TITLE: A Phase II randomized, placebo controlled, double-blind, 4 arms dose-ranging study to evaluate the efficacy and safety of SHR0302 compared to placebo in patients with moderate to severe active Ulcerative Colitis.

Compound Number : SHR0302
Compound Name :
Protocol number : RSJ10101
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Author (s) : [redacted]

Rivision History

Version Number	Version Date	Summary of Changes
v1.1 12NOV2018	12NOV2018	Original Protocol
v2.0 16APR 2019	16APR 2019	Amendment No.01 Number the inclusion and exclusion criteria. Refine the Chinese translation of "……and allow central over read turn over before randomization" as inclusion criteria to clarify the central reading result for endoscopy need to be ready before randomization. Clarify subjects who had inadequate response, loss of response or intolerance to conventional treatment (immune-suppressants or corticoserioids) could be included, whether the subjects previoulsy exposed to biological therapy or not. Clarify the definition of treatment naïve subjects in exclusion criteria. Correct the typos to claify the exclusion criteria for biological therapy use, "subjects receiving interferon therapy within 12 weeks prior to baseline and anti-TNFα therapy/other biological therapies within 12 weeks prior to baseline" will be excluded, instead of 8 weeks, in order to keep consistency with Section 5.2 Inclusion Criteria. Clarify subjects with hematopoietic disorders at screening should be excluded. Correct the typos in Table 1 in Section 5.12 Time and Event Table, and the footnotes to ensure the procedures are consistent with subject selection criteria. Clarify chext X-ray to be performed if no chest X-ray or CT scan available within 3 months of Visit 1 instead of 6 months in footnote 2. Typo correction to clarify the follow up visit is not a phone-call contact and clarify any SAEs will be recorded from the time of consent in footnote 7. Allow T-Spot as an alternative test for TB infection screening. Clarify only serum β-Human Chorionic Gonadotrophin (β-HCG) is requested for pregnancy testing at screening visit and urine test is to be done from baseline. Clarify concurrent medication assessment should be done in Follow up/EW visit, in order to keep consistent with Section 6.6 Concomitant Medications. Clarify the early withdrawal visit should

Version Number	Version Date	Summary of Changes
		be done within 2 weeks after last dose/decision of withdrawal rather than after 2 weeks of last dose/decision of withdrawal in footnote 11. FSH test is listed in the table to confirm postmenopausal status at screening. Provide oral steroids tapering guidance in Section 6.6.1 Permitted Concomitant Medications and refine the Chinese translation of oral steroids permission Remove the time period of "within baseline", to clarify the prohibition is throughout the duration of the study to avoid confusion in Section 6.6.2 Prohibited Medications. And add live vaccines immunization as prohibited mdications. Clarify that the images/video clips of endoscopy will be sent to central lab for central reading in Section 7.2.5 Mayo Score Assessment. Refine the Chinese translation of the intervals of 3 ECGs in Section 7.3.2, to clarify "Triplicate ECG measurements are collected at rate of 3 ECGs with 5 minutes between each.". Allow T-Spot test as an alternative test for TB infection screening according to local availability in Section 7.3.4 QuantiFERON test/or T-Spot test. And provide the guidance on initial QFT-G/or T-Spot is indeterminate. Correct typos in Table 3 in Section 7.3.5 Clinical Laboratory Testing. Update the reference.
v3.0 30JUL2019	30JUL 2019	Amendment No.02 Update Section 4.1 Study Design, Section 4.2 Discussion of the design and Section 5.12 Time and Event Table, to revise the screening period to -28 days to -1 day prior to baseline, based on the feasibility of the clinical procedure in each country. Update Section 5.2 Inclusion Criteria, to clarify the subjects deemed by the treating physician as having

Version Number	Version Date	Summary of Changes
		inadequate response, loss of response or intolerance to the conventional treatment include subjects with previous exposed to oral 5-ASA only. Clarify oral corticosteroids as permitted medications during study treatment is not applicable to subjects with previous 5-ASA treatment only. List the detailed discontinuation time prior to baseline of the biological treatment according to its half life. Clarify the definition of treatment naïve patients according clinical practice in the Section 5.3 Exclusion Criteria. Update the discontinuation time prior to baseline of interferon therapy to 8 weeks. In conjunction to the inclusion criteria regarding the requirement of discontinuation of biologicals, remove related requirement in exclusion criteria. Clarify the subjects with clinically significant infections or within 1 month of baseline instead of 6 months, will be excluded. Remove the requirement regarding to household contact with vaccinated individuals during study in exclusion criteria. Update Section 6.6.1 Permitted Concomitant Medications, clarify dose of steroids can be reduced at the discretion of the investigator if subject develops intolerance or significant saftey concerns to the oral steroids dose during the treatment phase. Update Section 7.3.10 Pregnancy, clarify the pregnancy occurs after first dose must be reported and the newborn should be followed up to 1 month after birth as pregnancy outcome.
v3.1 20AUG2020	20AUG2020	Update safety related features according to the FDA's recommendation. This includes safety related inclusion/exclusion criteria in Section 5.2, subject stopping criteria in Section 5.9, Adverse Event of Special Interest (AESI) in Section 7.3.15. These are to protect subject safety according to the new safety advice by the FDA.

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_____ **Date** _____

INVESTIGATOR PROTOCOL AGREEMENT PAGE

Protocol RSJ10101
I confirm agreement to conduct the study in compliance with the protocol.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: _____

_____ _____
Investigator Signature Date

Table of Contents

LIST OF ABBREVIATIONS

AUC	Area Under the Curve
AV	Atrioventricular
CD	Crohn's Disease
β-hCG	Beta-human Chorionic Gonadotropin
CI	Confidence Interval
Cmax	Maximal Plasma Concentration
CRF	Case Report Form
CRP	C-Reactive Protein
EW	Early Withdrawal
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
IB	Investigator's Brochure
JAK	Janus Kinase
IBDQ	Inflammatory Bowel Disease Questionnaires
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IND	Investigational New Drug
IRB	Independent Review Board
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
IUD	Intra-Uterine Device
LDH	Lactate Dehydrogenase
LLoQ	Lower Limit of Quantification
Mcg	Micrograms
MedRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
PP	Per Protocol
PPD	Purified Protein Derivatives
RA	Rheumatoid Arthritis
RAP	Reporting and Analysis Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SPM	Study Procedures Manual
SRC	Safety Review Committee
Tlast	Time of the Last Quantifiable Concentration
UC	Ulcerative Colitis

ULN	Upper Limit of Normal

1. Protocol Summary

1.1 Rationale

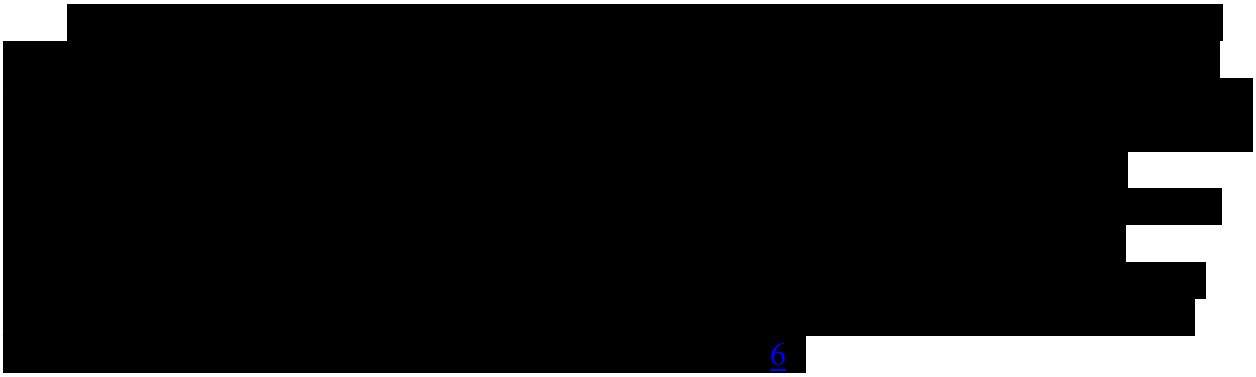
Ulcerative Colitis (UC) is a debilitating disease resulting in high morbidity and severely affect patients' quality of life. Patients with UC will experience periods of remission and flare up. It is a disease affecting the colon, characterized by altered bowel habit, bloody diarrhea, abdominal pain, weight loss and anaemia. The prevalence of UC is about 200/100,000 in the west compared to 50-60/100,000 in China or Japan. Its incidence has been higher in the West compared to the East. However, over the last decade, the prevalence has increased in the East. (1) The cause of UC remains unknown; it is thought to be closely linked to autoimmunity to large bowel mucosal. (2) UC can develop at any age, but peak incidence is between the ages of 20 and 30 years. It mainly affects the rectum, and a variable extent of the colon proximal to the rectum. Inflammation of the rectum is referred to as proctitis, and inflammation of the rectum and sigmoid as proctosigmoiditis. Symptoms of active disease or relapse include bloody diarrhoea, an urgent need to defaecate and abdominal pain.

Currently the only way to "cure" the disease is by total colectomy which is not without its risk and complication. The treatment goal in UC is to induce response in those in active stage and to continue maintaining remission, ultimately ensuring patients have minimal symptoms and good quality of life. Over many decades, these were achieved by applying oral and intravenous immune-suppressants. Conventional immune-suppressants treatments include oral glucocorticoids, mesalamine, and methotrexate. The introduction of biological treatment nearly two decades ago such as, anti-TNFα, a IgG monoclonal antibody has changed the treatment paradigm for moderate to severe UC over the last decide and has now become a gold standard. However, its use is still limited by its cost in some regions.

The understanding of cytokines and intracellular messenger pathway in UC has led to the discovery of Janus Kinase (JAK) enzymes, and their role in the activation of Signal Transducers and Activators of Transcription (STATs) via auto phosphorylation (3). The JAK-STATs pathway regulates the signaling of various interferon and interleukin which are implicated in the pathogenesis of UC. By blocking this pathway, it is thought that this immune-regulated inflammation could be halted, hence controlling the disease (4).

There are a number of Janus kinase (JAK) inhibitors currently under investigation for the treatments of immune-induced diseases, such as Rheumatoid Arthritis (RA), Psoriatic Arthritis, Psoriasis, Ulcerative Colitis, Crohn's Disease, and Ankylosing Spondylitis. These JAK inhibitors can be given orally, which could be an advantage compared to the intravenously given biological treatments. There is also an advantage of not having the risk of developing loss of response due to immunogenicity.

Tofacitinib, a 'pan-JAK inhibitor', blocking JAK3 and JAK1 and to a lesser extent JAK2 has been approved in the US for the treatment of RA. It has recently been approved for the treatment of Ulcerative Colitis in the US. Other JAK inhibitors with varying JAK selectivity profiles have already shown to be efficacious in RA, and some are under investigation for Ulcerative Colitis and Crohn's Disease indication. While inhibition of JAK1 and JAK3 contributed to the efficacy of RA treatment, inhibition of JAK2 may contribute to the safety concerns of anemia, and thrombocytopenia, by interfering with signaling through erythropoietin, thrombopoietin and colony-stimulating factors such as granulocytemacrophage colony-stimulating factor (5).



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1.2Objectives

The primary objective is to evaluate the efficacy of SHR0302 at 4mg once daily (QD), 8mg QD, and 4mg twice daily (BD) given orally compared to placebo in inducing clinical response in adult subjects with moderate to severe active Ulcerative Colitis at 8-week.

1.3 Study Design

This is an 8+8 weeks, randomized, double-blind, multi-center, placebo controlled, parallel group study to include adult patients with moderate to severe active Ulcerative Colitis. The study consists of an 8-week blinded treatment phase, followed by 8-week of blinded active arms extension phase. The primary endpoint is assessed at the end of treatment phase at week 8.

Eligible subjects will be randomized to either one of the 3 doses of active drugs or placebo in 1:1:1:1 ratio for 4mg QD, 4mg BD, 8mg QD and placebo group respectively for treatment phase. The total number of subjects to be randomized is 152. There will be a total of 9 outpatient clinic visits. Subjects randomized into placebo in treatment phase will also have a pre-assigned randomized treatment sequence for extension phase, which are 3 active groups (placebo -> 4mg QD, placebo -> 4mg BD, and placebo -> 8mg QD) in a 1:1:1 ratio. Subjects randomized to the active arms for treatment phase will remain in the same dose group in the extension phase.

At Visit 1 (screening), subject will be screened and if the subject meets the inclusion/exclusion criteria, the subject can be consented and enrolled into the study with a subject identifier number.

At Visit 2 (Day 0), subject will be randomized into the study if there is no further change to subject's criteria.

After randomization, the subject will be followed-up at week 1, week 4, and week 8, corresponding to Visit 3, Visit 4, and Visit 5 at treatment phase respectively. At Visit 5 (week 8) the primary endpoint assessment will be conducted. Following this treatment phase, subjects have the option to enroll into a further 8 weeks of active arms extension phase.

All subjects that have completed the initial 8 weeks (non-responders or responders) have the option to enter a blinded active arm 8-week extension phase according to the group they were randomized to for extension phase. All subjects have the option not enrolling into the extension phase after first 8 weeks of treatment. All subjects in the extension phase are followed-up for further 2 weeks until week 18 (last visit). Subjects who have completed the first 8-week of treatment phase, but decided not entering into extension phase are required to attend the 2-week follow-up visit. Early withdrawn subjects during the first treatment phase cannot enter the extension phase.

The total duration of the study participation, including extension and follow-up, will be approximately 18 weeks.

1.4 Study Endpoints

1.4.1 Primary Efficacy Endpoint

The percentage of subjects that achieve clinical response at week 8, defined as decrease from baseline in 9-point modified Mayo score of at least 2 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or absolute subscore for rectal bleeding of 0 or 1.

(Mayo Score is a scoring system designed to measure UC disease activity. It consists of 4 subscore, stool frequency, rectal bleeding, endoscopy score - findings of centrally read colonoscopy, and physician global assessment (PGA). Each graded from 0 to 3 with higher scores indicating more severe disease. These scores are summed up to give a total score from 0 to 12, where higher score indicate more severe disease.

9-point modified Mayo score is the Mayo score excluding physician global assessment (PGA)subscore, hence the maximum is 9 points and minimum 0 point

Partial Mayo score is the Mayo score excluding endoscopy subscore, hence the maximum is 9 points and minimum 0 point)

1.4.2 Secondary Efficacy Endpoints

- The percentage of subjects that achieve clinical remission per 9-point modified Mayo score at week 8, where stool frequency subscore ≤ 1, rectal bleeding subscore of 0, and endoscopic subscore ≤ 1
- The percentage of subjects that achieve clinical remission at week 8 as per total Mayo score of 2 points or lower than 2, with no individual subscore exceeding 1point and a rectal bleeding subscore of 0.
- The percentage of subjects that achieve endoscopic remission (mucosal healing) at week 8, defined by Mayo endoscopic subscore ≤ 1 point.
- Change from baseline in 9 point modified Mayo score at week 8.
- Change from baseline in total Mayo score at week 8.
- Change from baseline in partial Mayo score (Mayo score without endoscopy) at week 1, 4, 8, 9, 12 and 16.
- Change from baseline in the level of biomarkers CRP, faecal calprotectin.
- The systemic exposure of SHR0302 in steady state in Ulcerative Colitis patients (i.e. concentration and area under the curve).

1.4.3 Safety Endpoints

- To evaluate the safety and tolerability by laboratory parameters.
- To evaluate the safety and tolerability by collection of AE/SAE incidence
- To measure vital signs (blood pressure (BP), heart rate (HR), and body temperature)
- To measure subject's total lipid profile, which includes Triglyceride, LDL and HDL.
- To measure subject's thyroid profile: TSH, fT4 and fT3.
- 12 –lead ECG

2. Introduction

2.1 Background

Ulcerative colitis is an autoimmune disease resulting in the chronic inflammation of colon mucosal characterized by relapsing–remitting pattern. UC is a lifelong disease that is associated with significant morbidity. It can also affect patient's social and psychological wellbeing, if poorly managed. Current medical approaches focus on treating active disease to address symptoms, to improve quality of life, and thereafter to maintain remission. The treatment chosen for active disease is likely to depend on clinical severity, extent of disease and the patient's preference, and may include the use of aminosalicylates, corticosteroids or biological drugs. These drugs can be oral or topical (per rectum), and corticosteroids may be administered

intravenously in people with acute severe disease. Currently the only way to "cure" the disease is by total colectomy – the removal of the entire colon. This is a major surgery which carries risk and complications. Surgery is often reserved for those not responding to drug treatment.

The treatment goal in UC is to induce and maintain remission. Conventional treatments include oral glucocorticoids, mesalamine, and methotrexate. The introduction of biological treatment such as, anti-TNFα, a IgG monoclonal antibody has changed the treatment paradigm for moderate to severe UC over the last decade and has now become a gold standard. However, its use is still limited by its cost in some area.

The understanding of cytokines and intracellular messenger pathway in the pathophysiology of Ulcerative Colitis has led to the discovery of Janus Kinase (JAK) enzymes, and their role in the activation of Signal Transducers and Activators of Transcription (STATs) via auto phosphorylation. The JAK-STATs pathway regulates the signaling of various interferon and interleukin which are implicated in the pathogenesis of UC. By blocking this pathway, it is thought that this immune-regulated inflammation could be halted, hence controlling the disease (3,4).

There are a number of Janus kinase (JAK) inhibitors currently under investigation for the treatments of immune-induced diseases, such as Rheumatoid Arthritis, Psoriatic Arthritis, Psoriasis, Ulcerative Colitis, Crohn's Disease, and Ankylosing Spondylitis. These JAK inhibitors can be given orally, which could be an advantage compared to the intravenously given biological treatments. Small molecule, unlike biological treatment, has no risk of developing loss of response due to immunogenicity.

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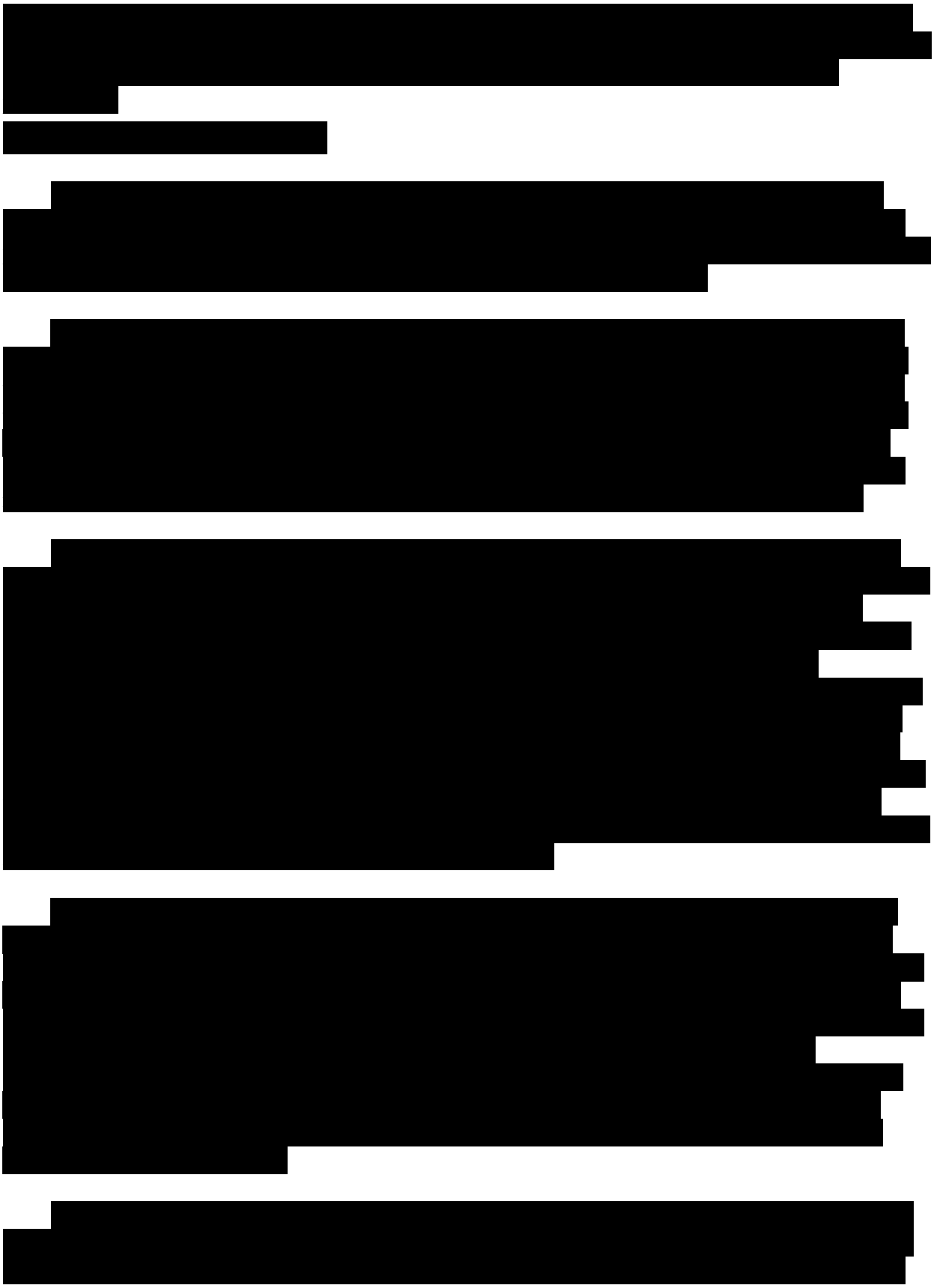

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3. Objectives

3.1 Primary Objectives

The primary objective is to evaluate the efficacy of SHR0302 at 4mg, 8mg QD, and 4mg BD given orally compared to placebo in inducing clinical response in adult subjects with moderate to severe active Ulcerative Colitis at Week 8.

3.2 Secondary Objectives

The secondary objectives are;

- To evaluate the safety and tolerability of oral SHR0302 in subjects with moderate to severe ulcerative colitis.
- To evaluate the efficacy of oral SHR0302 in inducing clinical remission in subjects with moderate to severe ulcerative colitis.
- To evaluate the efficacy of oral SHR0302 in inducing mucosal healing in subjects with moderate to severe ulcerative colitis.
- To evaluate the change from baseline in the following biomarkers; CRP, fecal calprotectin.
- To further evaluate the efficacy of SHR0302 in maintaining remission.
- To characterize the pharmacokinetics of SHR0302 in moderate to severe active Ulcerative Colitis patients, and explore the correlation of exposure-response.

4. Investigational Plan

4.1 Study Design

See Figure 1.

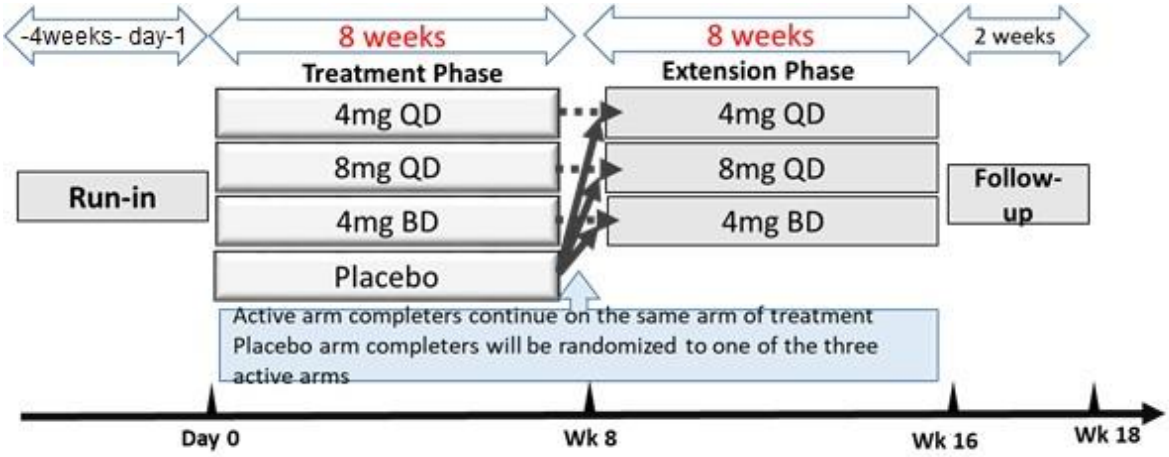

Figure 1. Study design diagram

4.2 Discussion of the design

This is a multi-national, multi-center, double-blind, randomized, placebo controlled phase II dose- ranging study to include 152 subjects with moderate to severe active ulcerative colitis. The study consists of an 8-week blinded treatment phase, followed by an 8-week active arms extension phase. Subjects will be screened between -28 days to -1 day before baseline visit (visit 2 at Day 0).

At the baseline visit, subjects with moderate-to-severe active ulcerative colitis, with a modified 9-point Mayo score of 5 to 9 points and endoscopic subscore of 2 to 3, and fulfilling all the inclusion/exclusion criteria will be randomized into one of the four treatment arms for the treatment phase; three active and one placebo; 4mg QD, 8mg QD, 4mg BD of SHR0302 or placebo. Subjects randomized into placebo in treatment phase will also have a pre-assigned randomized treatment sequence for extension phase, which are 3 active groups (placebo -> 4mg QD, placebo -> 4mg BD, and placebo -> 8mg QD) in a 1:1:1 ratio. Subjects randomized to the active arms for treatment phase will remain in the same dose group in the extension phase.

All the subjects will be stratified according to whether they have previously exposed to anti-TNFα/biological treatment. The double-blind treatment period will last for 8 weeks. Primary endpoint is collected at week 8. At the completion of treatment period, all subjects, responders or non-responders, have the option to enter a blinded active arms 8-week extension phase according to the group they were randomized to for the extension phase. All subjects are followed-up for further 2 weeks until week 18 (last visit). All the subjects have the option not enrolling into the extension phase after first 8 weeks of treatment. Early withdrawn subjects during the first treatment phase cannot enter the extension phase. The end-of-study is defined as the date of the last subject's last visit or the actual date of follow-up visit/contact, whichever is later.

5. Subject Selection and Withdrawal Criteria

5.1 Number of subjects

152 eligible subjects will be randomized to achieve an estimated 140 evaluable subjects in the study. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a particular subject is suitable to participate in this study. Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study. Subject must be able to provide an informed consent to participate in this study at his own will.

5.2 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrolment into the study;

1. Male and Female subject age ≥ 18 and ≤75 years of age at randomization.

2. Active ulcerative colitis with a 9-point modified Mayo score of 5 to 9 points and endoscopic subscore of 2 to 3 (The duration of the time between endoscopy and baseline should not exceed 10 days and allow central over read turn over before randomization).

3. Subject should have at least three-month history of Ulcerative Colitis diagnosis at randomization.

4. Subjects deemed by the treating physician as having inadequate response, loss of response or intolerance to the conventional treatment (oral 5-ASA, immune-suppressants or corticosteroids), or previously exposed to anti-TNF therapy (e.g. infliximab, adalimumab) or other biological treatment (e.g. Vedolizumab) having discontinued the treatment for:
   - Infliximab: a minimum of 8 weeks prior to baseline
   - Adalimumab: a minimum of 10 weeks prior to baseline
   - Ustekinumab: a minimum of 14 weeks prior to baseline
   - Vedolizumab: a minimum of 17 weeks prior to baseline
   - For the other biological treatments, they should discontinue for a minimum of 5 half-lives prior to baseline.

5. If subjects are currently receiving the following treatment for UC, they are eligible for the study, provided they are on stable dose for the required period of time:

   − Oral 5 ASA or Sulfasalazine, stable dose for at least 2 weeks prior to baseline and during the study treatment period.

   AND/OR

- Oral corticosteroids (prednisolone ≤ 30mg/day or less or equivalent) stable dose for at least 2 weeks prior to baseline. This is not applicable to the subjects who have only exposed to 5-ASA previously as per inclusion criteria 4.

6. Subject must have no evidence of active, latent, or inadequately treated infection with *Mycobacterium tuberculosis* (i.e., tuberculosis [TB]), as defined by the following:

   - A negative Mantoux Purified Protein Derivative (PPD) skin test result (≤ 5 mm of induration), or negative QuantiFERON TB Gold (QFT Gold test) /or T-Spot test performed within the 3 months prior to/within screening;

   AND

   - Subject must have a chest radiograph, taken within the 3 months prior to/within screening, and showing no changes suggestive of active TB infection.

   AND

   - Subject must have no history of either untreated or inadequately treated latent or active TB infection

7. All women of childbearing potential and all men must be willing to use at least one highly effective method of contraception from signing of informed consent, throughout the duration of the study, and for 1 month after last dose of study medication: (refer to Section 5.4 for further details on contraception requirements for this study)
   - Male subjects with a female partner of childbearing potential must be willing to use condom in addition to a highly effective contraceptive method.

8. Subjects who are willing and able to comply with the scheduled visits and treatment plan, laboratory testing and other study procedures.

9. Capable of providing a signed and dated informed consent form indicating the subject has been informed of all pertinent aspect of the study.

5.3 Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. Diagnosis of indeterminate colitis, or clinical findings suggestive of Crohn's disease.

2. Subjects with ulcerative colitis, which is confined to a proctitis (distal 15 cm or less).

3. Treatment naïve subjects diagnosed with ulcerative colitis (without previous exposure to any of the following therapies for UC treatment: oral 5-ASA, corticosteroids, immune-suppressants, or biological treatments).

4. Subjects displaying clinical signs of ischemic colitis, fulminant colitis or toxic megacolon.

5. Subject who have had previous surgery as a treatment for ulcerative colitis or likely to require surgery during the study period.

6. Subjects who have evidence of pathogenic bowel infection. Subjects had *Clostridium difficile* or other intestinal infection within 30 days of screening endoscopy, or test positive at screening for C. *difficile* toxin or other intestinal pathogens.

7. Subjects receiving the following therapy:
   - Azathioprine/6-mercaptopurine, methotrexate, thalidomide within 7 days prior to baseline.
   - Cyclosporine, mycophenolate, tacrolimus within 4 weeks prior to baseline.
   - Interferon therapy within 8 weeks prior to baseline.
   - Intravenous corticosteroids or rectally administered formulation of corticosteroids or 5-ASA within 2 weeks prior to baseline.

8. Subjects who have previously received JAK inhibitors, such as tofacitinib, baricitinib, upadacitinib, filgotinib. Please discuss with the medical monitor if need clarification.

9. Subjects with evidence of hematopoietic disorders at screening:
   - Hemoglobin levels <9.0 g/dL or hematocrit <30%.
   - An absolute white blood cell (WBC) count of $<3.0 \times 10^9$/L ($<3000/mm^3$) or Absolute Neutrophil Count (ANC) of $<1.2 \times 10^9$/L ($<1200/mm^3$).
   - Thrombocytopenia, as defined by a platelet count $<100 \times 10^9$/L ($<100,000/mm^3$).

10. Subjects with evidence of total bilirubin, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) more than 2 times the upper limit of normal at screening visit. Patients with liver cirrhosis will be excluded.

11. Subjects with eGFR ≤60 ml/min based on Cockcroft-Gault calculation (Appendix 2), or patient currently undergoes regular haemodialysis.

12. Subjects with current or recent history of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiac, or neurological disease.

13. Subjects with current clinically significant infections or within 1 month of baseline (e.g. those requiring hospitalization or parenteral antimicrobial therapy or opportunistic infections), or those with a history of more than one episode of herpes zoster, a history (single episode) of disseminated zoster, a history of any infection otherwise judged by the investigator to have the potential for exacerbation by participation in the study or any infection requiring antimicrobial therapy within 2 weeks of screening.

14. Subjects who may have current immunization with any live virus vaccine or history of immunization with any live virus vaccine within 8 weeks of baseline.

15. Subjects with a first-degree relative with a hereditary immunodeficiency.

16. History of any lymphoproliferative disorder (such as EBV-related lymphoproliferative disorder, as reported in some subjects on other immunosuppressive drugs), history of lymphoma, leukemia, myeloproliferative disorders, multiple myeloma, or signs and symptoms suggestive of current lymphatic disease.

17. Any prior treatment with lymphocyte-depleting agents/therapies (such as CamPath® [Alemtuzab], alkylating agents [eg Cyclophosphamide or Chlorambucil], total lymphoid irradiation, etc). Subjects who have received Rituximab or other selective B lymphocyte depleting agents are eligible if they have not received such therapy for at least 1 year prior to baseline.

18. Subjects who have any condition possibly affecting oral drug absorption eg gastrectomy, or clinically significant diabetic gastroenteropathy, or certain types of bariatric surgery such as gastric bypass. (Procedures such as gastric banding, gastric balloon that simply divide stomach into separate chambers, are NOT exclusionary.)

19. Women who are pregnant or lactating, or planning pregnancy while enrolled in the study.

20. History of alcohol or drug abuse with less than 6 months of abstinence prior to baseline.

21. Screening 12-lead ECG that demonstrates clinically relevant abnormalities which may affect subject safety if being enrolled into the study or interpretation of study results. (Appendix 3 ECG exclusion criteria)

22. Subjects that have donated blood in excess of 500 mL within 2 months prior to baseline.

23. Subjects that have undergone significant trauma or major surgery within 4 weeks of screening visit.

24. Subjects with a temperature of 38°C or higher at screening or baseline.

25. Subjects with malignancies or with a history of malignancies with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin.

26. Subjects infected with human immunodeficiency virus (HIV) or hepatitis B or C viruses.

27. Subjects who currently suffered from thyroid disorders, including hyperthyroidism, hypothyroidism, or currently on thyroid replacement therapy. Subjects with abnormal TSH, fT4 and fT3 at screening blood check must be excluded.

28. Subjects who have previously participated in any study that received SHR0302.

29. Subjects who have received any investigational drug or device within 3 months prior to baseline.

30. Subjects receiving or are expected to receive prohibited concomitant medication(s) (see Appendix 4) in the 4 weeks prior to the first dose of study drug.

31. Subjects who, in the opinion of the investigator or Reistone, will be uncooperative or unable to comply with study procedures.

32. Any other condition which in the opinion of the investigator would make the subject unsuitable for inclusion in the study.

33. Subjects with historical or current evidence of clinically significant cardiovascular, neurological, psychiatric, renal, hepatic, immunological, gastrointestinal, urogenital, nervous system, musculoskeletal, skin, sensory, endocrine (including uncontrolled diabetes or thyroid disease) or hematological abnormalities that are uncontrolled. Significant is defined as any disease that, in the opinion of the Investigator, would put the safety of the subject at risk through participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study.

34. Subjects with a history thrombotic events, including deep vein thromboses (DVT), pulmonary embolism (PE) and those with known inherited conditions that predispose to hypercoagulability.

5.4 Contraception advice

Contraceptive measures for both males and females of childbearing potential should be documented in the source documents.

5.4.1 Women of Non-Childbearing Potential

Female subjects of non-childbearing potential must meet at least one of the following criteria:

- Postmenopausal females who are at least 45 years of age with amenorrhea for at least 2 years. To confirm postmenopausal status (FSH level >30 IU/L), FSH testing should be performed for women within 5 years from their last menses;

OR

- Females with a physician documented hysterectomy, bilateral salpingectomy and/or a bilateral oophorectomy.

All other female subjects (including females with tubal ligations) will be considered to be of childbearing potential.

5.4.2 Women of Childbearing Potential

Female subjects of childbearing potential and their male partner must use at least 1 highly effective contraceptive method from the following list:

a. Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal).
b. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable).
c. Placement of intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
d. Documented bilateral tube occlusion at least 4 weeks before screening.
e. Vasectomised partner with medical confirmation of absence of sperm in the ejaculate at least 4 weeks before screening.

Female subjects and their male partners must be willing to continue use of these contraceptive methods from signing of informed consent, throughout the duration of the study, and for 1 month after last dose of study medication. Within these limits, the specific forms of contraception employed are left to the discretion of the subject, the principal investigator, and/or the subject's physician.

Absolute sexual abstinence, when this is consistent with the preferred and usual lifestyle of the subject, may be considered an acceptable method of contraception at the discretion of the investigator.

5.4.3 Pregnancy Testing

Female subjects of childbearing potential will be tested for serum beta-human chorionic gonadotropin (β-hCG) at screening visit. In addition, urine β-hCG test will be done at baseline and at each study visit until the end of follow-up period. If at any point there is a case of a positive urine β-hCG test, and this is confirmed by serum β-hCG, the subject will be withdrawn from the study and all the necessary follow up will be conducted.

5.4.4 Males

Non-vasectomized males with female partners of childbearing potential must be willing to use a condom, from signing of informed consent, throughout the duration of the study, and for 1 month after last dose of study medication, in addition to having their female partner use a highly effective form of contraception as described in Section 5.4.2:

Vasectomized males with female partners of childbearing potential are not required to use an additional form of contraception providing that surgical sterilization has been successful and an absence of sperm in the ejaculate has been confirmed at least 4 weeks before screening.

5.5 Randomization Criteria

Subjects will be randomized into the study in a 1:1:1:1 allocation ratio to SHR0302 8mg QD, placebo, SHR0302 4mg BD or SHR0302 4mg QD for the treatment phase provided they have satisfied all inclusion/exclusion criteria at randomization visit (Visit 2). [redacted]

[redacted] A computer-generated randomization schedule will be used to assign subjects to the treatment sequences. Subjects will be assigned a subject number in the order of their acceptance into the study. This identifying number will be retained throughout the study. Subjects randomized into placebo in treatment phase will also have a pre-assigned randomized treatment sequence for extension phase, which are 3 active groups (placebo -> 4mg QD, placebo -> 4mg BD, and placebo -> 8mg QD) in a 1:1:1 ratio. Subjects randomized to the active arms for treatment phase will remain in the same dose group in the extension phase.

After the completion of treatment phase, subject may choose to enroll into the extension phase according to the group they were randomized to for the extension phase. All the subjects have the option not entering into the extension phase after first 8 weeks of treatment phase. Early withdrawn subjects during the first treatment phase cannot enter the extension phase.

5.6 Withdrawal Criteria

A subject may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or Reistone Biopharma for behavioral or administrative reasons.

If a subject develops a serious infection during the study, defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials, he/she must be discontinued from the study.

All abnormal laboratory events of clinical significance should be followed until the laboratory values have returned to normal or baseline levels. In addition, any subject with a confirmed increase in serum creatinine at the end of study or at discontinuation of at least 0.2 mg/dL and at least 10% above the average of screening and baseline value will be followed up with retesting every one to two weeks until the creatinine elevation has fully reversed to within 10% of the subject's baseline value or has stabilized.

If a subject has any clinically significant, study-related abnormalities at the conclusion of the study, the medical monitor (or designated representative) should be notified and every effort should be made to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

The reason for a subject discontinuing from the study will be recorded in the eCRF. A discontinuation occurs when a randomized subject ceases participation in the study, regardless of the circumstances, prior to completion of the protocol. The investigator must determine the primary reason for discontinuation. Withdrawal due to adverse events should be distinguished from withdrawal due to insufficient response according to the definition of adverse event noted in Section 7.3.11 . The final evaluation required by the protocol will be performed at the time of the study discontinuation. The investigator will record the reason for study discontinuation, provide or arrange for appropriate follow-up if required.

5.7 Pre-Screen and Screen Failure

Subjects will be assigned a subject number after completing written informed consent and completing at least one additional study procedure (study procedures do not include washout of any medication).

A screen failure is defined as any subject who has been assigned a subject number, but does not continue in the study beyond Visit 1 (Screening) or any subject who completes Visit 1 and enters the run-in period but is subsequently found to be ineligible for the study based procedures (e.g., laboratory, ECG, or Endoscopy) conducted at Visit 1. The study interactive voice response system (IVRS) used to track study enrolment, will be contacted to report screen failures. Additionally, the following information will be collected in the eCRF for screen failures:

- Date of Screening Visit
- Subject number
- Demography information including race, age, and gender
- Inclusion/exclusion criteria
- Reason subject failed screening
- Primary method of subject recruitment
- Serious Adverse Events (SAEs) information, if any

In most circumstances, subjects who are screen failures cannot be re-screened. In rare instances, subjects may be eligible for re-screening. However, the re-screening of subjects must be approved by the study Medical Monitor prior to re-screening.

Subjects who meet all the Visit 1 eligibility criteria, but are not randomized will be considered Run-In failures. In addition to the information described above for screen failures, the reason for the Run-In failure will be recorded in the eCRF for Run-In failures.

5.8 Early Withdrawal

The definition of an early subject withdrawal from the study will be any subject who is randomized to double-blind medication and, for any reason, is withdrawn prior to completion of the Visit 5 procedures.

A subject may voluntarily discontinue participation in the study at any time. The investigator may also, at his/her discretion; discontinue the subject from participating in the study at any time. In addition, the investigator must make every effort to have the subject return to the clinic as soon as possible after discontinuation of study drug for an Early Withdrawal Visit. An Early Withdrawal Visit may occur at a regular scheduled clinic visit or between clinic visits. The following evaluations and procedures should be completed and recorded in the eCRF.

- Concomitant medication assessment
- AE/SAE assessment

- Physical examination (recorded in source documents only)
- Vital signs
- Collect and review electronic diary
- Collect used study medication (blinded study medication)
- Assess compliance with investigational drug
- 12-Lead ECG
- Laboratory assessments (including chemistry, haematology, and pregnancy test for females of childbearing potential and routine urinalysis)
- Call IVRS to report subject's early withdrawal from the study
- Endoscopy, Mayo score, 9-point modified Mayo score, and partial Mayo score, if feasible.

A subject that is withdrawn from the study after being randomised to treatment cannot be re-screened and subjects who are withdrawn from the study will not be replaced. If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before.

Thyroid specific criteria:

Subjects with deranged TSH level (outside of normal range) only, but normal free T4 or free T3. Investigator can follow-up the subject with thyroid function test and assess clinically in 4 weeks.

Deranged TSH level, with associated deranged free T4 and/or free T3(outside of normal range), the investigator should assess subject's clinical condition and decide if the subject should be withdrawn.

Subject with signs and/or symptoms suggestive of hypothyroidism or hyperthyroidism should have laboratory thyroid function performed. If any of the thyroid parameters (TSH, free T4, or free T3) were outside of normal range, the subject is to be withdrawn.

5.9 Stopping Criteria

The stopping safety criteria are as below: Subject who fulfil the following criteria should discontinue the study.

- Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance) Study treatment will be stopped if the liver chemistry stopping criteria is met. Refer to Section 7.3.9 Liver Chemistry Stopping and Follow-up Criteria.
- A subject that meets the QTc criteria below will be withdrawn from the study. The QT correction formula used to determine discontinuation should be the same one used throughout the study.

-QTc, QTcB/QTcF > 500 ms

-Change from baseline: QTc >60 ms

Use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study.

- Abnormal laboratory values of interests. (modified from CTCAE 5.1 criteria)

  - Hemoglobin (Hgb) <7.0 g/dL; or when blood transfusion is indicated.
  - Neutrophil count < 500/mm3
  - Platelet count < 25,000/mm3
  - Lymphocyte count < 200/mm3
  - Leukocyte count < 2000/mm^3

- Subject who develops Venous Thrombosis (eg Deep Vein Thrombosis).
- Subject who develops Pulmonary Embolism.
- Subject who develops Cerebrovascular Events (eg Thromboembolic Stroke, Transient Ischemic Attack (TIA), Myocardiac Infarction)
- An unacceptable adverse event, as determined by the Investigator and the medical monitor.
- Any unacceptable adverse event that is thought to be related to the investigational product may result in the study being terminated.
- Significant protocol deviation. The discovery that post-randomization the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
- If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 7.3.10.

5.10 Premature Study Termination

The sponsor may discontinue the study if the study becomes unjustifiable for medical ethical reasons, for poor enrollment, or because of discontinuation of clinical development of the investigational product.

The clinical study may be terminated prematurely or suspended at the request of health authorities or if new safety or efficacy information leads to an unfavorable risk benefit judgment for the investigational product.

If a study is prematurely terminated or discontinued, Reistone will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. As directed by Reistone, all study materials must be collected and all eCRFs completed to the greatest extent possible.

5.11 Safety Review Committee (SRC)

An SRC will be established in this study to assess overall safety data and early safety signal in order to protect the ethical and safety interests of the subjects recruited into the study, while maintaining, as far as possible, the scientific validity of the study. The SRC is independent of the study team and will comprise of at least one external independent statistician and an external independent physician.

During the study, the SRC will convene at least twice to review the safety and tolerability data after the study recruited the 50th and 100th subject treated for first 8 weeks of treatment phase. Based on the safety information, the SRC has the discretion to make recommendation to the study team based on predefined SRC Charter.

5.12 Time and Event Table

See Table1.

Table 1. Time and Event Table

Period	Screening	Baseline	Treatment Phase		End of Treatment Phase	Extension Phase		End of Extension Phase	Follow-up/EW[11]
VISIT	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Week	**-4 to -1**	**0**	**1**	**4**	**8**	**9**	**12**	**16**	**18**
Day	**-28 to -1**	**0**	**7± 2 days**	**28± 3 days**	**56± 3 days**	**63± 2 days**	**84± 3 days**	**112± 3 days**	**126± 5 days**
Procedures									
Written Informed Consent[1]	x								
Demography/Medical History	x								
Physical Examination	x	x	x	x	x	x	x	x	x
Chest X-ray[2]	x								
Inclusion/Exclusion Criteria	x								
Randomisation Criteria		x							
Study medication dispensing		x		x	x		x		
Study medication accountability				x	x		x	x	x [12]
Register Visit in IVRS[3]	x	x		x	x		x	x	x[12]
Endoscopy (colonoscopy)[4]		x [4]			x				x[12]
Efficacy Assessments									
Patient Dairy[5]	x	x	x	x	x	x	x	x	x
Mayo Score		x			x				x[12]
9-point Modified Mayo Score		x			x				x[12]
Partial Mayo Score		x	x	x	x	x	x	x	x
Safety Assessments									
12-lead ECG	x	x		x	x	x		x	x
Vital Signs[6]	x	x	x	x	x	x	x	x	x
Adverse Event Assessment[7]		x	x	x	x	x	x	x	x
Laboratory Assessments									

Period	Screening	Baseline	Treatment Phase		End of Treatment Phase	Extension Phase		End of Extension Phase	Follow-up/EW[11]
VISIT	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Week	**-4 to -1**	**0**	**1**	**4**	**8**	**9**	**12**	**16**	**18**
Day	**-28 to -1**	**0**	**7± 2 days**	**28± 3 days**	**56± 3 days**	**63± 2 days**	**84± 3 days**	**112± 3 days**	**126± 5 days**
Procedures									
Haematology and Chemistry Tests	x	x	x	x	x	x	x	x	x
Urinalysis	x	x	x	x	x	x	x	x	x
Lipid Profile (Fasting)		x		x	x	x		x	x
TSH, fT4, fT3	x	x	x	x	x	x	x	x	x
QuantiFERON /or T-Spot /or PPD test [8]	x								
Hep B sur Ag, Hep C Ab, HIV test	x								
Stool culture/ microscopy	x								
CRP	x	x	x	x	x	x	x	x	x
Faecal Calprotectin		x		x	x			x	
Urine Pregnancy Test[9]		x	x	x	x	x	x	x	x
β-HCG (blood)[10]	x								
[redacted]									
FSH[15]	x								
Medication									
Concurrent Medication Assessment	x	x	x	x	x	x	x	x	x

1. Written informed consent must be obtained prior to performing any Visit 1 procedures or initiating any alterations in a subject's medications
2. Only to be performed if there is no chest X-ray or CT scan available within 3 months of Visit 1
3. IVRS is a randomisation machine used to record all the patient visit.
4. Colonoscopy is completed by baseline (visit 2 – Day 0). The duration of time between endoscopy and baseline is no more than -10 days.
5. Subject use an electronic diary to record disease related medical problems experienced during the study.
6. Vital signs include resting blood pressure, heart rate, and body temperature. It is advised to measure them before any procedures or questionnaires.
7. Adverse events and Serious Adverse Events to be collected from the start of the study drug (visit 2) until the Follow-Up contact. However, any serious adverse events will be recorded from the time of consent.
8. Investigator has the option to use PPD test, QuantiFERON Gold test or T-Spot for TB screening. Subjects who have previously receive BCG vaccination will be tested by QuantiFERON Gold test/or T-Spot test, and the result will determine the subject eligibility for participation.
9. Urine pregnancy test to be done in females of childbearing potential only

10. β-Human Chorionic Gonadotrophin(β-HCG) to be done in females of childbearing potential at screening visit, and only to be done if urine pregnancy test positive at other study visits.
11. Early withdrawal visit should be done within 2 weeks after last dose/decision of withdrawal.
12. Only to be conducted in the early withdrawn subjects.

[redacted]

15. FSH to confirm postmenopausal status at screening visit only.

6. Study Treatments

6.1 Investigational Product/Placebo Supply

SHR0302 and matching placebo tablets will be provided by the sponsor and dispensed for oral administration. Subjects will be randomized to receive 4mg QD, 4mg BD, 8mg QD or Placebo in a ratio of 1:1:1:1 respectively for the first 8 week of treatment phase. Subjects randomized into placebo in treatment phase will also have a pre-assigned randomized treatment sequence for extension phase, which are 3 active groups (placebo -> 4mg QD, placebo -> 4mg BD, and placebo -> 8mg QD) in a 1:1:1 ratio. Subjects randomized to the active arms for treatment phase will remain in the same dose group in the extension phase.

SHR0302 will be provided as combination of 4mg tablets, including the matching placebo by the Sponsor. At study visits on Day 0, and Week 4, sufficient trial medication will be dispensed to complete dosing for four weeks.

For subjects enrolled into the blinded active arm extension phase, trial medications will be dispensed at week 8 and week 12, where trial medications will be dispensed sufficient for 4 weeks. At visits Week 4, Week 8, Week 12, and Week 16 (end of extension phase), or at follow-up visit/contact if the subject is withdrawn, the subject must return all trial medication and the amount returned will be recorded.

Note that only those patients enrolled into the extension phase will be dispensed with trial medications at week 8 and week 12.

6.1.1 Study Drug Dispensing

Investigational product will be assigned to subjects at the baseline visit once successfully randomized through the tele-randomization system. The investigator or appropriate delegate at the site will access the tele-randomization system (IVRS) at baseline visit to receive correct container numbers to be dispensed to the subject. All medication dispensed or returned will be documented in the eCRF.

After the completion of first 8-week treatment phase, all completers may be enrolled into the extension phase according to the group they were randomized to for the extension phase.

6.1.2 Study Drug Administration

Study medication will be self-administered by the subject twice daily, one (2 tablets) in the morning, another (2 tablets) in the afternoon. Approximately 8 - 12 hours between the morning and afternoon doses.

However, at baseline (Day 0) the first dose will be taken in the clinic. At Week 4 and at the end of treatment (Week 8) subjects should take their morning oral dose at the clinic. Study medication may be taken with or without food.

6.2 Treatment Assignment

Subjects will be randomized into the trial in a 1:1:1:1 allocation ratio to SHR0302 8mg QD, placebo, SHR0302 4mg QD or SHR0302 4mg BD for the treatment phase provided they have satisfied all inclusion/exclusion criteria. Subjects will be stratified according to whether or not they have had previous exposure to anti-TNFα/biological treatment and randomized at baseline according to a computer generated pseudo random code using the method of permutated blocks balanced within each randomization strata. Subjects randomized into placebo in treatment phase will also have a pre-assigned randomized treatment sequence for extension phase, which are 3 active groups (placebo -> 4mg QD, placebo -> 4mg BD, and placebo -> 8mg QD) in a 1:1:1 ratio. Subjects randomized to the active arms for treatment phase will remain in the same dose group in the extension phase.

After the completion of treatment phase, subject may choose to enroll into the extension phase according to the group they were randomized to for the extension phase. All the subjects that have completed the first treatment phase have the option not entering into the extension phase after first 8 weeks of treatment. Early withdrawn subjects during the first treatment phase cannot enter the extension phase.

6.3 Blinding

Investigational product taken during the 8-week treatment period will be double-blind. Neither the subject nor the study physician will know which study medication the subject is receiving. In the subsequent 8-week extension phase, although subjects are given active treatments, both the subjects and investigators are blinded to which dose of SHR0302 they are randomized to.

In order to preserve blinding and ensure patients compliance throughout the study, the study drug packaging has been designed with detailed consideration. All the arms are administered under twice daily (BD) dosing regime and placebo is used according to the schedule in the table below. (Table 2)

Table 2. Study drug packaging design for treatment arms

Study Arms-all BID	Dose 1 (am)	Dose 2 (pm)
4mg qd	4mg+ placebo	Placebo + placebo
8mg qd	4mg+ 4mg	Placebo + placebo
4mg bd	4mg +placebo	4mg +placebo
placebo	Placebo + placebo	Placebo + placebo

At each dosing time (morning, am or afternoon, pm), subject will be taking two tablets. In one day, a subject will take a total of four tablets, two tablets in the morning and two tablets in the afternoon.

The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency**, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject. Whenever possible, the investigator must first discuss options with the Reistone Biopharma/designated CRO Medical Monitor or appropriate Reistone Biopharma/designated CRO study personnel **before** unblinding the subject's treatment assignment. If this is impractical, the investigator must notify Reistone Biopharma/designated CRO as soon as possible, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be recorded in the appropriate data eCRF.

Reistone Biopharma/designated CRO staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to clinical investigators in accordance with local regulations.
Subjects will be withdrawn if the treatment code becomes unblinded. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the eCRF.

6.4 Drug Storage and Accountability

SHR0302 must be stored according to the labeled storage conditions in a locked area with restricted access. The investigator or appropriate delegate at the site (eg pharmacist), will ensure that all study drug is stored in a secured area, under recommended storage condition, and in accordance with regulatory requirements.

The investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product(s). To ensure adequate records, all drug supplies will be accounted for in the drug accountability inventory forms as instructed by Reistone Biopharma/designated CRO and will be monitored by counting of unused medications returned by the subject at Week 4, 8, 12 and 16 or at follow-up visit/contact if the subject is withdrawn.

At the end of trial, Reistone Biopharma/designated CRO will provide instructions as to the disposition of any unused investigational product. If Reistone/designated CRO authorizes destruction at the trial site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Reistone Biopharma/designated CRO. Destruction must be adequately documented. SHR0302 will not be made available to subjects at the end of study.

6.5 Treatment Compliance

Investigational product compliance will be assessed by the site at each clinic visit following

baseline (Day 0) up to the end of treatment. Non-compliance is defined as taking less than 80% of study drug products as directed by the dosing instructions. The investigator has the discretion to withdraw any subject from the study for reasons of non-compliance with the dosing regimen. Investigators should indicate on the appropriate eCRF page noncompliance with study treatment and provide an explanation.

Inventory control of all study medications must be rigorously maintained throughout the duration of the study until all medication has been accounted for and returned to the sponsor. Any discrepancies noted between drug dispensing records and the drug inventory must be reported to Reistone Biopharma/designated CRO.

6.6 Concomitant Medications

6.6.1 Permitted Concomitant Medications

All concomitant medication(s) taken during the trial must be recorded with indication, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant medication at each clinic visit. Following therapy for ulcerative colitis are allowed providing they are stable for the specified period of time:

- Oral 5-ASA or sulfasalazine are allowed providing that the dose is stable for at least 2 weeks prior to baseline and during the study treatment period.

- Oral steroids are allowed during the study up to the dose of 30 mg/day of prednisolone or equivalent, providing that the dose has not been commenced or changed within 2 weeks of baseline and until to the end of treatment phase (Week 8). During the treatment phase, if the subject cannot tolerate the oral steroids dose or there is a significant safety risk associated with continued use of the steroids, the dose may be reduced at the discretion of the investigator and the reasons for dose reduction need to be documented in the medical records. During the extension phase, tapering of the oral steroid dose can be commenced for subjects at investigator's discretion. Tapering scheduled treatment is provided as below:

    - Subjects receiving > 10 mg/day prednisolone or equivalent: taper dose by 5 mg/week until a 10 mg/day dose (or equivalent) is reached, then continue tapering at 2.5 mg/week until 0 mg/day.
    - Subjects receiving ≤ 10 mg/day prednisolone or equivalent: taper dose by 2.5 mg/week until 0 mg/day.

If subject experiences worsening of signs or symptoms during the tapering schedule, in the opinion of the investigator, due to reduction in oral steroid daily dose, the daily oral steroid dosage for the subject could be reverted to the preceeding daily dosage instructed by the investigator, but should not exceed Baseline dose.

6.6.2 Prohibited Medications

The following medications are prohibited throughout the duration of the study:

- azathioprine, 6-mercaptopurine, methotrexate and thalidomide;
- cyclosporine, mycophenolate and tacrolimus;
- interferon and
- anti-TNFα therapy/other biological treatment;
- intravenous corticosteroids or rectally administered formulation of corticosteroids or 5-ASA.
- Oral JAK inhibitors (except the trial medication)

In addition, concomitant administration of CYP3A inducers and moderate to potent CYP3A inhibitors with systemic effects should be avoided for the duration of the study.
Examples of medications that are prohibited from use from 28 days prior to the first dose of study medication until completion of follow up period, due to potential for drug interactions or confounding of data interpretation, are listed in Appendix 4.

All live vaccines immunization are prohibited from signing of informed consent, throughout the duration of the study, and for 1 month after last dose of study medication.

6.6.3 Traditional Chinese and Herbal Medicines

The following categories of traditional or herbal medicines are prohibited at Visit 1 and any time during the study:

- Traditional or herbal medicines used for the treatment of UC, including those that investigator believe to contain corticosteroids.
- Traditional or herbal medicines that have known effects on platelets and that increase the tendency to cause bleeding.

6.7 Treatment after study completion

The investigator is responsible for ensuring that consideration has been given to the post-study care of the patient's medical condition whether or not Reistone Biopharma/designated CRO is providing specific post study treatment after week 16. Reistone Biopharma/designated CRO has provided an 8-week extension phase of active therapy, and will not provide post-study treatment after the extension phase. Post-treatment UC therapy should not be entered into the eCRF.

6.8 Study Drug Overdose Management

An overdose is defined as a dose greater than the total doses described above which results in clinical signs and symptoms. These should be recorded by the investigator on the AE/SAE pages. In the event of an overdose of study medication, the investigator should use clinical judgment in treating the overdose and contact the study medical monitor.

Reistone Biopharma/designated CRO is not recommending specific treatment guidelines for overdose and toxicity management. The investigator is advised to refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the study drug being used in this study. Such documents may include, but not be limited to, the IB or equivalent document provided by Reistone Biopharma/designated CRO.

7. Study Assessments and Procedures

7.1 Critical Baseline Assessments

The following critical baseline assessments will be conducted at Visit 1:

- Demographic history (including gender, ethnic origin, date of birth, height and weight)
- Medical history of Ulcerative Colitis comprised of date of diagnosis (year of diagnosis is acceptable) and previous and/or current medical conditions
- Physical examination
- Heart rate, blood pressure, and body temperature measurement
- 12-Lead ECG
- Chest x-ray (or historical chest x-ray/CT-Scan obtained within 3 months of Screening (Visit 1))
- Clinical laboratory assessments (including chemistry, hematology, pregnancy test)
- Mayo Score – Mayo Scoring System for Ulcerative Colitis. 9-point modified Mayo score will be used to confirm patient eligibility for the study at baseline. The duration of the time between endoscopy and baseline should not exceed 10 days. Mayo score and Partial Mayo score will also be calculated and collected prior to randomization.

7.2 Efficacy Endpoints Assessments

7.2.1 Primary Efficacy Endpoints

The percentage of subject achieve clinical response at week 8, defined as decrease from baseline in 9-point modified Mayo score of at least 2 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or absolute subscore for rectal bleeding of 0 or 1.

7.2.2 Secondary Efficacy Endpoints

- The percentage of subjects achieve clinical remission per 9-point modified Mayo score at week 8, where stool frequency subscore ≤ 1, rectal bleeding subscore of 0, and endoscopic subscore ≤ 1

- The percentage of subjects achieve clinical remission at week 8 as per total Mayo score of 2 points or lower than 2, with no individual subscore exceeding 1point and a rectal bleeding subscore of 0.
- The percentage of subjects achieve endoscopic remission (mucosal healing) at week 8, defined by Mayo endoscopic subscore ≤ 1 point.
- Change from baseline in 9-point modified Mayo score at week 8.
- Change from baseline in total Mayo score at week 8.
- Change from baseline in partial Mayo score (Mayo score without endoscopy) at week 1, 4, 8, 9, 12 and 16.
- Change from baseline in the level of biomarkers CRP, fecal calprotectin.
- The systemic exposure of SHR0302 in steady state in Ulcerative Colitis patients (i.e. concentration and area under the curve).

7.2.3 Safety Endpoints

- To evaluate the safety and tolerability by laboratory parameters.
- To evaluate the safety and tolerability by collection of AE/SAE incidence
- To measure the vital signs (BP, HR, and Body temperature)
- To measure subject's total lipid profile, which includes Triglyceride, LDL and HDL.
- To measure subject's thyroid profile: TSH, free T4 and free T3.
- 12 –lead ECG.

7.2.4 Patient Diary Assessment

Subjects will be provided with an electronic diary at screening visit in order to collect the patient reported outcome components of the total Mayo score (see Appendix 1), including the following information:

- 'Normal' number of stools per day, when not having a flare, and will be collected only once.
- Number of stools currently per day.
- Presence of rectal bleeding currently (if any).

Diary data will be assessed at the clinic, at each study visit from baseline (Day 0) until the end of follow up period (Week 18). The information extracted will be used for calculation of Mayo score taking into account the data recorded over the last 3 days prior to each study visit. Should any bowel preparation be required to perform the endoscopy examination (colonoscopy), last 3 days patient diary must be completed and assessed prior to any bowel

preparations. If data on any of these days is missing, the last 3 days closer to that day of bowel preparation/visit within the last 7 days before the day for bowel preparation/visit will used for calculation. In order to encourage consistent diary recording, subjects are required to enter diary data continuously throughout the study.

7.2.5 Mayo Score Assessment

Mayo score is an instrument designed to measure disease activity of ulcerative colitis. Mayo score ranges from 0 to 12 points. It consists of 4 subscores, each graded from 0 to 3 with higher scores indicating more severe disease (see Appendix 1)

- stool frequency (0-3)
- rectal bleeding (0-3)
- findings of colonoscopy (0-3)
- physician global assessment (PGA) (0-3)

Mayo score is assessed at baseline and Week 8. If the subject scores ≥2 on the endoscopic sub-score of the Mayo Score at baseline and meet all other inclusion/exclusion criteria, the subject will be randomized. Should any bowel preparation be required to perform the colonoscopy, 3-day patient diary must be completed and assessed prior to any bowel preparation. For the baseline endoscopy, the duration of the time between endoscopy and baseline should not exceed 10 days. Baseline (Day 0 -Visit 2) endoscopy images/films (eligibility assessment) and Week 8 endoscopy images/films will be submitted to central lab for central reading. The central lab will send eligibility report to confirm eligibility.

The physician global assessment (PGA) acknowledges the three other criteria: the patient's daily recollection of abdominal discomfort and general sense of wellbeing, and other observations, such as physical findings and the patient's performance status.

Clinical response is defined as a decrease from baseline in Mayo score of at least 3 points and at least 30 percent, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or absolute subscore for rectal bleeding of 0 or 1. Clinical remission is defined as a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point.

Endoscopic response is defined as decrease from baseline in the findings of the colonoscopy subscore of the Mayo Score ≥ 1. Endoscopic remission is defined as the findings of colonoscopy subscore of the Mayo score equals 0.

7.2.6 9-point Modified Mayo Score

9-point modified Mayo score is the Mayo score excluding physician global assessment (PGA)subscore, hence the maximum is 9 points and minimum 0 point. By removing the PGA, it removes the subjective view/assessment from the physicians hence reducing bias. It is also a recommended assessment by the regulators. 9-point modified Mayo score will be collected as a primary endpoint at baseline (Visit 2) and week 8 (Visit 5). This has been advised by the US FDA according to FDA guidance on ulcerative colitis trial (10).

7.2.7 Partial Mayo Score Assessments

A partial Mayo score (Mayo score without endoscopy component) will be assessed at baseline, week 1, week 4, week 8, week 9, week 12, week 16 and week 18, as secondary endpoints.

7.2.8 Colonoscopy

Endoscopy examination (colonoscopy) will be required at baseline and Week 8 and it will be performed in order to establish Mayo endoscopic subscore and confirm patient eligibility for the study at baseline. The duration of the time between endoscopy and baseline should not exceed 10 days. As per Surveillance Guidelines for patients with ulcerative colitis, all subjects who have not had colonoscopy performed within last 10 years from onset of symptoms will require colonoscopy procedure for screening surveillance. An appropriately trained endoscopist should perform the colonoscopy. Where possible the same endoscopist should perform the endoscopy for both baseline and Week 8 visits, where this is not possible it should be clearly documented who performed each endoscopy procedure.

7.3 Safety Assessment

7.3.1 Vital Signs

Vital signs measurements will include heart rate and systolic and diastolic blood pressure, and body temperature. Vital signs will be obtained after subjects have rested for approximately 5 minutes and before performing ECG. A single set of values will be obtained.

Vital signs will be performed using equipment provided by investigational sites and will be obtained at visits and time points as detailed in the Section 5.12 –Time and Event Table.

7.3.2 12 lead ECG

12-lead ECG measurement and rhythm strip (10 seconds) will be obtained after measurement of vital signs. Triplicate ECG measurements are collected at rate of 3 ECGs over 5 minutes period. After vital signs are obtained subjects should be placed in the supine position for the ECG measurements.

ECG measurements will be taken at various visits and time points as detailed in Section 5.12 –Time and Event Table. The investigator, a designated sub-investigator, or other appropriately trained site personnel will be responsible for performing 12-lead ECG assessments. The investigator must provide his/her dated signature on the original paper tracing, attesting to the authenticity of the ECG machine interpretation. The investigator will review the ECG and determine if the subject should continue the study.

7.3.3 Tuberculin Test (PPD)

Subjects must have a screening tuberculin test (PPD) administered and then evaluated by a health care professional (nurse or doctor) 48 to 72 hours later in order to be eligible for the study, unless performed and documented within the last 3 months. The test consists of intracutaneous injection of Tuberculin, concentration as per local medical standard of practice, on the volar aspect of the forearm, using a short beveled 26- or 27- gauge needle (Mantoux test). The test is positive if the induration's diameter (not erythema) is ≥5 mm 48 to 72 hours after injection. Subjects who have previously received BCG vaccination will be tested by QuantiFERON Gold/or T-Spot test in place of Mantoux PPD and have these results determine patient eligibility for participation.

7.3.4 QuantiFERON test/or T-Spot test

At the discretion of the investigator, a QuantiFERON Gold®™ (11) test /or T-Spot test (11) conducted in local lab may be substituted for the PPD skin test. A description of the QuantiFERON Gold test follows: "This Enzyme-linked Immunosorbent Assay (ELISA) test detects the release of Interferon-gamma (IFN-γ) in fresh heparinized whole blood from sensitized persons when it is incubated with mixtures of synthetic peptides simulating two proteins present in *M. tuberculosis*: Early Secretory Antigenic Target-6 (ESAT-6) and Culture Filtrate Protein-10 (CFP-10). ESAT-6 and CFP-10 are secreted by all *M. tuberculosis* and pathogenic *M. bovis* strains. Because these proteins are absent from all Bacille Calmette-Guérin (BCG) vaccine strains and from commonly encountered Non Tuberculous. Mycobacteria (NTM) except *M. kansasii*, *M. szulgai,* and *M. marinum*, QFT-G is expected to be more specific for *M. tuberculosis* than tests that use tuberculin Purified Protein Derivative (PPD) as the antigen".

T-Spot is another IFN-γ release assays in diagnosing *M. tuberculosis* infection. For this test, peripheral blood mononuclear cells (PBMCs) are incubated with two mixtures of peptides, one representing ESAT-6 and the other representing CFP-10. The test uses an enzyme-linked immunospot assay (ELISpot) to detect increases in the number of cells that secrete IFN-γ.

In the situation QFT-G or T-Spot is unavailable by local testing, incubated whole blood sample could be sent to central lab for QFT-G testing. If QFT-G/or T-Spot result is indeterminate, a retest is required at earliest to determine the eligibility of the subject. If retest is indeterminate or positive, the subject should be screen failed. If retest is negative, the PI should assess the subject's clinical condition and decide if the subject could be included.

7.3.5 Clinical Laboratory Testing

Routine, non-fasting clinical laboratory (hematology and chemistry and urinalysis) tests will be performed as detailed in Section 5.12 –Time and Event Table. At the discretion of the investigator, additional samples may be taken for safety reasons. All blood samples will be measured at a designated central laboratory.

A urine pregnancy test will be performed for all females of child bearing potential as detailed in Table 3.

The study clinical laboratory tests including analytes for clinical chemistry and hematology are shown below in Table 3.

Table 3. Clinical Laboratory Testing Lists

CHEMISTRY	HEMATOLOGY	Urinalysis	OTHER
Albumin	Haemoglobin	pH	Hepatitis B surface antigen[1]
Alkaline phosphatase	Haematocrit	Protein	Hepatitis C virus antibody[1]
Alanine amino-transferase (ALT or SGPT)	Platelet count	Glucose	HIV test[1]
Aspartate amino-transferase (AST or SGOT)	WBC count	Bilirubin and White Cell Count	Urine pregnancy test (in clinic)[2]
Bilirubin, direct	RBC count		FSH [3]
Bilirubin, indirect	Neutrophils, absolute		β-HCG blood test [4]
Bilirubin, total	Neutrophils, segs (%)		Lipid Profile[5] (fasting): Total Cholesterol, Low Density Lipoprotein (LDL) High Density Lipoprotein (HDL) Triglycerides
Calcium	Neutrophils, bands (%)		Stool culture /microscopy for: Salmonella, Shigella, Campylobacter, Fecal Ova and Parasites
Chloride	Basophils (%)		Clostridium difficile toxin
CO_2 content/Bicarbonate	Eosinophils (%)		Fecal calprotectin[6]
Creatinine	Eosinophils , absolute		Thyroid Function Test, including TSH, free T4 and free T3.
Creatine phosphokinase (CPK), total	Lymphocytes (%)		PK sampling[7]
Gamma glutamyl transferase (GGT)	Monocytes (%)		CRP
Glucose			
Phosphorus			
Potassium			
Protein, total serum			
Sodium			
Urea nitrogen (BUN)			
Uric Acid			

1 Assessed at Visit 1 (Screening) only
2 all visits subsequent to the screening visit
3 FSH to confirm postmenopausal status at screening visit only
4 Only for females of child-bearing potential at screening, and if urine pregnancy test positive
5 fasting lipid profile will be done as per Section 5.12 Time and Event table.
6 for biomarker assessment
7 Only done as per Section 7.4 Pharmacokinetics

7.3.6 C-Reactive Protein (CRP)

C-reactive protein is considered an acute-phase protein which provides an objective criterion of inflammatory activity. CRP has a short half-life (19 hours) and therefore rises early after the onset of inflammation and rapidly decreases after resolution of the inflammation (12). It is induced by interleukin-6, TNF-α and other proinflammatory cytokines that are produced

within the intestinal lamina propria. CRP measurements will be collected at screening, baseline, Week 1, 4, 8, 9, 12, 16 and 18 and will be analyzed by a central laboratory.

7.3.7 Fecal Calprotectin

Fecal calprotectin is a 36kDa calcium and zinc binding protein which is neutrophil derived and it represents 60% of cytosolic proteins in granulocytes. It is considered as a measurement of neutrophil migration to the gastrointestinal tract. Fecal calprotectin is a very stable marker (stable for one week at room temperature). There is a growing body of evidence that fecal calprotectin correlates well with disease activity and making it a useful tool in monitoring disease and treatment (13). Fecal calprotectin measurement will be collected as detailed in Section 5.12 – Time and Event table, from screening until the end of study visit (week 18) and will be analyzed by a central laboratory.

Subjects will be supplied with stool sample collection kits in advance and will be instructed to collect the sample at home, 1 day before the upcoming visit at which they have to provide the sample. Fecal samples (~20 g) for analysis of fecal calprotectin will be collected into the labeled stool collection containers, at protocol specified times (see Section 5.12 –Time and Event table) and shipped to central laboratory based on the laboratory manual. Samples will be analyzed using a validated analytical method.

7.3.8 Lipid Profile Testing

A fasting lipid profile blood collection, as per Section 5.12 –Time and Event table, will require subjects to refrain from all food and liquids (water and non-study medications permitted) for at least 10 hours prior to scheduled laboratory tests.

7.3.9 Liver Chemistry – Stopping and Follow-up Criteria

Phase II liver chemistry stopping and follow up criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

Phase II liver chemistry stopping criteria 1-5 are defined below:

1. ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) (or ALT ≥3xULN **and** INR>1.5, if INR measured).

NOTE: if serum bilirubin fractionation is not immediately available, study drug should be discontinued if ALT ≥3xULN **and** bilirubin ≥2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

2. ALT ≥ 5xULN.

3. ALT ≥ 3xULN if associated with the appearance or worsening of symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia.

4. ALT ≥ 3xULN persists for ≥ 4 weeks.

5. ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks

When any of the liver chemistry stopping criteria 1-5 is met, do the following:

- **Immediately** withdraw investigational product.

- Report the event to Reistone/designated CRO **within 24 hours** of learning its occurrence.

- Complete the liver event eCRF and SAE data collection tool if the event also meets the criteria for an SAE. All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) (or ALT ≥3xULN **and** INR>1.5, if INR measured; INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**.

NOTE: if serum bilirubin fractionation is not immediately available, study drug should be discontinued if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

- Complete the liver imaging and/or liver biopsy eCRFs if these tests are performed
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below.

- Withdraw the subject from the **study** (unless further safety follow up is required) after completion of the liver chemistry monitoring as described below.

- Do not re-challenge with investigational product.

In addition, for criterion 1:

- Make every reasonable attempt to have subjects return to clinic within **24 hours** for repeat liver chemistries, liver event follow-up assessments (see below), and close monitoring.

- A specialist or hepatology consultation is recommended.

- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilise or return to within baseline values

For criteria 2, 3, 4 and 5:

- Make every reasonable attempt to have subjects return to clinic **within 24-72 hrs** for repeat liver chemistries and liver event follow up assessments (see below)

- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values; criterion 5 subjects should be monitored as frequently as possible.

Subjects with ALT ≥3xULN **but** <5xULN **and** bilirubin <2xULN, without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks:

- Notify the Reistone/designated CRO medical monitor within 24 hours of learning of the abnormality to discuss subject safety.

- Can continue investigational product.

- Must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline.

- If at any time these subjects meet the liver chemistry stopping criteria, proceed as described above.

- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

For criteria 1-5, make every attempt to carry out the **liver event follow up assessments** described below:

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody;
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);
  - Hepatitis C RNA;
  - Cytomegalovirus IgM antibody;
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
  - Hepatitis E IgM antibody

- Blood sample for pharmacokinetic (PK) analysis, obtained within 24 hours of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of investigational product prior to blood sample draw on the eCRF. If the date or time of the

last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.

- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin≥2xULN.
- Obtain complete blood count with differential to assess eosinophilia.
- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
- Record alcohol use on the liver event alcohol intake eCRF.

The following are required for subjects with ALT ≥3xULN and bilirubin ≥2xULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

7.3.10 Pregnancy

If the subject is found to be pregnant, the subject must be withdrawn immediately, and any sponsor-supplied drug (SHR0302, placebo) should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study, should also be recorded following authorization from the subject's partner. Any pregnancy that occurs after the first dose of investigational drug must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to Reistone Biopharma/designated CRO within 24 hours of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and the newborn should be followed up to 1 month after birth. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Pregnancies will remain blinded to the study team.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to

receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to placebo need not be followed in the treatment phase.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

Spontaneous abortions must be reported as an SAE. Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to Reistone Biopharma/designated CRO.

7.3.11 Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.3.12 Definition of AE

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.
Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE).

"Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition

AEs which meet all of the following criteria:

- Serious
- Unexpected (as per assessment according to safety information in Investigator Brochure)
- There is at least a reasonable possibility that there is a causal relationship between the event and the medicinal product

will be classified as Suspected Unexpected Serious Adverse Reactions **(SUSARs**) and should be reported to the relevant ethics committee and to the relevant Health Authorities in accordance with applicable regulatory requirements for expedited reporting. Sponsor/designated CRO will report SUSARs to the ethics committee and relevant health authorities.

7.3.13 Definition of SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

   NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

   NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

   Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT ³ 3xULN **and** bilirubin ³ 2xULN (>35% direct) (or ALT ³ 3xULN and INR>1.5, if INR measured) termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants).

NOTE: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ³ 2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

7.3.14 AE and SAE reporting requirement and timeline

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. AEs will be collected from the start of study treatment (Visit 2) and until the follow up contact. SAEs will be collected from the time a subject consent to participate in the study up to and including any follow up contact.

All SAEs will be reported to Reistone Biopharma/designated CRO within 24 hours. Prompt notification of SAEs by the investigator to Reistone Biopharma/designated CRO is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met. All SAEs will be followed up until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Once resolved, the SAE eCRF page will be updated. The investigator should report SAE/serious incident per local regulations and local EC requirement. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Reistone Biopharma/designated CRO has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation according to local regulations. Reistone Biopharma/designated CRO will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Reistone Biopharma/designated CRO policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from Reistone Biopharma/designated CRO will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.3.15 Adverse Event of Special Interest (AESI)

The AE of special interest (AESI) (serious or non-serious) are determined based on previous knowledge about the disease and the mechanism of action of the investigational drug, as well as safety information from a similar class of drug. AESI is one of scientific and medical concern specific to the product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events require heightened surveillance and further investigation in order to characterize and understand them. The AESI will be managed and follow-up according to the SAE timeline and procedure. The study's AESI includes.

- Serious infection: Serious infection is defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials for more than 3 days.

- Thromboembolic event: Thromboembolic events are divided into two major groups which are venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), and arterial thromboembolic events, including arterial thrombosis and cerebrovascular accident (CVA).

7.4 Pharmacokinetics

[redacted]

[redacted]

[redacted]		[redacted]	
[redacted]		[redacted]	

8. Data Management

For this study subject data will be entered into Reistone Biopharma/designated CRO defined electronic case report forms (eCRFs), transmitted electronically to Reistone Biopharma /designated CRO and combined with data provided from other sources in a validated data system. Management of clinical data will be performed in accordance with applicable Reistone Biopharma/designated CRO data review, verification and cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using MedDRA. An appropriate medical dictionary that covers all approved drugs in the region will be referenced. eCRFs (including queries and audit trails) will be retained by Reistone Biopharma/designated CRO, and copies will be sent to the investigator to maintain as the investigator copy. In all cases, subject initials will not be collected or transmitted to Reistone Biopharma/designated CRO.

9. Data Analysis and Statistical Considerations

9.1 Hypothesis

The primary objective of the study will be evaluated for SHR0302 dose groups (8mg QD, 4mg BD, 4mg QD) compared to placebo group with respect to the percentage of patients with clinical response at week 8.

The Hochberg method will be used to maintain the 2-sided study-wise Type I error rate at 0.1. The null and alternative hypothesis for the primary endpoint that will be tested are:

H_{01}: The percentage of patients with clinical response at week 8 in SHR0302 8mg group – the percentage of patients with clinical response at week 8 in placebo group = 0;
H_{11}: The percentage of patients with clinical response at week 8 in SHR0302 8mg group – the percentage of patients with clinical response at week 8 in placebo group ≠ 0.

H_{02}: The percentage of patients with clinical response at week 8 in SHR0302 4mg BD group – the percentage of patients with clinical response at week 8 in placebo group = 0;
H_{12}: The percentage of patients with clinical response at week 8 in SHR0302 4mg BD group – the percentage of patients with clinical response at week 8 in placebo group ≠ 0.

H_{03}: The percentage of patients with clinical response at week 8 in SHR0302 4mg QD group – the percentage of patients with clinical response at week 8 in placebo group = 0;
H_{13}: The percentage of patients with clinical response at week 8 in SHR0302 4mg QD group – the percentage of patients with clinical response at week 8 in placebo group ≠ 0.

Two-sided p-values for the treatment group differences will be provided for all comparisons by using CMH test. Thus, 3 p-values will be gained and start with the least significant comparison and continue as long as tests are not significant until the first time when a significant comparison occurs and all remaining hypotheses will be rejected. Order the three p values as ($p_{(3)}$, $p_{(2)}$, $p_{(1)}$), where $p_{(3)} \geq p_{(2)} \geq p_{(1)}$. The decision rules are provided in below figure (Figure 2).

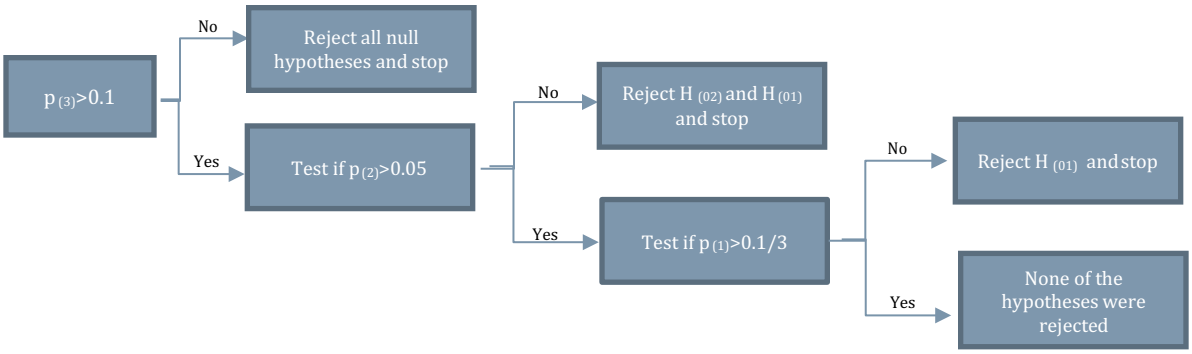

Figure 2. The decision rules of hypothesis

9.2 Study Design Considerations

9.2.1 Sample Size Assumptions

The sample size calculation is based on pairwise comparison of clinical response at week 8 among SHR0302 8mg, 4mg QD, 4mg BD dose group and placebo group at the 2-sided 0.1 significance level. 57%, 57%, 50%, 30% clinical response are assumed for 8mg QD, 4mg BD and 4mg QD dose group, placebo group at week 8 respectively. The planned sample size of 35 evaluable subjects per treatment group will provide 80% global power to detect at least 1 dose

group is different from placebo group by using Hochberg's step up test. The total sample size is 152 randomized subjects with consideration of 8% drop out rate.

9.3 Data Analysis Considerations

9.3.1 Analysis Dataset

- Full analysis set (FAS)

Full analysis set (FAS) will comprise of all randomized subjects who have received any amount of IP and have observed analysis data in at least one valid Mayo related score. All summaries of baseline and demographic data and all listings will be produced for the FAS population. In the full analysis set, subjects will be analyzed according to randomized treatment, regardless of the treatment received.

- Per protocol Analysis set (PPS)

Per protocol set (PPS) is defined as all subjects from FAS who do not have significant protocol violation.

- Safety analysis Set (SS)

The Safety analysis set will comprise all subjects who received any amount of investigational product (IP) and will be based on the actual treatment received, if this differs from that to which the subject was randomized to. The Safety analysis set will be used for all summaries of safety data.

9.3.2 Treatment Comparison of interest: Primary and others

Primary comparison:
SHR0302 8mg QD versus placebo, Week 8;
SHR0302 4mg BD versus placebo, Week 8;
SHR0302 4mg QD versus placebo, Week8.

9.3.3 Interim Analysis

The primary analysis will occur after all subjects have the opportunity to complete the 8-week treatment phase study visit

9.3.4 Key Elements of Analysis Plan

9.3.4.1 General Approach

In general, continuous variables will be summarized using number of non-missing observations, mean, median, standard deviation (SD), minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

9.3.4.2 Missing Data

Binary data: Non-completers considered failure (NCF) will be used.
Continuous data: Last-observation-carried-forward (LOCF) approach will be used

9.3.4.3 Efficacy Analysis

Analysis of the Primary Efficacy Endpoint

The primary analysis will be based on the FAS population. In addition, an analysis of the PPS population will be used to support the primary efficacy analysis.

For clinical response at week 8, the comparisons of the percentage of subjects achieving clinical response in each treatment versus placebo will be made using a stratified Cochran-Mantel-Haenszel (CMH) test with stratification according to prior anti- TNFα/biological treatment (with or without). Missing data will be imputed as Non-completers considered failure (NCF).

Sensitivity analyses for the primary endpoint include: (1) the same analysis using the per-protocol analysis set (2) using last-observation-carried-forward (LOCF) imputation for subscore other than endoscopy of Mayo score.

Analysis of the Secondary Efficacy Endpoints

Dichotomized secondary efficacy endpoints listed below will be analyzed by using a CMH Chi-Square test with stratification according to prior anti- TNFα treatment (with or without). Missing data will be imputed as Non-completers considered failure (NCF).

- ✓ The percentage of subjects with clinical remission (per 9-point modified Mayo score) at week 8
- ✓ The percentage of subjects with clinical remission (per total Mayo score) at week 8
- ✓ The percentage of subjects achieve endoscopic remission at week 8

The continuous secondary endpoints listed below will be analyzed using an analysis of covariance (ANCOVA) model including treatment group, baseline value, with/without previous exposure to anti-TNFα treatment as main effects. Missing data will be imputed by using Last-observation-carried-forward (LOCF) approach for subscore other than endoscopy of Mayo score.

- ✓ Change from baseline in 9-point modified Mayo score at week 8
- ✓ Change from baseline in total Mayo score at week 8
- ✓ Changes from baseline in partial Mayo score (Mayo score without endoscopy) at week 1, 4, 8, 9, 12 and 16.
- ✓ Change from baseline in the level of biomarkers CRP, fecal calprotectin.

9.3.4.4 Safety Analysis

Summaries of safety data will be based on the safety analysis set.

Adverse events will be grouped by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) and summarized by actual treatment.
Treatment emergent AEs are defined as AEs which commence on or after the time of start of IP administration. Adverse events without an onset date or time or AEs with an onset date of the date of IP administration but without an onset time will be defined as treatment emergent, except if an incomplete date (e.g., month and year) clearly indicates that the event started before administration of IP or if the AE stop date indicates that the event stopped before administration of IP.

Treatment emergent AEs will be summarized for each SHR0302 dose level and placebo. The number and percentage of subjects experiencing AEs and the number of TEAEs will be tabulated.

The following summaries will be presented:
- ✓ Overall summary of TEAEs.
- ✓ All TEAEs by SOC and PT.
- ✓ All TEAEs by SOC, PT, and severity.
- ✓ All TEAEs by SOC, PT, and relationship to IP.
- ✓ Serious AEs by SOC and PT.

Separate listings will be prepared for deaths and AEs leading to study discontinuation.
Observed values and actual changes from baseline of continuous laboratory parameters (hematology and biochemistry), dipstick urinalysis results evaluation (Normal, Abnormal Not Clinically Significant, or Abnormal Clinically Significant), vital signs, and ECG parameters will be summarized at each protocol scheduled time point, by actual treatment at each time point. Actual values and actual changes from baseline will be presented. Categorical outcomes will be summarized by frequency tabulations. Abnormal laboratory values will be flagged and will be identified in the listings. Microscopy data, if available, will be listed.
Shift tables representing categorical change of laboratory results from baseline to each post baseline visit will be presented. QTcF prolongation and ECG interpretations will be summarized by frequency tabulations.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary and will be grouped by PT. The summary tables will show the number and percentage of subjects by PT, for all subjects overall. Prior medications are those medications that were stopped prior to first study treatment. Concomitant medications are medications taken at least once after first study treatment. Medications stopped on the same day as first study treatment will be considered as prior medication only. Only concomitant medications will be summarized. Prior medications will be listed only. Prior and concomitant medications will be listed separately. For the summaries of concomitant medications, subjects who take the same medication (in terms of the PT) more than once will only be counted once for that medication.

Physical examination and pregnancy data will be listed only.

10. Study Conduct Considerations

10.1 Regulatory and Ethical Consideration to GCP standard

Prior to initiation of a study site, Reistone/designated CRO will obtain approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements. The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

Reistone/designated CRO will provide full details of the above procedures, either verbally, in writing, or both. Written informed consent must be obtained from each subject prior to participation in the study.

10.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, molecular profiling supplement, informed consent forms, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Reistone/designated CRO.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Reistone/designated CRO in writing immediately after the implementation.

10.3 Informed Consent Process

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

In case of data transfer, Reistone/designated CRO will maintain high standards of confidentiality and protection of subject personal data. The informed consent form must be in compliance with ICH GCP, local regulatory requirements, and legal requirements. The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Reistone/designated CRO before use.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible
risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent form.

10.4 Study Monitoring and Quality Control

During study conduct, Reistone/designated CRO will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on eCRFs is accurate. The investigator and institution will allow Reistone/designated CRO monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.
The study site may be subject to review by the institutional review board (IRB)/independent ethics committee (IEC), and/or to quality assurance audits performed by Reistone, or companies working with or on behalf of Reistone, and/or to inspection by appropriate regulatory authorities. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

10.5 Study Site Closure

Upon completion or termination of the study, the Reistone/designated CRO monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, and GCP requirement. Reistone/designated CRO reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe non-compliance. If Reistone/designated CRO

determines that such action is required, Reistone/designated CRO will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, Reistone/designated CRO will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, Reistone/designated CRO will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. Reistone/designated CRO will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

10.6 Record Retention

To enable evaluations and/or audits from regulatory authorities or Reistone/designated CRO, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Reistone/designated CRO should be prospectively notified. The study records must be transferred to a designee acceptable to Reistone/designated CRO, such as another investigator, another institution, or to Reistone/designated CRO. The investigator must obtain Reistone/designated CRO's written permission before disposing of any records, even if retention requirements have been met.

10.7 Independent Data Monitoring Committee (IDMC)

A data monitoring committee for efficacy is not required for this study. Data safety monitoring will be conducted on an ongoing basis by the Sponsor study team.

10.8 Provision of study results to Investigators, posting to the Clinical Trial Registry and Publication.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a Reistone/designated CRO site or other mutually-agreeable location.

Reistone/designated CRO will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate. Reistone/designated CRO will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
The results summary will be posted to the Clinical Study Register when appropriate determined by Reistone.

In addition, a manuscript will be submitted to a peer-reviewed journal for publication.
The results summary will be posted to the Clinical Study Register if required by legal agreement, local law or regulation.

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10. US FDA. Ulcerative Colitis: Clinical trial endpoints. Guidance for industry. Aug 2016.

11. Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium tuberculosis Infection – United States, 2010 https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5905a1.htm

12. Vermiere S, Van Assche G, Rutgeerts P. C-Reactive Protein as a Marker for Inflammatory Bowel Disease. Inflamm Bowel Dis 2004; 10:661-665.

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12.Appendices

Appendix 1 Mayo Scoring System for Assessment of Ulcerative Colitis Activity*

Stool frequency†:
0 = Normal no. of stools for this patient
1 = 1 to 2 stools more than normal
2 = 3 to 4 stools more than normal
3 = 5 or more stools more than normal

Subscore, (0 to 3) = _____

Rectal bleeding‡:
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

Subscore, (0 to 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)

Subscore, (0 to 3) = _____

Physician's global assessment§:
0 = Normal
1 = Mild disease
2 = Moderate disease
3 = Severe disease

Subscore, (0 to 3) = _____

TOTAL score of (0-12) = _____

* The Mayo score ranges from 0 to 12, with higher scores indicating more severe disease.

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

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

£ Mild friability has been removed according to the guidance issued by the Food and Drug Administration.

§ The physician's global assessment acknowledges the three other criteria, the patient's daily recollection of abdominal discomfort and general sense of wellbeing, and other observations, such as physical findings and the patient's performance status.

9-point modified Mayo score and Partial Mayo score can be derived from the Mayo score.

Adapted from: Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987; 317 (26):1625-9
Food and Drug Administration, Center for Drug Evaluation and Research(CDER), Ulcerative Colitis: Clinical Trial Endpoints Guidance for Industry(August 2016).

Appendix 2 Cockcroft-Gault Calculation

The Cockcroft-Gault formula may be used to calculate an Estimated Creatinine Clearance, which in turn estimates Glomerular filtration rate (GFR).

$$\text{Est. Creatinine Clearance (mL/min)} = \frac{[140-\text{Age(years)}] \times \text{Weight(kg)} \times \text{Factor}^{a}}{(72 \times \text{Serum Creatinine [mg/dL]})}$$

[a] Factor is equal to 0.85 in females, and 1.00 in males

Appendix 3 ECG Exclusion criteria

An ECG finding that would preclude a subject from entering the trial is defined as a 12-lead tracing that is interpreted as, but not limited to, any of the following:

- Sinus tachycardia ³110bpm

  *Note: sinus tachycardia ³110bpm should be confirmed by two additional readings at least 5 minutes apart

- Sinus bradycardia <45bpm

  *Note: Sinus bradycardia <45bpm should be confirmed by two additional readings at least 5 minutes apart.

- Multifocal atrial tachycardia
- Junctional tachycardia (heart rate >100bpm)
- Junctional escape complexes
- Supraventricular tachycardia (>100bpm)
- Ventricular tachycardias (sustained, polymorphic, or monomorphic)
- Atrial fibrillation with rapid ventricular response (rate >100bpm)
- Atrial flutter

- Evidence of bigeminy, trigeminy or multifocal premature ventricular complexes
- Ventricular flutter
- Ventricular fibrillation
- Torsades de Pointes
- R on T phenomenon
- Wide QRS tachycardia (diagnosis unknown)
- Electrical alternans
- Pacemaker
- Idioventricular rhythm – heart rate <100bpm
- Evidence of Mobitz type II second degree or third degree atrioventricular (AV) block
- AV dissociation
- Bifascicular block
- Trifascicular block
- Left bundle branch block
- For subjects **without complete right bundle branch block**: QTc(F) ³450msec or an ECG that is unsuitable for QT measurements (e.g., poor defined termination of the T wave).
- For subjects **with complete right bundle branch block**: QTc(F) ³480msec or an ECG that is unsuitable for QT measurements (e.g., poor defined termination of the T wave).

*Note: All potentially exclusionary QT measurements should be confirmed by two additional readings at least 5 minutes apart.

- Accessory pathway (Wolff-Parkinson-White, Lown-Ganong-Levine)
- Myocardial infarction (anterior, inferior, posterior, lateral, septal, non-Q wave)
- Pathological Q waves (defined as wide [>0.04 seconds] and deep [>0.4mV (4mm with 10mm/mV setting)] or >25% of the height of the corresponding R wave, providing the R wave was >0.5mV [5mm with 10mm/mV setting], appearing in at least two contiguous leads.

*Note: prior evidence (i.e., ECG obtained at least 12 months prior) of pathological Q waves that are unchanged are not exclusionary

Appendix 4 Prohibited Concomitant Medications

The list of prohibited concomitant medications includes the following medications with moderate to potent inhibitory or inducing CPY3A systemic properties.
Topical medications, eg, Ketoconazole cream, and grapefruit juice are not prohibited.

CYP3A INHIBITORS	**CYP3A INDUCERS**
Atazanavir	Barbiturates
Telithromycin	Carbamazepine
Clarithromycin	Efavirenz
Clotrimazole	Modafinil
Delaviridine	Nevirapine
Fluvoxamine	Phenobarbital
Indinavir	Phenytoin
Itraconazole	Rifabutin
Ketoconazole	Rifampin
Mibefradil	Saint John's Wort
Mifepristone	Nevaripine
Nefazodone	Oxcarbazepine
Nelfinavir	Troglitazone
Ritonavir	
Saquinavir	
Aprepitant	

Erythromycin	
Fluconazole	
Diltiazem	

Protocol Amendment No.01

1. Section 1.4.2 Secondary Efficacy Endpoints, page 13, 14

Change from

1.4.2 Secondary Efficacy Endpoints

- The percentage of subjects that achieve clinical remission per 9-point modified Mayo score at week 8, where stool frequency subscore ≤ 1, rectal bleeding subscore of 0, and endoscopic subscore ≤ 1
- The percentage of subjects that achieve clinical remission at week 8 as per total Mayo score of 2 points or lower ≤2, with no individual subscore exceeding 1point and a rectal bleeding subscore of 0.
- ……

Change to

1.4.2 Secondary Efficacy Endpoints

- The percentage of subjects that achieve clinical remission per 9-point modified Mayo score at week 8, where stool frequency subscore ≤ 1, rectal bleeding subscore of 0, and endoscopic subscore ≤ 1
- The percentage of subjects that achieve clinical remission at week 8 as per total Mayo score of 2 points or lower **than** 2, with no individual subscore exceeding 1point and a rectal bleeding subscore of 0.
- ……

Rationale: Refine Chinese translation of related secondary efficacy endpoints.

[redacted]

[redacted]

3. Section 5.2 Inclusion Criteria and 5.3 Exclusion Criteria, page 20 to 24

Change from

Bullet

Change to

Number

Rationale: Number the inclusion and exclusion criteria.

4. Section 5.2 Inclusion Criteria, page 20, 21

Change from

2. Active ulcerative colitis with a 9-point modified Mayo score of 5 to 9 points and endoscopic subscore of 2 to 3 (The duration of the time between endoscopy and baseline should not exceed 10 days and allow central over read turn over before randomization).

~~4. Subjects previously not exposed to anti-TNF treatment (e.g., anti-TNF-naïve) or subjects previously exposed to anti-TNF therapy (eg; infliximab, adalimumab or certolizumab pegol) or other biological treatment (eg Vedolizumab) at a dose registered for the treatment of UC. The patients previously exposed to biological therapy should have discontinued the treatment for a minimum of 12 weeks prior to baseline. Subjects deemed by the treating physician as having inadequate response or intolerance to the conventional immune-suppressants (eg azathioprine, 6-mercaptopurine), anti-TNF or other biological treatments, or unable to receive these treatments for other reasons.~~

6. Subject must have no evidence of active, latent, or inadequately treated infection with *Mycobacterium tuberculosis* (i.e., tuberculosis [TB]), as defined by the following:

   A negative Mantoux Purified Protein Derivative (PPD) skin test result (≤ 5 mm of induration), or negative QuantiFERON TB Gold (QFT Gold test) performed within the 3 months prior to/within screening;

   AND

   Subject must have a chest ~~X-ray~~, taken within the 3 months prior to/within screening, and showing no changes suggestive of active TB infection.

AND

Subject must have no history of either untreated or inadequately treated latent or active TB infection

Change to

2. Active ulcerative colitis with a 9-point modified Mayo score of 5 to 9 points and endoscopic subscore of 2 to 3 (The duration of the time between endoscopy and baseline should not exceed 10 days and allow central over read turn over before randomization).

4. <u>Subjects deemed by the treating physician as having inadequate response, loss of response or intolerance to the conventional treatment (immune-suppressants or corticosteroids), AND</u>

- **<u>Naïve to anti-TNF treatment (e.g. infliximab, adalimumab or certolizumab pegol) or other biological treatment (e.g. Vedolizumab);</u>**

OR

- **<u>Previously exposed to anti-TNF therapy or other biological treatment having discontinued the treatment for a minimum of 12 weeks prior to baseline.</u>**

6. Subject must have no evidence of active, latent, or inadequately treated infection with *Mycobacterium tuberculosis* (i.e., tuberculosis [TB]), as defined by the following:

- A negative Mantoux Purified Protein Derivative (PPD) skin test result (≤ 5 mm of induration), or negative QuantiFERON TB Gold (QFT Gold test) **<u>/or T-Spot test</u>** performed within the 3 months prior to/within screening;

AND

- Subject must have a chest **<u>radiograph</u>**, taken within the 3 months prior to/within screening, and showing no changes suggestive of active TB infection.

AND

- Subject must have no history of either untreated or inadequately treated latent or active TB infection

Rationale: Refine the Chinese translation of the 2nd inclusion criteria, to clarify the central reading result of endoscopy need to be ready before randomization. Clarify subjects who had inadequate response, loss of response or intolerance to conventional treatment (immune-suppressants or corticoserioids) could be included, whether the subjects previoulsy exposed to biological therapy or not. Allow T-Spot as an alternative test for TB infection screening.

5. Section 5.3 Exclusion Criteria, page 21, 22

Change from

3. Treatment naïve subjects diagnosed with ulcerative colitis (without previous exposure to treatment).
7. Subjects receiving the following therapy:
   - Azathioprine/6-mercaptopurine, methotrexate, thalidomide within 7 days prior to baseline.
   - Cyclosporine, mycophenolate, tacrolimus within 4 weeks prior to baseline.
   - Interferon therapy within ~~8~~ weeks prior to baseline.
   - Anti-TNFα therapy/other biological therapies within ~~8~~ weeks prior to baseline.
   - Intravenous corticosteroids or rectally administered formulation of corticosteroids or 5-ASA within 2 weeks prior to baseline.
9. Subjects with evidence of hematopoietic disorders:
   - Hemoglobin levels <9.0 g/dL or hematocrit <30% ~~at screening visit or within the 3 months prior to baseline~~.
   - An absolute white blood cell (WBC) count of <3.0 x 10^9/L (<3000/mm^3) or Absolute Neutrophil Count (ANC) of <1.2 X 10^9/L (<1200/mm^3) ~~at screening visit or within the 3 months prior to baseline~~.
   - Thrombocytopenia, as defined by a platelet count <100 x 10^9/L (<100,000/mm^3) ~~at screening visit or within the 3 months prior to baseline~~.

Change to

3. Treatment naïve subjects diagnosed with ulcerative colitis, (without previous exposure to **any of the following therapies for UC** treatment: **corticosteroids, immune-suppressants, or biological treatments**).

7. Subjects receiving the following therapy:
   - Azathioprine/6-mercaptopurine, methotrexate, thalidomide within 7 days prior to baseline.
   - Cyclosporine, mycophenolate, tacrolimus within 4 weeks prior to baseline.
   - Interferon therapy within **12** weeks prior to baseline.
   - Anti-TNFα therapy/other biological therapies within **12** weeks prior to baseline.
   - Intravenous corticosteroids or rectally administered formulation of corticosteroids or 5-ASA within 2 weeks prior to baseline.
9. Subjects with evidence of hematopoietic disorders **at screening**:
   - Hemoglobin levels <9.0 g/dL or hematocrit <30%.
   - An absolute white blood cell (WBC) count of <3.0 x 10^9/L (<3000/mm^3) or Absolute Neutrophil Count (ANC) of <1.2 X 10^9/L (<1200/mm^3).
   - Thrombocytopenia, as defined by a platelet count <100 x 10^9/L (<100,000/mm^3).

Rationale: Clarify the definition of treatment naïve subjects in exclusion criteria. Claify the exclusion criteria for biological therapy use, in order to keep consistency with Section 5.2 Inclusion Criteria. Refine the Chinese translation to clarify subjects receiving 5-ASA in rectally administrated formulation within 2 weeks prior to baseline should be excluded. Clarify subjects with hematopoietic disorders at screening should be excluded.

6. Section 5.7 Pre-Screen and Screen Failure, page 27

Change from

- ……
- Reason subject failed screening
- Primary method of subject recruitment
- Serious Adverse Events (SAEs) information, if ~~applicable only for any SAE considered as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a concomitant medication~~

Change to

- ……
- Reason subject failed screening
- Primary method of subject recruitment
- Serious Adverse Events (SAEs) information, if **any**

Rationale: Clarify SAEs will be recorded for screen failures, if any.

7. Section 5.8 Early Withdrawal, page 28

Change from

- ……
- Laboratory assessments (including chemistry, haematology, and pregnancy test for females of childbearing potential and routine urinalysis)
- ~~Evaluation of smoking status and smoking cessation counselling~~
- Call IVRS to report subject's early withdrawal from the study
- Endoscopy, Mayo score, 9-point modified Mayo score, and partial Mayo score.

Change to

- ……
- Laboratory assessments (including chemistry, haematology, and pregnancy test for females of childbearing potential and routine urinalysis)
- Call IVRS to report subject's early withdrawal from the study
- Endoscopy, Mayo score, 9-point modified Mayo score, and partial Mayo score, **if feasible**.

Rationale: Typo corretion. Clarify if data avalible, Endoscopy, and relevant Mayo scoring will be assessed.

8. Section 5.9 Stopping Criteria, page 29

Change from

~~Withdrawal decisions are to be based on an average QTc value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period, and then~~ use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study.

Change to

Use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study.

Rationale: Clarify the procedure of ECG to keep consistent with the Section 7.3.2 12 lead ECG, that triplicate ECGs mesurements are required, no matter the QT interval prolonged or not.

9. Section 5.12 Time and Event Table, page 30-32

Change from

5.12 Time and Event Table
See Table1.

Table 1. Time and Event Table

Period	Screening	Baseline	Treatment Phase		End of Treatment Phase	Extension Phase		End of Extension Phase	Follow-up/EW[11]
VISIT	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Week	**-3 to -1**	**0**	**1**	**4**	**8**	**9**	**12**	**16**	**18**
Day	**-21 to -4**	**0**	**7± 2 days**	**28± 3 days**	**56± 3 days**	**63± 2 days**	**84± 3 days**	**112± 3 days**	**126± 5 days**
Procedures									
Written Informed Consent[1]	x								
Demography/Medical History	x								
Physical Examination	x	x	x	x	x	x	x	x	x
Chest X-ray[2]	x								
Inclusion/Exclusion Criteria	x								
Randomisation Criteria		x							
Study medication dispensing		x		x	x		x		
Study medication accountability				x	x		x	x	x [12]
Register Visit in IVRS[3]	x	x		x	x		x	x	x[12]
Endoscopy (colonoscopy)[4]		x [4]			x				x[12]
Efficacy Assessments									
Patient Dairy[5]	x	x	x	x	x	x	x	x	x
Mayo Score		x			x				x[12]
9-point Modified Mayo Score		x			x				x[12]
Partial Mayo Score		x	x	x	x	x	x	x	x
Safety Assessments									
12-lead ECG	x	x		x	x	x		x	x

Vital Signs[6]	x	x	x	x	x	x	x	x	x
Adverse Event Assessment[7]		x	x	x	x	x	x	x	x
Laboratory Assessments									
Haematology and Chemistry Tests	x	x	x	x	x	x	x	x	x
Urinalysis	x	x	x	x	x	x	x	x	x
Lipid Profile (Fasting)		x		x	x	x		x	x
TSH, fT4, fT3	x	x	x	x	x	x	x	x	x
QuantiFERON / PPD test [8]	x								
Hep B sur Ag, Hep C Ab, HIV test	x								
Stool culture/ microscopy	x								
CRP	x	x	x	x	x	x	x	x	x
Faecal Calprotectin		x		x	x			x	
Urine Pregnancy Test[9]	~~x~~	x	x	x	x	x	x	x	x
β-HCG (blood)[10]	x								
[redacted]									
Medication									
Concurrent Medication Assessment	x	x	x	x	x	x	x	x	

1. Written informed consent must be obtained prior to performing any Visit 1 procedures or initiating any alterations in a subject's medications
2. Only to be performed if there is no chest X-ray or CT scan available within ~~6~~ months of Visit 1
3. IVRS is a randomisation machine used to record all the patient visit.
4. Colonoscopy is completed by baseline (visit 2 – Day 0). The duration of time between endoscopy and baseline is no more than -10 days.
5. Subject use an electronic diary to record disease related medical problems experienced during the study.
6. Vital signs include resting blood pressure, heart rate, and body temperature. It is advised to measure them before any procedures or questionnaires.
7. Adverse events and Serious Adverse Events to be collected from the start of the study drug (visit 2) until the Follow-Up ~~phone call~~ contact. However, any serious adverse events ~~recorded as related to study participation~~ will be recorded from the time of consent.
8. Subjects who have previously receive BCG vaccination ~~may~~ be tested by QuantiFERON Gold test, and the result will determine the subject eligibility for participation. ~~Investigator also has the option to use alternative PPD test.~~
9. Urine pregnancy test to be done in females of childbearing potential only
10. β-Human Chorionic Gonadotrophin(β-HCG) to be done in females of childbearing potential only if urine pregnancy test positive
11. Early withdrawal visit should be done 2 weeks after last dose/decision of withdrawal.
12. Only to be conducted in the early withdrawn subjects.

[redacted]

[redacted]

Change to

5.12 Time and Event Table
See Table1.

Table 1. Time and Event Table

Period	Screening	Baseline	Treatment Phase		End of Treatment Phase	Extension Phase		End of Extension Phase	Follow-up/EW[11]
VISIT	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Week	**-3 to -1**	**0**	**1**	**4**	**8**	**9**	**12**	**16**	**18**
Day	**-21 to -4**	**0**	**7± 2 days**	**28± 3 days**	**56± 3 days**	**63± 2 days**	**84± 3 days**	**112± 3 days**	**126± 5 days**
Procedures									
Written Informed Consent[1]	x								
Demography/Medical History	x								
Physical Examination	x	x	x	x	x	x	x	x	x
Chest X-ray[2]	x								
Inclusion/Exclusion Criteria	x								
Randomisation Criteria		x							
Study medication dispensing		x		x	x		x		
Study medication accountability				x	x		x	x	x [12]
Register Visit in IVRS[3]	x	x		x	x		x	x	x[12]
Endoscopy (colonoscopy)[4]		x [4]			x				x[12]
Efficacy Assessments									
Patient Dairy[5]	x	x	x	x	x	x	x	x	x
Mayo Score		x			x				x[12]
9-point Modified Mayo Score		x			x				x[12]
Partial Mayo Score		x	x	x	x	x	x	x	x
Safety Assessments									

Period	Screening	Baseline	Treatment Phase		End of Treatment Phase	Extension Phase		End of Extension Phase	Follow-up/EW[11]
VISIT	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Week	**-3 to -1**	**0**	**1**	**4**	**8**	**9**	**12**	**16**	**18**
Day	**-21 to -4**	**0**	**7± 2 days**	**28± 3 days**	**56± 3 days**	**63± 2 days**	**84± 3 days**	**112± 3 days**	**126± 5 days**
Procedures									
12-lead ECG	x	x		x	x	x		x	x
Vital Signs[6]	x	x	x	x	x	x	x	x	x
Adverse Event Assessment[7]		x	x	x	x	x	x	x	x
Laboratory Assessments									
Haematology and Chemistry Tests	x	x	x	x	x	x	x	x	x
Urinalysis	x	x	x	x	x	x	x	x	x
Lipid Profile (Fasting)		x		x	x	x		x	x
TSH, fT4, fT3	x	x	x	x	x	x	x	x	x
QuantiFERON **/or T-Spot /or** PPD test [8]	x								
Hep B sur Ag, Hep C Ab, HIV test	x								
Stool culture/ microscopy	x								
CRP	x	x	x	x	x	x	x	x	x
Faecal Calprotectin		x		x	x			x	
Urine Pregnancy Test[9]		x	x	x	x	x	x	x	x
β-HCG (blood)[10]	x								
[redacted]									
FSH[15]	**x**								
Medication									
Concurrent Medication Assessment	x	x	x	x	x	x	x	x	**x**

1. Written informed consent must be obtained prior to performing any Visit 1 procedures or initiating any alterations in a subject's medications
2. Only to be performed if there is no chest X-ray or CT scan available within **3** months of Visit 1
3. IVRS is a randomisation machine used to record all the patient visit.
4. Colonoscopy is completed by baseline (visit 2 – Day 0). The duration of time between endoscopy and baseline is no more than -10 days.
5. Subject use an electronic diary to record disease related medical problems experienced during the study.
6. Vital signs include resting blood pressure, heart rate, and body temperature. It is advised to measure them before any procedures or questionnaires.

7. Adverse events and Serious Adverse Events to be collected from the start of the study drug (visit 2) until the Follow-Up contact. However, any serious adverse events will be recorded from the time of consent.
8. **Investigator has the option to use PPD test, QuantiFERON Gold test or T-Spot for TB screening.** Subjects who have previously receive BCG vaccination **will** be tested by QuantiFERON Gold test **/or T-Spot test**, and the result will determine the subject eligibility for participation.
9. Urine pregnancy test to be done in females of childbearing potential only
10. β-Human Chorionic Gonadotrophin(β-HCG) to be done in females of childbearing potential **at screening visit, and** only **to be done** if urine pregnancy test positive **at other study visits.**
11. Early withdrawal visit should be done **within** 2 weeks after last dose/decision of withdrawal.
12. Only to be conducted in the early withdrawn subjects.

[redacted]

14. [redacted]

15. FSH to confirm postmenopausal status at screening visit only.

Rationale: Correct the typos in Table 1 in Section 5.12 Time and Event Table, and the footnotes to ensure the procedures are consistent with subject selection criteria. Clarify chext X-ray to be performed if no chest X-ray or CT scan available within 3 months of Visit 1 instead of 6 months in footnote 2. Typo correction to clarify the follow up visit is not a phone-call contact and clarify any SAEs will be recorded from the time of consent in footnote 7. Allow T-Spot as an alternative test for TB infection screening.Clarify only serum β-Human Chorionic Gonadotrophin (β-HCG) is requested for pregnancy testing at screening visit and urine test is to be done from baseline. Clarify concurrent medication assessment should be done in Follow up/EW visit, in order to keep consistent with Section 6.6 Concomitant Medications. Clarify the early withdrawal visit should be done within 2 weeks after last dose/decision of withdrawl rather than after 2 weeks of last dose/decision of withdrawl in footnote 11. FSH test is listed in the table to confirm postmenopausal status at screening.

10. Section 6.1 Investigational Product/Placebo Supply, page 33

Change from

SHR0302 will be provided as combination of 4mg tablets, including the matching placebo by the Sponsor. At study visits on Day 0, and Week 4, sufficient trial medication will be dispensed to complete dosing for four weeks.

Change to

SHR0302 will be provided as combination of 4mg tablets, including the matching placebo by the Sponsor. At study visits on Day 0, and Week 4, sufficient trial medication will be dispensed to complete dosing for four weeks.

Rationale: Refine the Chinese translation.

11. Section 6.6.1 Permitted Concomitant Medications, page 36

Change from

- Oral 5-ASA or sulfasalazine are allowed providing that the dose is stable for at least 2 weeks prior to baseline and during the study treatment period.

- Oral steroids are allowed during the study up to the dose of 30 mg/day of prednisolone or equivalent, providing that the dose has not been commenced or ~~increased~~ within 2 weeks of baseline.

Change to

- Oral 5-ASA or sulfasalazine are allowed providing that the dose is stable for at least 2 weeks prior to baseline and during the study treatment period.

- Oral steroids are allowed during the study up to the dose of 30 mg/day of prednisolone or equivalent, providing that the dose has not been commenced or **changed** within 2 weeks of baseline **and until to the end of treatment phase (Week 8). During the extension phase, tapering of the oral steroid dose can be commenced for subjects at investigator's discretion, in accordance with the predefined tapering scheduled treatment:**

  - **Subjects receiving > 10 mg/day prednisolone or equivalent: taper dose by 5 mg/week until a 10 mg/day dose (or equivalent) is reached, then continue tapering at 2.5 mg/week until 0 mg/day.**
  - **Subjects receiving ≤ 10 mg/day prednisolone or equivalent: taper dose by 2.5 mg/week until 0 mg/day.**

If subject experiences worsening of signs or symptoms during the tapering schedule, in the opinion of the investigator, due to reduction in oral steroid daily

dose, the daily oral steroid dosage for the subject could be reverted to the preceding daily dosage instructed by the investigator, but should not exceed Baseline dose.

Rationale: Provide oral steroids tapering guidance in permitted concomitant medications and refine the Chinese translation of oral steroids permittion.

12. Section 6.6.2 Prohibited Medications, page 36, 37

Change from

The following medications are prohibited throughout the duration of the study:

- azathioprine, 6-mercaptopurine, methotrexate and thalidomide ~~within 7 days of baseline~~;
- cyclosporine, mycophenolate and tacrolimus ~~within 4 weeks of baseline~~;
- interferon ~~within 8 weeks of baseline~~ and
- anti-TNFα therapy/other biological treatment ~~within 8 weeks of baseline~~;
- intravenous corticosteroids or rectally administered formulation of corticosteroids or 5-ASA ~~within 2 weeks prior to baseline~~.
- Oral JAK inhibitors (except the trial medication)

In addition, concomitant administration of CYP3A inducers and moderate to potent CYP3A inhibitors with systemic effects should be avoided for the duration of the study.

Examples of medications that are prohibited from use from 28 days prior to the first dose of study medication until completion of follow up period, due to potential for drug interactions or confounding of data interpretation, are listed in Appendix 4.

Change to

The following medications are prohibited throughout the duration of the study:

- azathioprine, 6-mercaptopurine, methotrexate and thalidomide;
- cyclosporine, mycophenolate and tacrolimus;
- interferon and
- anti-TNFα therapy/other biological treatment;
- intravenous corticosteroids or rectally administered formulation of corticosteroids or 5-ASA.
- Oral JAK inhibitors (except the trial medication)

In addition, concomitant administration of CYP3A inducers and moderate to potent CYP3A inhibitors with systemic effects should be avoided for the duration of the study.

Examples of medications that are prohibited from use from 28 days prior to the first dose of study medication until completion of follow up period, due to potential for drug interactions or confounding of data interpretation, are listed in Appendix 4.

All live vaccines immunization are prohibited from signing of informed consent, throughout the duration of the study, and for 1 month after last dose of study medication.

Rationale: Remove the time period of "within baseline", to clarify the prohibition is throughout the duration of the study to avoid confusion. Refine the Chinese translation to clarify 5-ASA in rectally administrated formulation is prohibited. And add live vaccines immunization as prohibited medications.

13. Section 7.1 Critical Baseline Assessments, page 38

Change from

- ……
- 12-Lead ECG
- Chest x-ray (or historical CT-Scan obtained within ~~6~~ months of Screening (Visit 1))
- Clinical laboratory assessments (including chemistry, hematology, ~~urine~~ pregnancy test)
- ……

Change to

- ……
- 12-Lead ECG
- Chest x-ray (or historical **chest x-ray**/CT-Scan obtained within **3** months of Screening (Visit 1))
- Clinical laboratory assessments (including chemistry, hematology, pregnancy test)
- ……

Rationale: Typo correction.

14. Section 7.2.2 Secondary Efficacy Endpoints, page 38

Change from

7.2.2 Secondary Efficacy Endpoints

- The percentage of subjects achieve clinical remission per 9-point modified Mayo score at week 8, where stool frequency subscore ≤ 1, rectal bleeding subscore of 0, and endoscopic subscore ≤ 1
- The percentage of subjects achieve clinical remission at week 8 as per total Mayo score of 2 points or lower ≤2, with no individual subscore exceeding 1point and a rectal bleeding subscore of 0.

- ……

Change to

7.2.2 Secondary Efficacy Endpoints

- The percentage of subjects achieve clinical remission per 9-point modified Mayo score at week 8, where stool frequency subscore ≤ 1, rectal bleeding subscore of 0, and endoscopic subscore ≤ 1
- The percentage of subjects achieve clinical remission at week 8 as per total Mayo score of 2 points or lower **than** 2, with no individual subscore exceeding 1point and a rectal bleeding subscore of 0.

- ……

Rationale: Refine Chinese translation of related secondary efficacy endpoints.

15. Section 7.2.4 Patient Diary Assessment, page 39

Change from

Subjects will be provided with an electronic diary at screening visit ~~and at baseline visit~~ in order to collect the patient reported outcome components of the total Mayo score (see Appendix 1)……

Change to

Subjects will be provided with an electronic diary at screening visit in order to collect the patient reported outcome components of the total Mayo score (see Appendix 1)……

Rationale: Correct electronic diary is provided at screening visit.

16. Section 7.2.5 Mayo Score Assessment, page 40

Change from

Mayo score is assessed at baseline and Week 8. ~~If at baseline the subject scores ≥ 4 points on the Mayo score excluding the endoscopy sub-score, appropriate endoscopy examination (colonoscopy) will be performed.~~ If the subject scores ≥2 on the endoscopic sub-score of the Mayo Score at baseline and meet all other inclusion/exclusion criteria, the subject will be randomized. Should any bowel preparation be required to perform the colonoscopy, 3-day patient diary must be completed and assessed prior to any bowel preparation. For the baseline endoscopy, the duration of the time between endoscopy and baseline should not exceed 10 days.

Change to

Mayo score is assessed at baseline and Week 8. If the subject scores ≥2 on the endoscopic sub-score of the Mayo Score at baseline and meet all other inclusion/exclusion criteria, the subject will be randomized. Should any bowel preparation be required to perform the colonoscopy, 3-day patient diary must be completed and assessed prior to any bowel preparation. For the baseline endoscopy, the duration of the time between endoscopy and baseline should not exceed 10 days. **Baseline (Day 0 -Visit 2) endoscopy images/films (eligibility assessment) and Week 8 endoscopy images/films will be submitted to central lab for central reading. The central lab will send eligibility report to confirm eligibility.**

Rationale: According the study procedure, endoscopy is completed by baseline, remove the requirement of "If at baseline the subject scores ≥ 4 points on the Mayo score excluding the endoscopy sub-score, appropriate endoscopy examination (colonoscopy) will be performed", to avoid misunderstanding. Clarify that the images/films of endoscopy will be sent to central lab for central reading.

17. Section 7.3.2 12 Lead ECG, page 41

Change from

12-lead ECG measurement and rhythm strip (10 seconds) will be obtained after measurement of vital signs. Triplicate ECG measurements are collected at rate of 3 ECGs over 5 minutes period. After vital signs are obtained subjects should be placed in the supine position for the ECG measurements.

Change to

12-lead ECG measurement and rhythm strip (10 seconds) will be obtained after measurement of vital signs. Triplicate ECG measurements are collected at rate of 3 ECGs over 5 minutes period. After vital signs are obtained subjects should be placed in the supine position for the ECG measurements.

Rationale: Refine Chinese translation of the intervals of 3 ECGs.

18. Section 7.3.3 Tuberculin Test (PPD), page 41, 42

Change from

Subjects must have a screening tuberculin test (PPD) administered and then evaluated by a health care professional (nurse or doctor) 48 to 72 hours later in order to be eligible for the study, unless performed and documented within the last 3 months. The test consists of intracutaneous injection of Tuberculin, concentration as per local medical standard of practice, on the volar aspect of the forearm, using a short beveled 26- or 27- gauge needle (Mantoux test). The test is positive if the induration's diameter (not erythema) is ≥5 mm 48 to 72 hours after injection. Subjects who have previously received BCG vaccination ~~may~~ be tested by QuantiFERON Gold in place of Mantoux PPD and have these results determine patient eligibility for participation.

Change to

Subjects must have a screening tuberculin test (PPD) administered and then evaluated by a health care professional (nurse or doctor) 48 to 72 hours later in order to be eligible for the study, unless performed and documented within the last 3 months. The test consists of intracutaneous injection of Tuberculin, concentration as per local medical standard of practice, on the volar aspect of the forearm, using a short beveled 26- or 27- gauge needle (Mantoux test). The test is positive if the induration's diameter (not erythema) is ≥5 mm 48 to 72 hours after injection. Subjects who have previously received BCG vaccination **will** be tested by QuantiFERON Gold **/or T-Spot test** in place of Mantoux PPD and have these results determine patient eligibility for participation.

Rationale: Allow T-Spot test as an alternative test for TB infection screening for subjects who have previously received BCG vaccination.

19. Section 7.3.4 QuatiFERON test, page 42

Change from

7.3.4 QuantiFERON test

At the discretion of the investigator, ~~subject to local testing availability,~~ a QuantiFERON Gold®™ (11) test may be substituted for the PPD skin test. A description of the QuantiFERON Gold test follows: "This Enzyme-linked Immunosorbent Assay (ELISA) test detects the release of Interferon-gamma (IFN-γ) in fresh heparinized whole blood from sensitized persons when it is incubated with mixtures of synthetic peptides simulating two proteins present in *M. tuberculosis*: Early Secretory Antigenic Target-6 (ESAT-6) and Culture Filtrate Protein-10 (CFP-10). ESAT-6 and CFP-10 are secreted by all *M. tuberculosis* and pathogenic *M. bovis* strains. Because these proteins are absent from all Bacille Calmette-Guérin (BCG) vaccine strains and from commonly encountered Non Tuberculous. Mycobacteria (NTM) except *M. kansasii*, *M. szulgai,* and *M. marinum*, QFT-G is expected to be more specific for *M. tuberculosis* than tests that use tuberculin Purified Protein Derivative (PPD) as the antigen".

Change to

7.3.4 QuantiFERON test**/or T-Spot test**

At the discretion of the investigator, a QuantiFERON Gold®™ (11) test **/or T-Spot test (11) conducted in local lab** may be substituted for the PPD skin test. A description of the QuantiFERON Gold test follows: "This Enzyme-linked Immunosorbent Assay (ELISA) test detects the release of Interferon-gamma (IFN-γ) in fresh heparinized whole blood from sensitized persons when it is incubated with mixtures of synthetic peptides simulating two proteins present in *M. tuberculosis*: Early Secretory Antigenic Target-6 (ESAT-6) and Culture Filtrate Protein-10 (CFP-10). ESAT-6 and CFP-10 are secreted by all *M. tuberculosis* and pathogenic *M. bovis* strains. Because these proteins are absent from all Bacille Calmette-Guérin (BCG) vaccine strains and from commonly encountered Non Tuberculous. Mycobacteria (NTM) except *M.*

kansasii, *M. szulgai,* and *M. marinum*, QFT-G is expected to be more specific for *M. tuberculosis* than tests that use tuberculin Purified Protein Derivative (PPD) as the antigen".

T-Spot is another IFN-γ release assays in diagnosing *M. tuberculosis* infection. For this test, peripheral blood mononuclear cells (PBMCs) are incubated with two mixtures of peptides, one representing ESAT-6 and the other representing CFP-10. The test uses an enzyme-linked immunospot assay (ELISpot) to detect increases in the number of cells that secrete IFN-γ.

In the situation QFT-G or T-Spot is unavailable by local testing, incubated whole blood sample could be sent to central lab for QFT-G testing. If QFT-G/or T-Spot result is indeterminate, a retest is required at earliest to determine the eligibility of the subject. If retest is indeterminate or positive, the subject should be screen failed. If retest is negative, the PI should assess the subject's clinical condition and decide if the subject could be included.

Rationale: Allow T-Spot as an alternative test for TB infection screening according to local availability. And provide the guidance on initial QFT-G/or T-Spot is indeterminate.

20. Section 7.3.5 Clinical Laboratory Test, page 43

Change from

Table 3. Clinical Laboratory Testing Lists

CHEMISTRY	HEMATOLOGY	Urinalysis	OTHER
Albumin	Haemoglobin	pH	Hepatitis B surface antigen[1]
Alkaline phosphatase	Haematocrit	Protein	Hepatitis C virus antibody[1]
Alanine amino-transferase (ALT or SGPT)	Platelet count	Glucose	HIV test[1]
Aspartate amino-transferase (AST or SGOT)	WBC count	Bilirubin and White Cell Count	Urine pregnancy test (in clinic)[2]
Bilirubin, direct	Neutrophils, absolute		FSH [3]
Bilirubin, indirect	Neutrophils, segs (%)		β-HCG blood test [4]
Bilirubin, total	Neutrophils, bands (%)		Stool culture~~5~~ /microscopy for: Salmonella, Shigella, Campylobacter, Fecal Ova and Parasites
Calcium	Basophils (%)		Clostridium difficile toxin
Chloride	Eosinophils (%)		Fecal calprotectin[6]
CO_2 content/Bicarbonate	Eosinophils , absolute		Lipid Profile (fasting): Total Cholesterol, Low Density Lipoprotein (LDL) High Density Lipoprotein (HDL) Triglycerides
Creatinine	Lymphocytes (%)		Thyroid Function Test, including TSH, free T4 and free T3.
Creatine phosphokinase (CPK), total	Monocytes (%)		[redacted]
Gamma glutamyl transferase (GGT)			
Glucose			
Phosphorus			
Potassium			
Protein, total serum			
Sodium			
Urea nitrogen (BUN)			
Uric Acid			

1 Assessed at Visit 1 (Screening) only~~, result is not exclusionary~~
2 all visits subsequent to the screening visit
3 FSH to confirm postmenopausal status at screening visit only
4 Only females of child-bearing potential if urine pregnancy test positive
5 fasting lipid profile will be done as per Section 5.12 Time and Event table.
6 for biomarker assessment
[redacted]

Change to

Table 3. Clinical Laboratory Testing Lists

CHEMISTRY	HEMATOLOGY	Urinalysis	OTHER
Albumin	Haemoglobin	pH	Hepatitis B surface antigen[1]
Alkaline phosphatase	Haematocrit	Protein	Hepatitis C virus antibody[1]
Alanine amino-transferase (ALT or SGPT)	Platelet count	Glucose	HIV test[1]
Aspartate amino-transferase (AST or SGOT)	WBC count	Bilirubin and White Cell Count	Urine pregnancy test (in clinic)[2]
Bilirubin, direct	**RBC count**		FSH [3]
Bilirubin, indirect	Neutrophils, absolute		β-HCG blood test [4]
Bilirubin, total	Neutrophils, segs (%)		Lipid Profile[5] (fasting): Total Cholesterol, Low Density Lipoprotein (LDL) High Density Lipoprotein (HDL) Triglycerides
Calcium	Neutrophils, bands (%)		Stool culture /microscopy for: Salmonella, Shigella, Campylobacter, Fecal Ova and Parasites
Chloride	Basophils (%)		Clostridium difficile toxin
CO_2 content/Bicarbonate	Eosinophils (%)		Fecal calprotectin[6]
Creatinine	Eosinophils , absolute		Thyroid Function Test, including TSH, free T4 and free T3.
Creatine phosphokinase (CPK), total	Lymphocytes (%)		[redacted]
Gamma glutamyl transferase (GGT)	Monocytes (%)		**CRP**
Glucose			
Phosphorus			
Potassium			
Protein, total serum			
Sodium			
Urea nitrogen (BUN)			
Uric Acid			

1 Assessed at Visit 1 (Screening) only
2 all visits subsequent to the screening visit
3 FSH to confirm postmenopausal status at screening visit only
4 Only **for** females of child-bearing potential **at screening, and** if urine pregnancy test positive
5 fasting lipid profile will be done as per Section 5.12 Time and Event table.
6 for biomarker assessment
[redacted]

Rationale: Typo correction in the table and footnotes. Add RBC count and CRP test items listed in the table, and clarify HBV, HCV and HIV test is for exclusionary purpose.

21. Section 7.3.14 AE and SAE reporting requirement and timeline, page 50

Change from

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. AEs will be collected from the start of study treatment (Visit 2) and until the follow up ~~phone~~ contact. SAEs will be collected ~~over the same time period as stated above for AEs. However, any SAEs assessed, will be recorded~~ from the time a subject consent to participate in the study up to and including any follow up contact.

Change to

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. AEs will be collected from the start of study treatment (Visit 2) and until the follow up contact. SAEs will be collected from the time a subject consent to participate in the study up to and including any follow up contact.

Rationale: Typo correction to clarify the follow up visit is not a phone-call contact. Clarify any SAEs will be recorded from the time of consent.

22. Section 11 Reference, page 60

Change from

11. Guidelines for Using the QuantiFERON®-TB Gold Test for Detecting Mycobacterium tuberculosis Infection, US: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5415a4.htm.

Change to

11. Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium tuberculosis Infection – United States, 2010 https://

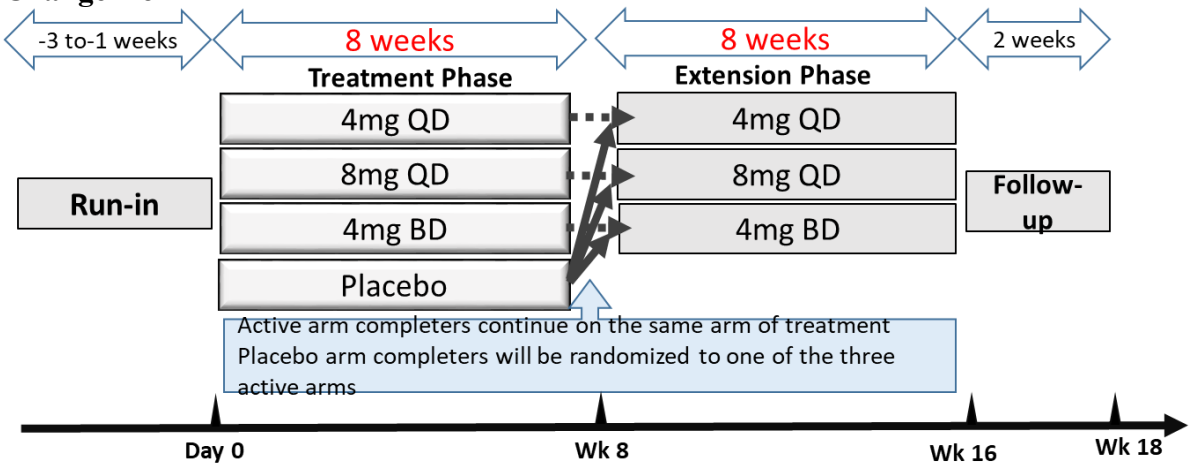
www.cdc.gov/mmwr/preview/mmwrhtml/rr5905a1.htm Rationale:

Reference update.

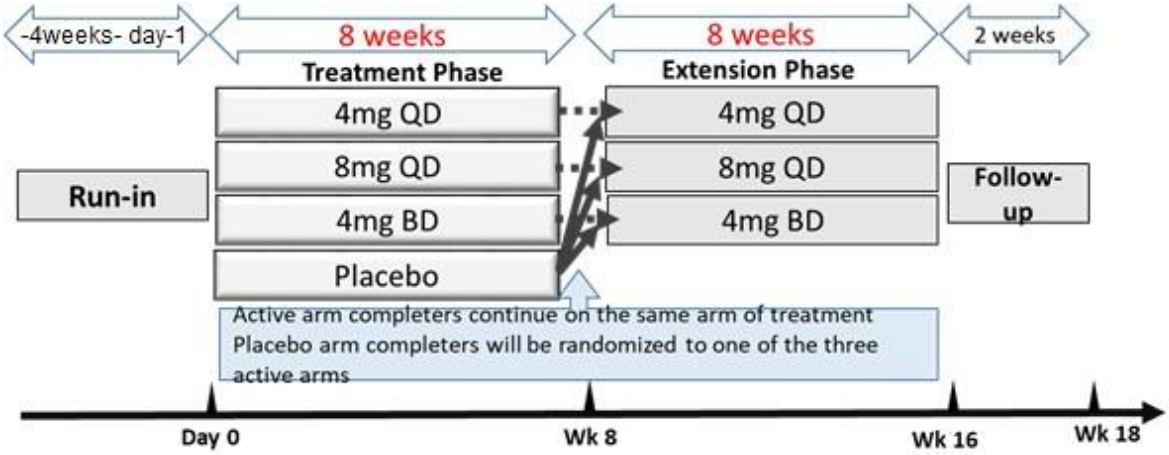
Protocol Amendment No.02

1. Section 4.1 Study design, page 19

Change from



Change to



Rationale: Revise the screening period from 3 weeks to -4 days prior to baseline to 4 weeks to -1 day prior to baseline, based on the feasibility of the clinical procedure in each country.

2. Section 4.2 Discussion of the design, page 19

Change from

This is a multi-national, multi-center, double-blind, randomized, placebo controlled phase II dose- ranging study to include 152 subjects with moderate to severe active ulcerative colitis. The study consists of an 8-week blinded treatment phase, followed by an 8-week active arms extension phase. Subjects will be screened between ~~-21 days to -4 days~~ before baseline visit (visit 2 at week 0).

Change to

This is a multi-national, multi-center, double-blind, randomized, placebo controlled phase II dose- ranging study to include 152 subjects with moderate to severe active ulcerative colitis. The study consists of an 8-week blinded treatment phase, followed by an 8-week active arms extension phase. Subjects will be screened between **-28 days to -1 day** before baseline visit (visit 2 at week 0).

Rationale: Revise the screening period from 3 weeks to -4 days prior to baseline to 4 weeks to -1 day prior to baseline, based on the feasibility of the clinical procedure in each country, and keep consistent with study design diagram.

3. Section 5.2 Inclusion Criteria, page 20

Change from

3. ……

~~4.~~ Subjects deemed by the treating physician as having inadequate response, loss of response or intolerance to the conventional treatment (immune-suppressants or corticosteroids)~~, **AND**~~

- ~~Naïve to anti-TNF treatment (e.g. infliximab, adalimumab or certolizumab pegol) or other biological treatment (e.g. Vedolizumab);~~

~~OR~~

- ~~Previously exposed to anti-TNF therapy or other biological treatment having discontinued the treatment for a minimum of 12 weeks prior to baseline.~~

~~5.~~ If subjects are currently receiving the following treatment for UC, they are eligible for the study, provided they are on stable dose for the required period of time:

- Oral 5 ASA or Sulfasalazine, stable dose for at least 2 weeks prior to baseline and during the study treatment period.

AND/OR

- Oral corticosteroids (prednisolone ≤ 30mg/day or less or equivalent) stable dose for at least 2 weeks prior to baseline.

6. ……

Change to

3. ……

4. Subjects deemed by the treating physician as having inadequate response, loss of response or intolerance to the conventional treatment (**oral 5-ASA,** immune-suppressants or corticosteroids), **or previously exposed to anti-TNF therapy (e.g. infliximab, adalimumab) or other biological treatment (e.g. Vedolizumab) having discontinued the treatment for:**
   - **Infliximab: a minimum of 8 weeks prior to baseline**
   - **Adalimumab: a minimum of 10 weeks prior to baseline**

- **Ustekinumab: a minimum of 14 weeks prior to baseline**
- **Vedolizumab: a minimum of 17 weeks prior to baseline**
- **For the other biological treatments, they should discontinue for a minimum of 5 half-lives prior to baseline.**

5. If subjects are currently receiving the following treatment for UC, they are eligible for the study, provided they are on stable dose for the required period of time:

   − Oral 5 ASA or Sulfasalazine, stable dose for at least 2 weeks prior to baseline and during the study treatment period.

   AND/OR

   − Oral corticosteroids (prednisolone ≤ 30mg/day or less or equivalent) stable dose for at least 2 weeks prior to baseline. **This is not applicable to the subjects who have only exposed to 5-ASA previously as perinclusion criteria 4.**

6. ……

Rationale: Clarify the subjects deemed by the treating physician as having inadequate response, loss of response or intolerance to the conventional treatment include subjects with previous exposed to oral 5-ASA. Clarify oral corticosteroids as permitted medications during study treatment is not applicable to subjects with previous 5-ASA treatment only. List the detailed discontinuation time prior to baseline of the biological treatment according to its half life.

4. Section 5.3 Exclusion Criteria, page 21 to 24

Change from

2. ……

3. Treatment naïve subjects diagnosed with ulcerative colitis (without previous exposure to any of the following therapies for UC treatment: corticosteroids, immune-suppressants, or biological treatments).

   ……

7. Subjects receiving the following therapy:
   - Azathioprine/6-mercaptopurine, methotrexate, thalidomide within 7 days prior to baseline.
   - Cyclosporine, mycophenolate, tacrolimus within 4 weeks prior to baseline.
   - Interferon therapy within ~~12~~ weeks prior to baseline.
   - ~~Anti-TNFα therapy/other biological therapies within 12 weeks prior to baseline.~~
   - Intravenous corticosteroids or rectally administered formulation of corticosteroids or 5-ASA within 2 weeks prior to baseline.

   ……

13. Subjects with current clinically significant infections or within ~~6~~ months of baseline (eg; those requiring hospitalization or parenteral antimicrobial therapy or opportunistic infections), or those with a history of more than one episode of herpes zoster, a history (single episode) of disseminated zoster, a history of any infection otherwise judged by the investigator to have the potential for exacerbation by participation in the study or any infection requiring antimicrobial therapy within 2 weeks of screening.

14. Subjects who may have current immunization with any live virus vaccine or history of immunization with any live virus vaccine within 8 weeks of baseline.

15. ~~Subjects who may have, during the 16 weeks of treatment and for 8 weeks following completion of study treatment, routine household contact with individuals who have received:~~
    - ~~FluMist® (intranasal influenza vaccine) within 1 week of such contact;~~
    - ~~attenuated rotavirus vaccine within 10 days of such contact;~~
    - ~~varicella or attenuated typhoid fever vaccine within 4 weeks of such contact; or oral polio vaccine within 6 weeks of such contact.~~

16. Subjects with a first-degree relative with a hereditary immunodeficiency.

……

Change to

2. ……

3. Treatment naïve subjects diagnosed with ulcerative colitis (without previous exposure to any of the following therapies for UC treatment: **5-ASA,** corticosteroids, immune-suppressants, or biological treatments).

……

7. Subjects receiving the following therapy:
   - Azathioprine/6-mercaptopurine, methotrexate, thalidomide within 7 days prior to baseline.
   - Cyclosporine, mycophenolate, tacrolimus within 4 weeks prior to baseline.
   - Interferon therapy within **8** weeks prior to baseline.
   - Intravenous corticosteroids or rectally administered formulation of corticosteroids or 5-ASA within 2 weeks prior to baseline.

   ……

13. Subjects with current clinically significant infections or within **1** month of baseline (eg; those requiring hospitalization or parenteral antimicrobial therapy or opportunistic infections), or those with a history of more than one episode of herpes zoster, a history (single episode) of disseminated zoster, a history of any infection otherwise judged by the investigator to have the potential for exacerbation by participation in the study or any infection requiring antimicrobial therapy within 2 weeks of screening.

14. Subjects who may have current immunization with any live virus vaccine or history of immunization with any live virus vaccine within 8 weeks of baseline.

15. Subjects with a first-degree relative with a hereditary immunodeficiency.
……

Rationale: Clarify the definition of treatment naïve patients according clinical practice. Update the discontinuation time prior to baseline of interferon therapy. In conjunction to the inclusion criteria regarding the requirement of discontinuation of biologicals, remove related requirement in exclusion criteria. Clarify the subjects with current clinically significant infections or within 1 month of baseline instead of 6 months, will be excluded. Remove the requirement regarding to household contact with vaccinated individuals during study in exclusion criteria.

5. Section 5.12 Time and Event Table, page 30

Change from

Period	Screening	Baseline	Treatment Phase		End of Treatment Phase	Extension Phase		End of Extension Phase	Follow-up/EW[11]
VISIT	1	2	3	4	5	6	7	8	9
Week	~~-3~~ to -1	0	1	4	8	9	12	16	18
Day	~~-21 to -4~~	0	7± 2 days	28± 3 days	56± 3 days	63± 2 days	84± 3 days	112± 3 days	126± 5 days
Procedures									

Change to

Period	Screening	Baseline	Treatment Phase		End of Treatment Phase	Extension Phase		End of Extension Phase	Follow-up/EW[11]
VISIT	1	2	3	4	5	6	7	8	9
Week	-4 to -1	0	1	4	8	9	12	16	18
Day	-28 to -1	0	7± 2 days	28± 3 days	56± 3 days	63± 2 days	84± 3 days	112± 3 days	126± 5 days
Procedures									

Rationale: Revise the screening period from 3 weeks to -4 days prior to baseline to 4 weeks to -1 day prior to baseline, based on the feasibility of the clinical procedure in each country, and keep consistent with study design diagram.

6. Section 6.6.1 Permitted Concomitant Medications, page 36

Change from

- ……

- Oral steroids are allowed during the study up to the dose of 30 mg/day of prednisolone or equivalent, providing that the dose has not been commenced or changed within 2 weeks of baseline and until to the end of treatment phase (Week 8). During the extension phase, tapering of the oral steroid dose can be commenced for subjects at investigator's discretion~~, in accordance with the predefined tapering scheduled treatment:~~

  - Subjects receiving > 10 mg/day prednisolone or equivalent: taper dose by 5 mg/week until a 10 mg/day dose (or equivalent) is reached, then continue tapering at 2.5 mg/week until 0 mg/day.
  - Subjects receiving ≤ 10 mg/day prednisolone or equivalent: taper dose by 2.5 mg/week until 0 mg/day.

If subject experiences worsening of signs or symptoms during the tapering schedule, in the opinion of the investigator, due to reduction in oral steroid daily dose, the daily oral steroid dosage for the subject could be reverted to the preceding daily dosage instructed by the investigator, but should not exceed Baseline dose.

Change to

- ……

- Oral steroids are allowed during the study up to the dose of 30 mg/day of prednisolone or equivalent, providing that the dose has not been commenced or changed within 2 weeks of baseline and until to the end of treatment phase (Week 8). **During the treatment phase, if the subject cannot tolerate the oral steroids dose or there is a significant safety risk associated with continued use of the steroids, the dose may be reduced at the discretion of the investigator and the reasons for dose reduction need to be documented in the medical records.** During the extension phase, tapering of the oral steroid dose can be commenced for subjects at investigator's discretion. **Tapering scheduled treatment is provided as below:**

  - Subjects receiving > 10 mg/day prednisolone or equivalent: taper dose by 5 mg/week until a 10 mg/day dose (or equivalent) is reached, then continue tapering at 2.5 mg/week until 0 mg/day.
  - Subjects receiving ≤ 10 mg/day prednisolone or equivalent: taper dose by 2.5 mg/week until 0 mg/day.

If subject experiences worsening of signs or symptoms during the tapering schedule, in the opinion of the investigator, due to reduction in oral steroid daily dose, the daily oral steroid dosage for the subject could be reverted to the preceding daily dosage instructed by the investigator, but should not exceed Baseline dose.

Rationale: Clarify dose of steroids can be reduced at the discretion of the investigator if subject develops intolerance to the original dose or significant saftey concerns during the treatment phase.

7. Section 7.3.10 Pregnancy, page 48

Change from

7.3.10 Pregnancy

If the subject is found to be pregnant, the subject must be withdrawn immediately, and any sponsor-supplied drug (SHR0302, placebo) should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study, should also be recorded following authorization from the subject's partner. Any pregnancy that occurs ~~during study participation~~ must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to Reistone Biopharma/designated CRO within 24 hours of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and ~~child.~~ Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Pregnancies will remain blinded to the study team.

Change to

7.3.10 Pregnancy

If the subject is found to be pregnant, the subject must be withdrawn immediately, and any sponsor-supplied drug (SHR0302, placebo) should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study, should also be recorded following authorization from the subject's partner. Any pregnancy that occurs **after the first dose of investigational drug** must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to Reistone Biopharma/designated CRO within 24 hours of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and **the newborn should be followed up to 1 month after birth**. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Pregnancies will remain blinded to the study team.

Rationale: Clarify the pregnancy occurs after first dose must be reported and the newborn should be followed up to 1 month after birth as pregnancy outcome.

Protocol Amendment No.03

1. Section 5.3 Exclusion Criteria, page 22

Change from

33. Subjects with historical or current evidence of clinically significant cardiovascular, neurological, psychiatric, renal, hepatic, immunological, gastrointestinal, urogenital, nervous system, musculoskeletal, skin, sensory, endocrine (including uncontrolled diabetes or thyroid disease) or hematological abnormalities that are uncontrolled. Significant is defined as any disease that, in the opinion of the Investigator, would put the safety of the subject at risk through participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study.

Change to

33. Subjects with historical or current evidence of clinically significant cardiovascular, neurological, psychiatric, renal, hepatic, immunological, gastrointestinal, urogenital, nervous system, musculoskeletal, skin, sensory, endocrine (including uncontrolled diabetes or thyroid disease) or hematological abnormalities that are uncontrolled. Significant is defined as any disease that, in the opinion of the Investigator, would put the safety of the subject at risk through participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study.

34. Subjects with a history thrombotic events, including deep vein thromboses (DVT), pulmonary embolism (PE) and those with known inherited conditions that predispose to hypercoagulability.

Rationale: Update safety related exclusion criteria, add exclusion criteria 34 about the thrombotic events according to the FDA's recommendation.

2. Section 5.9 Stopping Criteria, page 29

Change from

The stopping safety criteria are as below:

- Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance) Study treatment will be stopped if the liver chemistry stopping criteria is met. Refer to Section 7.3.9 Liver Chemistry Stopping and Follow-up Criteria.
- A subject that meets the QTc criteria below will be withdrawn from the study. The QT correction formula used to determine discontinuation should be the same one used throughout the study.
  - QTc, QTcB/QTcF > 500 ms.

- Change from baseline: QTc >60 ms.

Use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study.

- An unacceptable adverse event, as determined by the Investigator and the medical monitor.
- Any unacceptable adverse event that is thought to be related to the investigational product may result in the study being terminated.
- Significant protocol deviation. The discovery that post-randomization the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.

If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 7.3.10.

Change to

The stopping safety criteria are as below: Subject who fulfil the following criteria should discontinue the study.

- Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance) Study treatment will be stopped if the liver chemistry stopping criteria is met. Refer to Section 7.3.9 Liver Chemistry Stopping and Follow-up Criteria.
- A subject that meets the QTc criteria below will be withdrawn from the study. The QT correction formula used to determine discontinuation should be the same one used throughout the study.
  - QTc, QTcB/QTcF > 500 ms.
  - Change from baseline: QTc >60 ms.

Use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study.

- Abnormal laboratory values of interests. (modified from CTCAE v5.1 criteria)
  - Hemoglobin (Hgb) <7.0 g/dL; or when blood transfusion is indicated.
  - Neutrophil count < 500/mm^3.
  - Platelet count < 25,000/mm^3.
  - Lymphocyte count < 200/mm^3.
  - **Leukocyte count < 2000/mm^3. (Normal: 4000-10,000/mm^3)**
- Subject who develops Venous Thrombosis (e.g., Deep Vein Thrombosis).
- Subject who develops Pulmonary Embolism (PE).
- Subject who develops Cerebrovascular Events (e.g., Thromboembolic Stroke, Transient Ischemic Attack (TIA), Myocardiac Infarction).

- An unacceptable adverse event, as determined by the Investigator and the medical monitor.
- Any unacceptable adverse event that is thought to be related to the investigational product may result in the study being terminated.
- Significant protocol deviation. The discovery that post-randomization the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.

If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 7.3.10.

Rationale: According to the FDA's recommendation, add the abnormal laboratory values of interest (e.g., at minimum, for anemia, leukopenia, neutropenia, thrombocytopenia, and abnormal coagulation profile).

3. Section 7.3.15 Adverse Event of Special Interest (AESI), page 60

Change from

7.3.14 AE and SAE reporting requirement and timeline

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. AEs will be collected from the start of study treatment (Visit 2) and until the follow up contact. SAEs will be collected from the time a subject consent to participate in the study up to and including any follow up contact.

All SAEs will be reported to Reistone Biopharma/designated CRO within 24 hours. Prompt notification of SAEs by the investigator to Reistone Biopharma/designated CRO is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met. All SAEs will be followed up until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Once resolved, the SAE eCRF page will be updated. The investigator should report SAE/serious incident per local regulations and local EC requirement. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Reistone Biopharma/designated CRO has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation according to local regulations. Reistone Biopharma/designated CRO will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Reistone Biopharma/designated CRO policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from Reistone Biopharma/designated CRO will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Change to

7.3.14 AE and SAE reporting requirement and timeline

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. AEs will be collected from the start of study treatment (Visit 2) and until the follow up contact. SAEs will be collected from the time a subject consent to participate in the study up to and including any follow up contact.

All SAEs will be reported to Reistone Biopharma/designated CRO within 24 hours. Prompt notification of SAEs by the investigator to Reistone Biopharma/designated CRO is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met. All SAEs will be followed up until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Once resolved, the SAE eCRF page will be updated. The investigator should report SAE/serious incident per local regulations and local EC requirement. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Reistone Biopharma/designated CRO has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation according to local regulations. Reistone Biopharma/designated CRO will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Reistone Biopharma/designated CRO policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from Reistone Biopharma/designated CRO will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.3.15 Adverse Event of Special Interest (AESI)

<u>The AE of special interest (AESI) (serious or non-serious) are determined based on previous knowledge about the disease and the mechanism of action of the investigational drug, as well as safety information from a similar class of drug. AESI is one of scientific and medical concern specific to the product or program, for which ongoing monitoring and rapid communication by the</u>

investigator to the sponsor may be appropriate. Such events require heightened surveillance and further investigation in order to characterize and understand them. The AESI will be managed and follow-up according to the SAE timeline and procedure. The study's AESI includes:

- Serious infection: Serious infection is defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials for more than 3 days.

- Thromboembolic event: Thromboembolic events are divided into two major groups which are venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), and arterial thromboembolic events, including arterial thrombosis and cerebrovascular accident (CVA).

Rationale: According to the FDA's recommendation, add the AEs of special interest (e.g., serious infection associated with all JAK-inhibitors).