Medicine preparations) need to be recorded in the original medical record and the e-CRF. Concomitant treatment prohibited in the protocol is shown in Section 6.6.

7.3.10. Monitoring of AEs and SAEs

Throughout the study, the investigator will do his/her best to closely monitor the occurrence of

AEs and SAEs. See Section 8.1 for the definition of an AE/SAE and relevant follow-up and reporting. For AEs of special interest, please refer to Section 7.5.

7.3.11. Safety laboratory parameters

In the study, all samples except the PK blood sample will be analyzed in the central laboratory (Q Squared Solutions).

It is required to collect blood samples according to the Table 10 below. Details involving sample collection, transportation, results reporting, as well as laboratory reference ranges and abnormalities warning will be specified in the laboratory manual and provided to each study site prior to the initiation of the study.

This protocol clearly specifies the time points for collecting blood, urine and fecal samples (Table 2, Table 3, Table 4). To evaluate safety, the investigator can decide to conduct unscheduled laboratory tests at any time during the study.

Table 10. Safety Laboratory Parameters

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 chemistry (fasting)	
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, parasite ovas and parasites, and fecal calprotectin
Others	
Virological and serological tests	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.

1. Abnormal laboratory parameters or potential medical condition inconsistent with the clinical manifestations of UC should be repeatedly measured. At any visit 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 be fasting for 9 hours before a laboratory test.
3. If urinalysis shows occult blood or abnormal urine protein in subjects' urine samples, a microscopy examination needs to be performed. A microscopy examination will mainly focus on the presence of white blood cells and red blood cells. All other parameters will be tested with test strips.
4. Fecal culture/microscopy (including fecal culture, C. difficile, parasite ovas and parasites) is required to be performed at screening. During the screening period and at any time point during the study, if the subject has symptoms including aggravation of the disease condition or recurrence of previous disease activity, stool samples can be collected for fecal culture/microscopy and C. difficile analysis.
5. Women of childbearing potential are required to take a pregnancy test (including blood β-human chorionic gonadotropin and urine pregnancy test). At screening, postmenopausal women with amenorrhea for <5 years are required to undergo measurement of follicle stimulating hormone to confirm postmenopausal condition.
6. Subjects with documented evidence of previously successfully treated TB accompanied with negative Quantiferon or Quantiferon Plus test result at screening can be enrolled in the study. If Quantiferon or Quantiferon Plus test result is indeterminate at screening, it could be retested during screening period. If Quantiferon or Quantiferon Plus retest result is indeterminate, 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.

The investigator must assess clinical significance for all abnormal laboratory test results, including the clinical significance of each abnormal value in the source document of the subject. The laboratory test results will be submitted with the subject's source document. Any diagnosis related to abnormal findings (or presenting symptoms or signs in case a diagnosis cannot be made) should be recorded in the medical record and the AE page of eCRF.

7.4. Pharmacokinetics/pharmacodynamics assessment (Applicable only for study stage 1)

7.4.1. Pharmacokinetics

To measure the concentration of CBP-307 in plasma and its metabolic characteristics in plasma,

the investigator will ask subjects whether they are willing to participate in a PK study. Subsequently, blood will be collected from the PK subgroup. Approximately 90 subjects will be scheduled to enter the PK subgroup for sparse sampling, and plasma samples will be collected at the following time points:

- 15-30 minutes before administration and 4-6 hours after administration at week 1 (day 1 and day 5), week 2 (day 8), week 4 (day 28), week 8 (day 56) and week 12 (day 84).
- 1-2 hours after administration at week 1 (day 1 and day 5) and week 4 (day 28).

Three mL venous blood will be collected from upper limb at each time point of blood sampling.

During the study, approximately 45 mL blood will be collected from each subject who participates into PK analysis subgroup for PK evaluation. See separate laboratory manual for specific procedures of blood collection, storage conditions and transport instructions.

The plasma concentration of CBP-307 will be measured by Frontage Laboratories (Shanghai) Co. Ltd. Results will be presented in biological analysis report.

Actual collection time of each blood sample and all information relevant to blood collection and handling have to be recorded on eCRF.

Blood sample handling and transport

The following information should be clearly indicated for plasma samples:

- Protocol No.
- Subject No.
- Theoretical sampling time point
- No. 1 or 2 blood sample

Contents on sample label cannot be erased. Samples 1 and 2 collected from each sampling time point (to be separately sent by post) should be sent to the designated central laboratory under dry ice conditions. Before completion of the clinical study report, all remaining samples will be stored at ≤ -70℃, and can only be destroyed after sponsor acknowledges the final clinical study report.

7.4.2. Pharmacodynamics and biomarker evaluation

Biomarkers of UC activity include various substances detected in the blood, urine or feces that are associated with intestinal inflammation, clinical symptoms, and disease status. Biomarkers in this study include CRP and fecal calprotectin. Pharmacodynamic indicators include absolute

number of lymphocytes and total Igs.

The blood collection points for biomarker evaluation are shown in Table 1, 2 and 3. Details involving sample collection, transportation, results reporting, as well as laboratory reference ranges and abnormalities warning will be specified in the laboratory manual and provided to each study site prior to the initiation of the study.

7.4.2.1 Peripheral blood lymphocyte count

The lymphocyte count as a maker of the pharmacodynamic effect will be derived from hematology test results. The PK subgroup is required to undergo measurement of lymphocyte counts (used for the PD study) at all time points for the collection of PK blood samples. According to Table 1, if there are corresponding hematology tests at the time points for the collection of PK blood samples, such as before and 4-6 hours after dose on day 1, it is not necessary to collect additional PD blood samples, otherwise it is required to collect PD blood samples simultaneously. In the non-PK subgroup, lymphocyte counts used for the PD study will be obtained from hematology tests, so it is not necessary to collect additional PD blood samples. Samples will be tested by the central laboratory. See Table 1 and the laboratory manual for details.

7.4.2.2 Total immunoglobulins

Measurements of total immunoglobulins in blood samples (including IgA, IgG and IgM) will be completed by the central laboratory at screening, week 12 and week 48.

7.4.2.3 C-reactive protein

C-reactive protein is induced by interleukin-6, tumor necrosis factor, and other pro-inflammatory cytokines produced in the intrinsic membrane of the intestine. It is an acute-phase protein that can be used as an objective indicator for the evaluation of inflammatory activity. The half-life of CRP is short (19 hours), so CRP level rises in the early stage of the onset of inflammation and then drops rapidly after inflammation resolves.

In this study, a CRP test will be completed by the central laboratory according to the study flow chart, Table 1, 2 and 3.

7.4.2.4 Fecal calprotectin

Fecal calprotectin is a calcium and zinc binding protein with a molecular weight of 36,000 Daltons. It is derived from neutrophils and accounts for 60% of the cytoplasmic proteins in granulocytes. Fecal calprotectin is confirmed to be a measure of the migration of neutrophils into the gastrointestinal tract. Fecal calprotectin is a very stable marker (stable for 1 week at

room temperature).

Fecal calprotectin testing will be completed by the central laboratory at screening, week 12, week 24 (only for sub-study 2 of the study stage 2) and week 48.

7.5. Monitoring of adverse events of special interest

During the study on CBP-307, AEs caused by S1P1 receptor stimulation that were found in previous clinical studies on other similar drugs will be closely monitored. These AEs include:

a. Bradycardia and cardiac conduction abnormalities: It was reported that the adverse reactions caused by the first dose of similar drugs mainly included reversible bradycardia, first grade atrioventricular block and sinus arrest. Reduced heart rate is an expected adverse reaction to S1P1 agonists. These negative chronotropic effects of S1P1R agonists appear to attenuate over time after S1PR desensitization and internalization into cardiac myocytes. This effect appears to occur with increasing exposure to study drug; thus, gradual titration of the dose of CBP-307 within 1 week may mitigate against larger reductions in heart rate.
b. Pulmonary toxicity: An initial sharp decrease followed by slow progressive decline over time in FEV_1 was observed in clinical studies of the same category of drugs. In this study, FEV_1 and FVC in all subjects will be measured; DLCO will be measured in sites that are equipped with the right facilities. Each subject with abnormal pulmonary function test results will be followed up. If the subject's pulmonary function test results (FEV_1 and/or FVC) fall below 50% of the predicted values, treatment should be discontinued immediately, and appropriate clinical follow-up (for at least 3 months) should be performed until the resolution is confirmed or no further aggravation is expected by investigator.
c. Hepatotoxicity: fingolimod caused frequent, reversible liver enzyme elevations greater than 3-fold above the ULN in up to 12% of patients. In the completed phase I clinical study on CBP-307, ALT levels slightly increased in individual subjects but were all below 3 times the ULN; and this side effect was also milder than that of fingolimod. In this study, blood chemistry analysis will include measurement of LFT levels. Subjects with abnormal LFT levels will be continuously followed up until the LFT values returns to the normal/baseline level.
d. Macular edema: In the preclinical and clinical phase I studies of CBP-307, no eye-related toxicity was observed yet. In this trial, OCT examination will be included. Subjects with macular edema must discontinue the investigational product and undergo examinations including a dilated fundus examination. Every subject whose ophthalmic evaluations reveal abnormalities will be followed until values return to baseline.
e. Opportunistic infection or severe infection: Tuberculosis, serious bacterial infections, systemic fungal infections, viral infections such as herpes infections (including herpes

zoster and disseminated herpes simplex) and protozoal infections during the study should be reported as AESI.

f. Basal cell carcinoma: In a 2-year placebo-controlled clinical study on fingolimod (a similar drug), the incidences of basal cell carcinoma are 2.0% in the group treated with fingolimod 0.5 mg and 0.1% in the placebo control group, respectively. Subjects should be observed for suspected skin lesions, and a specialist assessment should be performed immediately if any suspected skin lesions are noted.
g. Posterior reversible encephalopathy syndrome and progressive multifocal leukoencephalopathy.

The following steps should be followed:

a. At every visit, vital signs should be measured in the supine position.
b. Subjects will be closely monitored in the clinic after their first dose of the initial dose titration regimen for a period of 6 hours after administration. ECGs will be performed predose and at 4 and 6 hours after drug administration, with more frequent assessments as clinically indicated. Vital signs will be measured before administration and at every hour in 6 hours after administration. During titration period, continuous overnight cardiac monitoring should be performed in patients who experience symptomatic bradycardia that requires pharmacologic intervention. In these patients, the first-dose monitoring strategy will continue the following days until the symptoms improve by investigator's assessment, even if the study drug is discontinued. If anyone has prolonged QTc interval during 6-hour observation after dosing, repeated cardiac monitoring in the following days will be conducted until the abnormity improves.
c. Prior to drug administration in the clinical study, clinicians should pay attention to subjects with a lower heart rate (occurring spontaneously or being induced by β-blockers) at baseline. Atropine IV is recommended as the first line therapy for bradycardia, with a daily maximum dose of 3 mg. Furthermore, the common guidelines for treatment of bradycardia (e.g., Advanced Cardiac Life Support-ACLS guidelines) should be followed as appropriate:).
    - In case of clinical symptoms or hypotension, give subjects atropine 1 mg and repeated doses within 3-5 minutes.
    - If the heart rate and/or blood pressure remain unresponsive, consider administration of dopamine drip 5-20 μg/kg/min or epinephrine drip 2-10 μg/min can be given.
    - Performance Transcutaneous pacing can also be considered.
    - In the condition of decreased blood pressure, isoproterenol should be avoided or used with caution.
d. If there is any condition that may affect the pulmonary function test results (FEV_1, FVC, and DLCO), including infections, respiratory symptoms, occupational exposure (including asbestos) and smoking, it is required to collect information and document it in

the eCRF before each pulmonary function test. If the subject's pulmonary function test results (FEV_1 and/or FVC) fall below 50% of the predicted values, the investigational product treatment should be discontinued. If a subject discontinues due to respiratory AE, the investigator should ensure that the subject has adequate evaluations as clinically indicated by a pulmonologist (consider PFTs, chest X-ray or high-resolution computed tomography, based on findings of the other examinations) at the time of the AE. For subjects with pulmonary nodules, lung biopsy should be taken into account. Follow up the subject (for at least 3 months) until a resolution is confirmed or no further aggravation or improvement is expected by investigators.

e. If the subject's LFT (ALT or/and AST) is elevated and greater than 3 times the ULN, a retest should be performed within a week. Upon confirmation of the abnormality, retests should be performed weekly until the elevated LFT decreases below 3 times the ULN. If the LFTs increase is confirmed to be above 5 times the ULN the study drug must be permanently discontinued.
f. All subjects diagnosed with macular edema must discontinue the investigational product. Based on the judgment by the ophthalmologist, follow up subjects with macular edema monthly or more frequently if needed. Follow up the subject (for at least 3 months) until a resolution is confirmed or no further aggravation or improvement is expected by investigators. If the subject does not show definite signs of improvement on examination 6 to 8 weeks after discontinuation of study drug, then therapy for macular edema in conjunction with an ophthalmologist experienced in the management of this condition should be initiated.
g. Examination of the skin for lesions will be performed as part of the physical examination at screening and at the end of study. If skin lesions are noted, the subject will be referred to a dermatologist for evaluation and follow-up care.
h. Nervous system physical examinations are required for each visit, and the investigators should actively query about nervous system symptoms such as cephalgia, convulsions, confusion, vision loss, speech disturbances, facial drooping, weakness, problems with coordination, gait and sensory loss, and mental impairment. If any of the above symptoms appears, a neurology consult would be ordered for further assessment, and extra examinations including CT scanning, MRI examination and other related tests will be conducted by neurologists' judgment.

8 DEFINITION, MONITORING AND REPORTING OF A SAFETY EVENT

All AEs will be managed and reported in accordance with applicable regulations. If an AE occurs, the first thing that needs attention is the safety of the subject. If necessary, the subject needs to be treated accordingly. AEs will be summarized in the final clinical study report.

The informed consent form signed by the subject should include the name of the investigator

and the contacts used to report AEs and medical emergencies.

8.1. Adverse event

8.1.1. Definition and recording of adverse events

Definition: An adverse event refers to any untoward medical occurrence that occurs after the subjects signs the ICF, which does not necessarily have a causal relationship with the investigational product. Thus, an AE can be any unfavorable and unintended symptom, sign, disease or condition, or an abnormal test finding, whether or not it is related to the investigational product. AEs include:

- Symptoms described by the subject, or signs observed by the investigator, and
- Abnormal findings (involving laboratory tests, ECG, and an X-ray) that result in changes in medical care (diagnostic or therapeutic).
- Exacerbation of chronic or intermittent pre-existing diseases, including increased incidence and/or diseases severity.

An abnormality found at screening visit is not an AE unless it has reappeared after disappearance or is worsened during the trial.

Note: Regarding a heart rate decrease (bradycardia) and decreased lymphocyte count in peripheral blood in this study, please report them as follows:

- Since a decreased lymphocyte count in peripheral blood is due to the mechanism of action of the drug, it itself is not to be reported as an AE. However, clinical diagnosis related to a decreased lymphocyte count in peripheral blood indicates AE reporting (if no diagnosis is available, it is required to report related clinical symptoms or signs).
- The heart rate decrease (bradycardia) in this study is defined as a heart rate of <50 beats per minute in the awake state or a heart rate of ⩾50 beats per minute in the awake state whereas subjects experience clinical symptoms due to a reduced heart rate (if subjects have a heart rate <50 beats per minute in the awake state and need clinical treatment, such condition is considered a grade II AE).

In this study, AE data will be collected after subjects sign informed consent forms, and AEs will be persistently monitored throughout the study, i.e., until 28 days after the last dose.

The investigator will ask the subject at each follow-up visit if any AE has occurred since the last visit. All AEs will be recorded in medical records and eCRFs, including the AE terms, severity of AEs, the start date and time of occurrence, the stop date and time of occurrence, seriousness (i.e., whether it is a SAE), CTCAE grade, the relationship to the investigational product, actions taken on the investigational product, medications/treatments given, and outcomes of AEs. Once a written ICF is signed by the subject, the investigator will start recording the AE until 4 weeks after the last dose.

Outcome of an AE:

- Death: end of life as the result of the AE.
- Unrecovered/unresolved: subjects fail to recover, or an AE is not improved.
- Recovering/resolving: subjects are recovering, or an AE is improving.
- Recovered/resolved: subject has recovered or an AE has been resolved.
- Recovered/resolved with a sequela: an AE has been resolved, but subjects have been left with symptoms or pathological manifestations.
- Unknown: no detail, not observed, not recorded, or refusal to provide relevant information.

8.1.2. Grading of adverse events

All AEs in the trial will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. NCI CTCAE is originally a standard term designed to report AEs that occur during cancer clinical trials. CTCAE contains a grading scale representing the severity of an event, from grade 1 to grade 5.

- Grade 1: mild; asymptomatic or mild symptoms; clinically or diagnostically observed; no intervention required.
- Grade 2: moderate; indicating minimal local non-invasive intervention; instrumental activity of daily living corresponding to age is restricted (applicable to AEs involving metabolism, nutrition and immunity).
- Grade 3: a severe or medically important event, but not immediately life-threatening; resulting in hospitalization or prolonged hospital stay; disability; restriction of self-care activity of daily living.
- Grade 4: a life-threatening consequence; indicating emergency treatment.
- Grade 5: deaths related to AE.

Note: The CTCAE provides specific grading scales for abnormalities shown in a laboratory test. Grade 4 abnormality shown by a laboratory test does not automatically represent a life-threatening event. An abnormal result shown by a laboratory test still needs to be evaluated before it is determined whether such result is an AE or not.

The safety data from the ongoing trial will be submitted to the medical monitor for review.

8.1.3. Determination of causality between adverse events and investigational product

According to the categories below, a causal relationship between the AE and investigational

product will be evaluated as definitely related, possibly related, unlikely related and not related. A drug-related AE is defined as an AE that is definitely related or possibly related.

- Definitely related: the type of an AE has been identified as a known type of reaction to the investigational product and cannot be explained by other reasons, such as concomitant medications or comorbidities. The time of occurrence of an event strongly suggests a causal relationship (e.g., based on the outcome following drug withdrawal and restart).
- Possibly related: an AE occurs with a reasonable time sequence to the administration of the investigational product, indicating that the occurrence of such AE may be caused by the investigational product. The possibility that the AE is caused by other factors, such as a concomitant medication or comorbidity, cannot be ruled out. The drug is not withdrawn or re-administered orally.
- Unlikely related: no evidence shows a causal relationship between the occurrence of the event and the investigational product. The occurrence of the AE is more possibly related to other factors, such as a concomitant medication or comorbidity. There is a negative or ambiguous reaction after drug withdrawal. However, the relation between the drug and the event cannot be ruled out.
- Not related: the subject does not take the investigational product; the occurrence of the AE is not consistent with the time sequence of administration; or such event can be caused by other significant factors.

The investigator should re-assess the causal relationship based on subsequent follow-up information and update the corresponding AE/SAE report as required.

8.2. Serious adverse event

8.2.1. Definitions of serious adverse events

An SAE is any adverse medical event that meets any of the following criteria at any dose:

- Results in death;
- Life-threatening;
  Note: "life-threatening" refers to the risk for death in the subject at the time when an event occurs. It does not mean that a more serious event may cause death.
- Hospitalization or prolongation of existing hospitalization is required.

Note: Generally, hospitalization means that due to adverse medical events, subjects receive unscheduled observation and/or treatment (not indicated in outpatient clinics) in the hospital's inpatient department (going through the hospitalization procedure) or emergency wards (usually, subjects need to stay there for at least 24 hours for observation). A complication that

appears during hospitalization is an AE; if the complication prolongs hospitalization or satisfy any other serious criteria, the event is serious. If hospitalization or extended hospital stay is not related to an AE, it is not within the scope of reporting. For example:

a. Previous illness indicates hospitalization for examination or selective treatment, no new AE occurs, and also, the previous disease does not get worse;
b. Hospitalization for observation not due to relevant AE, e.g. for social and/or convenience;
c. Hospitalization required by the study procedure as indicated in the protocol;
d. Scheduled hospitalization not due to relevant AE, such as scheduled elective surgery;

- Results in persistent or significant disability/incapacity;
- Congenital anomaly or birth defects;
- Important medical events: These AEs may not be immediately life-threatening or result in death, or hospitalization, but may jeopardize the subject and needs intervention to prevent the occurrence of any of the above consequences. These important medical events include intensive treatment in the emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or drug dependence or drug abuse.

8.2.2. Reporting and follow-up of serious adverse events

SAEs will be collected after subjects sign the informed consent form and throughout the entire study, i.e., until 28 days after the last dose of investigational product.

For any SAEs in the study, whether related to investigational product or not, the investigator should provide timely emergency treatment, and must immediately (within a maximum of 24 hours after becoming aware of the event) inform the sponsor or its designee, and complete the SAE Report Form following specific completion instructions. In the meantime, the investigator should record the SAE in the medical records and eCRF in a timely manner. The investigator must provide causality assessment when reporting SAEs.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

For all SAEs, the investigator needs to conduct follow-up until subjects recover, have stable condition or returns to baseline condition, and provide detailed follow-up information. The timeline and procedure for the follow-up report are the same as the initial report, namely, the investigator should report any follow-up information about the SAEs within 24 hours after awareness.

Regarding follow-up:

- The investigator needs to take appropriate measures to protect the safety of the subject, and it is particularly required that each subject with AEs (abnormal clinical signs, laboratory test results, or others) should be followed up until he/she returns to normal or has stable condition.
- Subjects experiencing SAEs must be followed up until they recover clinically, return to normal or have stable condition. This may require follow-up visits after subjects leave the study and require additional investigation by sponsor.

The original report in written form should be presented in time with details, including a copy of the hospital medical record, a discharge summary, autopsy report (if applicable) and other necessary documents.

8.3. Reporting of adverse events of special interest

In a phase I clinical study on CBP-307 conducted in Australia, potential risk for cardiovascular events was observed in the high-dose group (treated with a dose more than 10 times the therapeutic dose to be administered in this study). Besides, in the post marketing studies of the marketed S1P1 agonist fingolimod and other clinical studies of S1P1 agonists, other potential safety risks were also observed, including pulmonary toxicity, hepatotoxicity, macular edema, severe and opportunistic infections, and skin tumors. Although these potential risks were not observed in the phase I clinical study of CBP-307, special attention is still needed in this study. AEs that require special attention include (see Section 7.5 for detail):

a. bradycardia and cardiac conduction abnormalities: significant bradycardia (heart rate $\leq$ 45 beats/min), Mobitz type II or third degree atrioventricular block, and other significant cardiac conduction abnormalities,
b. pulmonary toxicity: difficulty in breathing and clinically significant wheezing, and
c. hepatotoxicity: e.g., two consecutive liver function tests in a subject suggesting elevated liver enzymes, AST or ALT > 3 times the ULN, or other clinically significant liver dysfunction.
d. Macular edema
e. Opportunistic infection or severe infection: tuberculosis, serious bacterial infections, systemic fungal infections, viral infections such as herpes infections (including herpes zoster and disseminated herpes simplex) and protozoal infections.
f. Malignant neoplasm of skin

All AEs of special interest specified in the protocol (see Section 7.5) have to be reported to sponsor and CRO, regardless of seriousness and relationship to the investigational product.

- For events conforming to the requirements of SAE, report according to expedited reporting procedures for SAE (see Section 8.2);
- Regarding an event that does not meet the criteria for a SAE, it is only needed to be recorded in the eCRF.

8.4. Follow up of subjects with adverse events/serious adverse events

The investigator should closely monitor every subject experiencing an AE, including monitoring the clinical changes in the subjects. The investigator needs to proactively follow up each subject and provide sponsor and CRO with more detailed information about AE/SAE. During the study, all AEs/SAEs should be followed up until resolved, stabilized or returned to baseline status, unless the investigator believes that given the subject's underlying condition, there is little hope that the AEs/SAEs will be resolved.

8.5. Handling of abnormal laboratory test results

If the laboratory test data is abnormal and cannot be explained, the test should be repeated immediately. If retest confirms that a result is abnormal and clinically significant, it should be recorded as an AE (except a decreased lymphocyte count, see Section 8.1 for details).

8.6. Clinical laboratory parameters and abnormal laboratory test results

Regarding major abnormal changes in laboratory parameters, which are judged by the investigator to be clinically significant, they will be recorded as AEs (except a decreased lymphocyte count, see section 8.1.1 for details).

During treatment, both the total white blood cell count and the white blood cell classification data is blinded.

If any of the following results are observed, the investigator will need to repeat the test:

- Absolute lymphocyte count $< 0.2 \times 10^9$/L
- Absolute neutrophil count $< 1.0 \times 10^9$/L
- Total white blood cell count $> 20 \times 10^9$/L

If the value of the repeated test also exceeds the above numerical limit, the investigator should be informed of the abnormal results of the subject.

If the absolute lymphocyte count or total white blood cell count is determined to be below an acceptable threshold, the medical monitor will contact the investigator responsible for treatment to ask him/her to closely monitor the event that may lead to serious infection and to follow up the subject appropriately.

If the absolute lymphocyte count is < 0.2 $\times 10^9$/L, the subject should temporarily discontinue the investigational product. The absolute lymphocyte count should be retested every 3 days. If the retest result shows that the lymphocyte count rises to > 0.5 $\times 10^9$/L, the investigator will be informed that the value is within the acceptable range, and the investigational product can be restarted (the statement of investigational product restart after interruption is shown in Section 6.2). If the lymphocyte count could not return to at least 0.5 $\times 10^9$/L after 2 weeks, the investigator should discuss with sponsor and the medical director of CRO whether subjects can continue participating in the study.

Bradycardia

The results of the completed phase I clinical trial showed that at clinically relevant dose levels, heart rate decrease was observed on the first two days of single and multiple dosing. This effect on heart rate was observed in other S1P1 modulators. Given that this is due to the mechanism of action of the drug, the AE of heart rate decrease (bradycardia) in this study is defined as a heart rate of <50 beats per minute in the awake state or a heart rate of ≥50 beats per minute in the awake state whereas subjects experience clinical symptoms due to a reduced heart rate (if subjects have a heart rate <50 beats per minute in the awake state and need clinical treatment, such condition is considered a grade II AE). In the completed Australian Phase I clinical study, it was defined that a heart rate of < 45 beats per minute in the awake state was required to be reported as an AE, and this adverse event does not serve as a criterion for termination of the trial/treatment.

Reduction of peripheral blood lymphocyte count

The results of the completed Australian Phase I clinical trial indicate that at clinically relevant dose levels, the drug may reduce the peripheral blood lymphocyte count, which is the efficacy indicator of the drug. It itself is not to be reported as an AE. However, clinical diagnosis related to a decreased lymphocyte count in peripheral blood indicates AE reporting (if no diagnosis is available, it is required to report related clinical symptoms or signs).

Reduction of peripheral blood lymphocyte count

A reduction in the peripheral blood lymphocyte count directly leads to a reduction in the WBC count.

Note: In this study, heart rate decrease (bradycardia), a reduction in the peripheral blood lymphocyte count and a reduction in the peripheral WBC count (a reduction in the peripheral blood lymphocyte count directly leads to a reduction in the WBC count) are not considered as criteria for termination of the trial/treatment.

8.7. Treatment of overdose

Overdose refers to the oral administration of the drug in any CBP-307 group at a dose higher than that required in the protocol. Any overdose, whether AEs occur or not, should be reported to sponsor/CRO. Because the effect of CBP-307 on the heart rate is directly related to the dose, subjects should be fully informed of the risks caused by an overdose, which should be contraindicated. If subjects experience an overdose in the study, they should immediately contact the investigator for an ECG test, heart rate monitoring and even emergency observation. Generally, an overdose event will not be recorded as an AE, but in cases where an overdose may be related to an AE, it should be recorded in the medical record and the AE/SAE page of eCRF.

8.8. Pregnancy report

Pregnancy in itself is not considered an AE/SAE unless it is suspected that the investigational product has affected the efficacy of a contraceptive. However, any adverse pregnancy outcome (e.g., stillbirth, spontaneous abortion, fetal malformation) is considered a SAE and needs to be reported in accordance with the requirements for SAE reporting.

Within 24 hours after being informed of pregnancy of a subject or a subject's partner, the investigator should notify sponsor/CRO monitor and complete a pregnancy report form. Subjects should stop taking the investigational product immediately if pregnant. The investigator is required to follow up the outcome of the pregnancy and make records in the pregnancy report forms.

9 DATA MANAGEMENT AND STATISTICAL ANALYSIS

9.1. Data management

In this study, the study data will be documented in the eCRF, and the data management solution will be provided by the CRO.

9.2. Determination of 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 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.

9.3. Statistical analysis plan

Details of the statistical methods will be provided in the statistical analysis plan (SAP) according to the study protocol.

Statistical analysis will be conducted using SAS® 9.4 or higher version (SAS Institute Inc., Cary, NC, USA).

9.4. Randomization

Subjects meeting all inclusion/exclusion criteria will be randomized into the study stage 1 and stratified according to whether the previous treatment with a tumor necrosis factor (TNF)-α antagonist failed. Sub-study 1 of the study stage 2 will include subjects who have achieved clinical response to 12-week induction therapy in study stage 1 as shown by efficacy evaluation and meet eligibility criteria for the study stage 2: they will undergo blinded maintenance treatment with the regimen used during the stage 1. Sub-study 2 of the study stage 2 will include subjects who have no clinical response to induction therapy in the stage 1 and meet eligibility criteria for the study stage 2: they will undergo open-label treatment with CBP-307 0.2 mg once daily.

9.5. Analysis population

Statistical analysis will include the following populations:

Stage 1 analysis populations

All Subjects Screened in stage 1: The all subjects screened set will contain all subjects who signed informed consent for stage 1.

All Randomized Set in stage 1: The all 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 FAS will contain all randomized subjects who receive at least 1 dose of study medication or placebo in stage 1. FAS will be based on the planned drug taken.

Per-Protocol Set (PPS) in stage 1: The PPS will contain a subset of FAS subjects who do not have major protocol deviation in stage 1.

Safety Set (SS) in stage 1: The SS will contain all randomized subjects who receive at least 1 dose of study medication or placebo. SS will be based on the actual drug taken.

PK analysis set: The PK analysis set will include all subjects who has both baseline and post-baseline PK evaluation.

Stage 2 analysis populations

All Subjects 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 FAS will contain all screened subjects who receive at least 1 dose of study medication or placebo in stage 2. FAS will be based on the planned drug taken.

Per-Protocol Set (PPS) in stage 2: The PPS will contain a subset of FAS subjects who do not have major protocol violation in stage 2.

Safety Set (SS) in stage 2: The SS will contain all randomized subjects who receive at least 1 dose of study medication or placebo in stage 2. SS will be based on the actual drug taken.

Efficacy analysis will be performed in the FAS and PPS according to treatment assignment. Safety analysis will be performed based on the SS. According to the SAP, data locking and primary analysis methods will be predefined by project statisticians (summarizing results in a blinded fashion).

9.6. Demographic and baseline data

Demographic data and baseline data will be summarized.

9.7. Subjects treatment

The subject treatment should be summarized.

9.8. Efficacy analysis

9.8.1. Study endpoints

Primary study 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.

Secondary study endpoints

The secondary efficacy endpoints include:

- Change in adapted Mayo score from baseline at week 12 compared between CBP-307 0.1 mg and placebo
- Change in complete Mayo score from baseline at week 12 after treatment
- Comparison of clinical response rate at week 12 by adapted Mayo score (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)
- Comparison of clinical response rate at week 12 by complete Mayo score (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)
- Comparison of clinical remission rate at week 12 by adapted Mayo score (defined as a rectal bleeding subscore = 0 and stool frequency sub score ≤ 1, with an Endoscopy subscore ≤ 1 [excluding friability])
- Comparison of clinical remission rate at week 12 by complete Mayo score (defined as a total Mayo score of ≤ 2 points with no individual subscore > 1 point)
- Mucosal healing rate at week 12 after treatment (mucosal healing is defined as Mayo endoscopic subscore ≤ 1)

Exploratory study endpoint

Exploratory endpoints include:

- Changes in the total IBDQ score and subscore from baseline at week 12 after treatment (in study stage 1), at week 24, and week 48 (in study stage 2) after treatment
- To explore the following efficacy endpoints in subjects with moderately to severely active UC who respond after 12 weeks of induction therapy in study stage 1:
    - Percentage of subjects who maintain clinical response at week 48

- Percentage of subjects who achieve clinical remission at week 48
- Percentage of subjects who achieve mucosal healing under endoscope at week 48
- Percentage of subjects who take corticosteroids orally at baseline and discontinue the treatment with corticosteroids at week 48 and achieve clinical remission.
- Change in the complete Mayo score at week 48 from baseline
- Change in the adapted Mayo score at week 48 from baseline

- To explore the following efficacy endpoints in subjects with moderately to severely active UC who do not achieve response after 12 weeks of induction therapy in study stage 1:
  - Percentage of subjects who achieve clinical response at week 24 (at week 12 after treatment in sub-study 2 of study stage 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 complete Mayo score at week 24 (at week 12 after treatment in sub-study 2) from week 12
  - Change in the adapted 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 after 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

9.8.2. Efficacy analysis

9.8.2.1 Analysis for primary study endpoints

The primary efficacy analysis will be based on FAS and PPS. The primary efficacy analysis will be performed after all subjects complete (or possibly complete) the treatment with the investigational product.

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.

9.8.2.2 Analysis for secondary study endpoints

For all categorical secondary efficacy endpoints, their statistical summaries need to be made based on the treatment group: number of cases, percentage, and 95% confidence interval. The stratified Cochran-Mantel-Haenszel (CMH) χ^2 test will be used with a 95% confidence interval for the difference in each category of rates.

For the quantitative secondary efficacy endpoints, the statistical method is similar to that for primary efficacy endpoint.

All secondary efficacy analyses will be performed between treatment groups (0.2 mg, 0.1 mg) and placebo and based on FAS and PPS. All results of these comparative analyses are used for exploratory purpose. More details of analyses are provided in the SAP.

9.8.2.3 Analysis of exploratory study endpoints

The content about exploratory analysis will be detailed in SAP.

9.9. Pharmacokinetic analysis

PK data will be analyzed using PK analysis set based on individual CBP-307 concentration-time curve data collected to PK (Section 9.5).

Listing and descriptive statistics will be used to summarize the CBP-307 individual plasma concentration at each sampling point, including arithmetic mean, minimum, median, maximum, standard deviation, coefficient of variation. Moreover, scatter plot (linear/semilog) will be provided for the CBP-307 plasma concentration at each sampling point. In addition, descriptive statistics of concentration of blood medicine valley (C_{min}) will be performed by arithmetic mean, geometric mean, median, reference range, standard deviation and coefficient of variation. Details will be provided in the statistical analysis plan (SAP). If other PK parameters have to be calculated, details will also be provided in SAP.

In cases where the data are sufficient, a population pharmacokinetic (PopPK) analysis of the plasma concentration-time profile of CBP-307 will be performed based on existing data from other clinical trials. In addition, the PK parameters of CBP-307, such as the apparent clearance and apparent volume of distribution, will be estimated using a model. If a PopPK analysis can be performed, more details will be specified in PopPK SAP, and the analysis results will be described in a separate report.

9.10. Pharmacodynamics and biomarker analysis

Exploratory analysis on dose-effect relationship of exposure quantity (dose) and safety of CBP-307, efficacy and pharmacodynamics is performed for the first time. The relationship between CBP-307's efficacy and the changes in the following indicators will be evaluated:

- Absolute lymphocyte count
- Total Igs: IgA, IgG, IgM
- CRP
- Fecal calprotectin

In cases where the data are sufficient, an exploratory PK/PD analysis will be conducted for the relation between the exposure to CBP-307 and indicators of its efficacy (such as a change in the absolute lymphocyte count from baseline). The studies will be described in SAP.

9.11. Safety analysis

AEs will be summarized based on their severity and their relationship to the investigational product. SAEs will be recorded. The incidence of each event will be summarized. If the same subject experiences the same AEs more than once, only the worst-case severity will be counted. When an event related to the investigational product occurs, it is only recorded once. Laboratory data, vital signs, ECG, and pulmonary function tests data are listed in the summary table.

9.12. Missing data

For the analysis based on FAS for the quantitative efficacy endpoints, the Last Observation Carried Forward (LOCF) imputation will be applied for missing data. For the analysis based on PPS for these endpoints, no imputation will be applied for missing data.

In the trial, the endoscopic score of the clinical center will be used as the Mayo score to assess clinical efficacy. The endoscopic score read by the investigator will be used as the SES-CD score in the event of loss of data from one major endoscope.

For all secondary categorical efficacy endpoints, subjects who have no data at a specific time point will be considered as non-responders.

The effect of missing data on the efficacy evaluation results will be studied through the sensitivity analysis of the primary and secondary efficacy indicators, including completed events, observed events, and multiple model-based analysis.

Methods for calculating some or all missing data regarding time will be explained in SAP.

9.13. Interim analysis

One interim analysis 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 unblinded study team will carry out the analysis on primary efficacy endpoint after database lock. The primary efficacy endpoint is the change in adapted Mayo score from baseline at week 12 compared between CBP-307 0.2 mg and placebo in stage 1 while the stage 2 analysis will be exploratory, and no α reserved for stage 2. Exclusive of primary efficacy analysis in stage 1, all other comparative analysis results of the treatment groups and the placebo group are used for exploratory purpose.

9.14. Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) will be responsible for monitoring data of this study, including the main aspects of the study implementation process.

The IDMC will meet regularly during the study trial to monitor enrollment of subjects into the treatment groups, treatment compliance, compliance with follow-up plans, and safety data of the study. It may propose to amend or terminate the study based on the safety concerns during study data review. It will also review the primary efficacy indicators and give recommendations based on efficacy results and safety.

The double-blinded plan of this study will be clearly clarified to the IDMC to ensure that relevant information is blinded to sponsor and study personnel.

10 DATA QUALITY ASSURANCE

The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF. The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Sponsor has the obligation of ethical, legal and scientific to carry out this study in accordance with the established clinical trial protocol, GCP and ICH-GCP guidelines. In order to fulfill these obligations and achieve study progress, in addition to ensuring telephone and written communication, sponsor's monitor or representative will visit the study site throughout the study. Sponsor's monitor or representative will conduct site monitoring visit, making calls, and do regular eCRF review, to evaluate subject enrollment, study protocol compliance, and integrity and accuracy of data entered into EDC system, and conduct source data verification and AE checking according to the original documents. Investigator must provide the monitor with all resources and study documents.

10.1. Electronic case report form

The eCRF will be used to save and record subject information. Sponsor or other representative will provide the file structure and format of the eCRF and record according to the corresponding rules.

The investigator should review, sign and date the eCRF.

The eCRF access permission should be strictly protected and should be provided to only those directly involved in the study. The study data should be entered into the eCRF by qualified personnel or study coordinators. After study assessments, relevant information should be recorded into the eCRF as soon as possible. If data needs to be modified due to entry errors or any other reasons, there will be a corresponding electronic audit trail. The monitoring agency and other regulatory departments must have access to the eCRF and the computer where the eCRF is saved.

10.2. Data collection

At each visit, the study site will record all important observations of each subject. These records should contain at least the visit date time and the scheduled visit time on the study flow sheet (e.g., at screening, day 0, etc.); the overall status and important indicators of the subjects, including any important medical findings; severity, frequency, duration and coping methods of the reported AEs, and information whether these events are judged by the investigator as a drug-related AE; concomitant medications or dose changes; main reference for completion of procedures; and signature and date of medical data recording by all physicians.

In addition, any agreement to provide important clinical information, reached by telephone or other means, will also be recorded in the medical records (progress notes) as described above.

The information recorded on the medical records (progress notes) and other original documents will be entered into the eCRF.

Modifications to the medical records (progress notes), eCRF, and other original documents should be signed & dated by the investigator or appointee. If there is no significant reason for these modifications, an explanation should be attached to these modifications.

10.3. Monitoring and source data review

The monitor designated by sponsor will conduct regular on-site monitoring of the study site to

monitor all aspects of the clinical trial. If required, the investigator must agree to give the personnel authorized by sponsor a direct access to clinical (or related) documents clinical trial supplies (drug distribution & storage areas) to validate data entered in the eCRF.

In addition to monitoring visits, the monitor will make frequent communications (by letter, phone and fax) to ensure that the study is carried out according to the protocol design and regulatory requirements.

Monitoring will be carried out as determined by the risk assessment process conducted on the study.

10.4. Audit and inspection

Domestic and foreign regulatory agencies, ethic committees, and auditor/inspector authorized by sponsor may request direct access to all original documents, case report forms and other study documents for on-site audits or inspections. The investigator must ensure auditor/inspector direct access to these documents and support audits or inspections at any time. During audits or inspections, if the subject name has been blacked out to make it confidential, it will be allowed to copy medical records and other study documents.

The audits or inspections are made to assess whether the clinical trial meets ethical, regulatory and quality requirements.

10.5. Storage of original documents and records

The original documents include the original observation records and the clinical study results. The original documents include but are not limited to medical records (progress notes), computer printouts, screening logs, and data recorded by automated instruments.

The investigator cannot destroy any study records unless he/she obtains the written approval from sponsor.

Study records must be saved in accordance with the ICH-GCP and local guidelines. All necessary documents, including subject records, original documents, eCRF, and certificates about storage of the investigational product, will be archived. Source documents should be retained for at least 2 years after obtainment of the last approval for marketing in the ICH regions and until no pending or anticipated application for marketing in the ICH regions; or at least 2 years after the clinical development of the investigational product is officially stopped, however, sponsor may request an extension of the retention period due to international regulations or country-specific requirements.

11 TRIAL MANAGEMENT

11.1. Protocol compliance or deviations

The dosing date and time of investigational product and any deviations from any protocol procedure need to be recorded in the subject's eCRF.

11.2. Publication policy

The investigator can work with sponsor to make preparation for the publication of the study related content after the study is completed. Without written consent from sponsor, the investigator must ensure that no data of the study is published.

11.3. Clinical study report

The final clinical study report will be prepared according to the ICH guidelines. The report submitted to each regulatory authority should comply to the language and format requirements of that regulatory authority. The final study report must be prepared no matter whether the study is completed or prematurely terminated. Sponsor will provide each investigator with a final study report for archiving.

11.4. Contract and financial details

Prior to the beginning of the study, the investigator must disclose to sponsor any property right or financial interest he/she has related to the investigational product or sponsor’s company, as shown in the financial disclosure form provided by sponsor. The investigator must agree to update this information if significant changes occur during the study or within 1 year after study ended. The investigator also must agree that sponsor can submit this financial information to a domestic or foreign regulatory agency to apply for a marketing approval if required by laws or regulations.

If required by regulations, sponsor will also submit the financial arrangements for the study to the regulatory agencies.

Co-investigators who are authorized by the investigator to perform important study responsibilities should provide similar information.

11.5. Insurance, compensation and remuneration

The provisions on responsibilities and insurance of this study are given in a separate agreement.

Sponsor has already signed an insurance contract, whose terms and conditions involve compensation for injuries that the subjects suffer from in this study that is executed in strict accordance with the study protocol and applicable laws and professional standards.

11.6. Clinical trial termination

Sponsor has the right to terminate the study. In view of assurance of the subject's best interests and medical & ethical considerations, the study can be prematurely terminated at any time, with the consent from the investigator and sponsor. When the study is terminated, sponsor, CRO, and the investigator will ensure that the subject's interests are protected.

11.7. Management of study site documents

The investigator is responsible for the management of investigator site file. The investigator site file include but not limited to, Investigator's Brochure, eCRF (sample form), clinical study agreement (signed), clinical study-related normal values for lab tests, shipping orders for the investigational product and study-related materials, updates to Investigator's Brochure, updates to normal values for medical or lab tests or operations, mid-term or annual reports, investigator signature samples, and other documents (updates to the protocol, eCRF, ICF, written notifications).

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13 ANNEXES

ANNEX 1 INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

INSTRUCTIONS FOR SELF-ADMINISTERED IBDQ

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

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

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

EXAMPLE

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

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

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

QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

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

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

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

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

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

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

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

IBDQ

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

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

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

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

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

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

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

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

IBDQ

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

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

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

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

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

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

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

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

IBDQ

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

IBDQ

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

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

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

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

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

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

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

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

IBDQ

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

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

ANNEX 2: AMENDMENTS TO THE STUDY PROTOCOL

Version No.	**Version Date**
2.0	19 Apr 2018
3.0	24 Jul 2018
3.1	17 Sep 2018
4.0	10 Apr 2019
5.0	17 Dec 2019
6.0	25 Dec 2020

Electronic Signature Manifestation

This page is a manifestation of the electronic signature(s) used in compliance with the organization's electronic signature policies and procedures.

Signer Full Name	Meaning of Signature	Date and Time
Boran Zheng	Document Approval (I certify that I have the education, training and experience to perform this task)	05 Jan 2021 07:27:50 UTC