Statistical Analysis Plan

PROTOCOL NO. RSJ10101

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

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V 1.2 (Dated 23Mar2021) for Protocol RSJ10101.

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

	Name	Signature	Date
Approved By:	[redacted]		
Position:	[redacted]		
Company:	[redacted]		

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
Final v1.0	08Jan2020	[redacted]	Not Applicable-First Version
Final v1.1	12Oct2020	[redacted]	1. Reistone study statistician changed from [redacted] to [redacted]. 2. Updated the per protocol set definition and added the reason for changes in the section of 3.3 changes to analysis from protocol . 3. Reference for CMH weighted average of stratum specific rate differences and stratified Wald confidence interval was added. 4. A listing for patients whose trial participation are impacted by COVID-19 was added
Final v1.2	23Mar2021	[redacted]	1. Reistone study statistician changed from [redacted] to [redacted].

LIST OF ABBREVIATIONS AND RELEVANT TERMS

Initials/Abbreviations	Terms
ACS	Abnormal Clinically Significant
AE	Adverse Event
ANCOVA	Analysis of Covariance
ANCS	Abnormal Not Clinically Significant
ATC	Anatomical Therapeutic Chemical
BD	Twice Daily
β-hCG	Beta - human Chorionic Gonadotropin
BLQ	Below the Lower Limit of Quantification
BMI	Body Mass Index
BOCF	Baseline Observation Carried Forward
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ENR	Enrolled Set
FAS	Full Analysis Set
IP	Investigational Product
JAK	Janus Kinase
LOCF	Last Observation Carried Forward
LS Mean	Least Square Mean
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
NCF	Non-completers Considered Failure
PPS	Per Protocol Analysis Set
PT	Preferred Term
PGA	Physician Global Assessment
QD	Once a Day

RND	Randomized Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
SRC	Safety Review Committee
SS	Safety Analysis Set
TEAE	Treatment Emergent Adverse Event
ULQ	Upper Limit of Quantification
UC	Ulcerative Colitis

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1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol RSJ10101. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This Statistical Analysis Plan (SAP) is based on protocol version 3.0, dated July 31, 2019. Pharmacokinetic analysis is not in [redacted] work scope and analysis method for pharmacokinetic analysis is not included in this SAP.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective is:

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

2.2 SECONDARY OBJECTIVES

The secondary objectives are:

- To evaluate the safety and tolerability of oral SHR0302 in patients with moderate to severe ulcerative colitis.
- To evaluate the efficacy of oral SHR0302 in inducing clinical remission in patients with moderate to severe ulcerative colitis.
- To evaluate the efficacy of oral SHR0302 in inducing mucosal healing in patients 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.

3. STUDY DESIGN

3.1 GENERAL DESCRIPTION

Ulcerative Colitis 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 understanding of cytokines and intracellular messenger pathway in UC has led to the discovery of Janus Kinase (JAK) enzymes. There are a number of Janus kinase 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. There is also an advantage of not having the risk of developing loss of response due to immunogenicity.

SHR0302 is a highly selective JAK1 inhibitor. An in vitro study has demonstrated that its selectivity to JAK1 compared to JAK2 is about 16 times more than tofacitinib, and baricitinib, while 10 times more than filgotinib. In an animal model study, SHR0302 significantly attenuated gross bleeding and stool consistency while also relieved body weight loss in DSS-induced Colitis mice. Meanwhile the study has also demonstrated SHR0302's ability in reducing colon inflammation score by reducing crypt score and inflammation score in these mice to the extent comparable to tofacitinib, an active comparator. These in vitro and animal studies have demonstrated the potential efficacy of SHR0302 in addressing colon inflammation, hence the potential for the treatment of inflammatory Bowel Disease. The high selectivity of SHR0302 to JAK1 also makes it a favourable candidate from a benefit risk safety perspective.

The proposed study is a multi-national, multi-center, double-blind, randomized, placebo controlled phase II dose- ranging study to include 152 patients 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. All patient have the option not enrolling into the extension

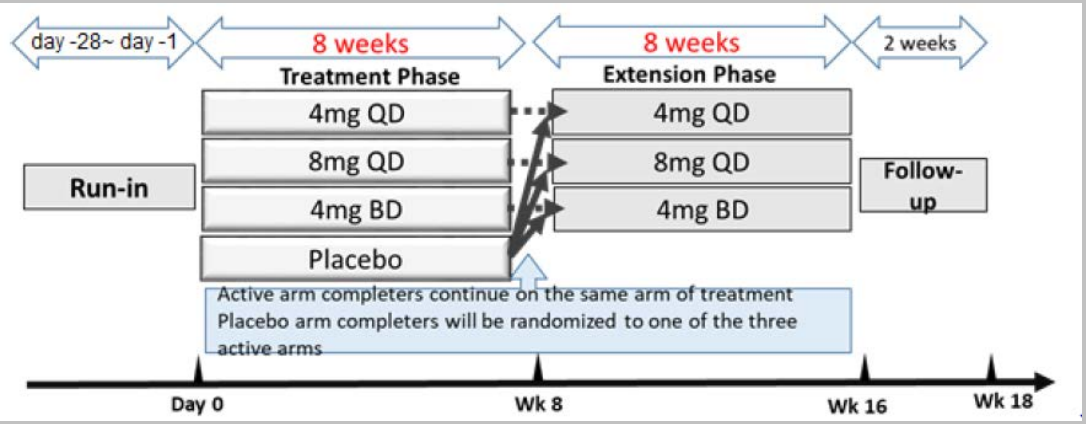
phase after first 8 weeks of treatment. All patients in the extension phase are followed-up for further 2 weeks until week 18. Patients who have completed the first 8-week of treatment phase, but decided not entering into extension phase are required to attend the 2-week follow-up visit. Early withdrawn patients during the first 8-week treatment phase cannot enter the extension phase. Early withdrawal visit should be done within 2 weeks after last dose/decision of withdrawal. The total duration of the study participation, including extension and follow-up, will be approximately 18 weeks.

At the baseline visit, patients 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: 4mg QD, 8mg QD, 4mg BD of SHR0302 or placebo. All the patients will be stratified according to whether they have previously exposed to anti-TNFα/biological treatment. Patients 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. Patients randomized to the active arms for treatment phase will remain in the same dose group in the extension phase.

Primary endpoint assessment will be conducted at week 8. 9-point modified Mayo score is the Mayo score excluding physician global assessment (PGA) subscore. 9-point modified Mayo score will be collected as the primary endpoint. This has been advised by the US FDA according to FDA guidance on ulcerative colitis trial. At the completion of the first 8-week treatment period, all patients, 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. The end-of-study is defined as the date of the last patient's last visit or the actual date of follow-up visit/contact, whichever is later. The study design diagram is provided in below figure (Figure 1).

The efficacy, safety, tolerability, and anti-inflammatory data generated by this proposed phase II study will be essential for evaluating the potential of this promising, novel anti-inflammatory agent as a treatment for moderate to severe active ulcerative colitis so that one or two doses can be selected to progress into further clinical development.

Figure 1: Study Design Diagram



The sample size calculation is based on pairwise comparison of clinical response at week 8 among SHR0302 8mg, 4mg BD, 4mg QD 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 patients 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-p test. The total sample size is 152 randomized patients with consideration of 8% drop out rate. 152 eligible patients will be randomized to achieve an estimated 140 evaluable patients in the study.

3.2 SCHEDULE OF EVENTS

Schedule of events can be found in Section 5.12 Time and Event Table of the protocol.

3.3 CHANGES TO ANALYSIS FROM PROTOCOL

- Two new analysis sets which are all patients enrolled set and all patients randomized set have been added in this SAP. The reason for these changes is to summarize patient disposition clearly.
- In protocol, per protocol set is defined as all patients from FAS who do not have significant protocol violation. Based on the data before the interim database lock, there are some subjects who do not have primary efficacy results at week 8. In order to assess the primary efficacy results based on observed results without non-completers considered failure (NCF) imputation, these subjects without week 8 efficacy results will be excluded from PP set.

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Two Analyses for Safety Review Committee (SRC) Meetings
- Interim Analysis
- Final Analysis

4.1 DATA MONITORING COMMITTEE (DMC)

A data monitoring committee for efficacy is not required for this study.

A safety review committee 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 patients 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 patient 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.

4.2 INTERIM ANALYSIS

One interim analysis will take place for this study. The primary analysis of primary endpoint will occur after all patients have the opportunity to complete the 8-week treatment phase study visit. The results will be based on unblinded treatment groups.

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

The list of outputs provided with the full set of output templates (planned for the final analysis) will highlight which of these outputs will be provided for the interim analysis.

The [redacted] study team, including those responsible for creating the programs to produce the

outputs for the Interim Analysis, will remain blinded. Once the programs have been produced by the [redacted] blinded study team in Beijing, these programs will be sent to the [redacted] unblinded statistician, who will apply the randomization schedule and provide the Reistone unblinded team with a set of unblinded outputs.

4.3 FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by [redacted] Biostatistics following sponsor authorization of this Statistical Analysis Plan, Database Lock, Sponsor Authorization of Analysis Sets and Unblinding of Treatment.

5. ANALYSIS SETS

Agreement and authorization of patients included/ excluded from each analysis set will be conducted prior to the unblinding of the study.

5.1 ALL PATIENTS ENROLLED SET [ENR]

The all patients enrolled set will contain all patients who provide informed consent for this study.

5.2 ALL PATIENTS RANDOMIZED SET [RND]

The all patients randomized set will contain all patients in the ENR set who were randomized to study medication.

For analyses and displays based on RND, patients will be classified according to randomized treatment.

5.3 FULL ANALYSIS SET [FAS]

Full analysis set will comprise of all randomized patients who have received any amount of investigational product (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, patients will be analyzed according to randomized treatment, regardless of the treatment received.

5.4 PER PROTOCOL ANALYSIS SET [PPS]

Per protocol set is defined as all patients from FAS who have week 8 efficacy data and do not have significant protocol violation.

5.5 SAFETY ANALYSIS SET [SS]

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

If there is any doubt whether a patient was treated or not, they will be assumed treated for the purposes of analysis.

6. GENERAL CONSIDERATIONS

6.1 REFERENCE START DATE AND STUDY DAY

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

Reference start date is defined as the day of the first dose of investigational product (Day 0 is the day of the first dose of investigational product) and Study Day will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date, then:
  Study Day = (date of event – reference date) .

- If the date of the event is prior to the reference date, then:
  Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings.

6.2 BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement (including unscheduled assessments) taken prior to first dose on or before Day 0. In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-baseline. However, Adverse Events (AEs) and medications commencing on the first dose date will be considered as post-baseline. For the related assessments such as systolic blood pressure (SBP) and diastolic blood pressure (DBP), it is desirable that both baseline values come from the same measurement and not from different dates/visits in case one value is missing.

6.3 DERIVED TIMEPOINTS

For some endpoints, Last-observation-carried-forward (LOCF) or Baseline-observation-carred-forward (BOCF) approach will be applied for subscore other than endoscopy of Mayo score. In the by-visit summary, “LOCF imputation” or “BOCF imputation” will be used to make it clear what is being shown in the outputs.

6.4 UNSCHEDULED VISITS, RETESTS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries but will contribute best/ worst case value where required .

In the case of a retest (same visit number assigned), the latest available measurement for that visit will be used for by-visit summaries.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.5 WINDOWING CONVENTIONS

No visit windowing will be performed in the statistics for this study.

6.6 STATISTICAL TESTS

The default significant level will be 2-sided 0.1; confidence intervals (CI) will be 90% and

statistical tests will be two-sided, unless otherwise specified in the description of the analyses.

6.7 COMMON CALCULATIONS

- For quantitative measurements, change from baseline will be calculated as:
  Change from baseline =Test Value at Visit X – Baseline Value

- For quantitative measurements, percent change from baseline will be calculated as:
  Percent change from baseline= ((Test Value at Visit X – Baseline Value) /Baseline Value)*100

6.8 SOFTWARE VERSION

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

7. STATISTICAL CONSIDERATIONS

7.1 MULTICENTRE STUDIES

This study will be conducted by multiple investigators at multiple centers internationally.

7.2 MISSING DATA

In general, missing values will not be imputed for descriptive statistics.

Unless otherwise specified, all analysis will be based on the number of observations in the relative population, i.e. patients with missing information will be included in the denominator when calculating percentages.

Missing efficacy data will be handled as described in section 15.1 and 15.2.2 of this analysis plan.

Missing or incomplete data will not be imputed unless indicated otherwise.

7.3 EXAMINATION OF SUBGROUPS

Subgroup analyses for primary endpoint will be conducted as exploratory analysis. It should be noted that the study was not designed to detect response differences with high statistical power within subgroups. Forest plots will be used to display differences in clinical response rate across subgroups in each SHR0302 dose level compared to placebo group.

The following subgroups will be assessed and described:

- Age (years)
    - < 45 years
    - ≥ 45 years
- Sex
    - Male
    - Female
- Country
    - USA
    - Ukraine
    - Poland
    - China
- Ethnicity Origin
    - Not Hispanic or Latino
    - Hispanic or Latino
    - Not reported or Unknown
- Duration of UC (years)
    - < 5
    - ≥ 5
- Overall Compliance before Week 8

- Yes (≥ 80% compliance)
- No (< 80% compliance)

- Previous exposure to anti-TNFα/biological treatment
  - Yes
  - No

- Baseline total Mayo score
  - ≤10
  - >10

8. OUTPUT PRESENTATIONS

Appendix 1 of the analysis plan shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by [redacted] Biostatistics.

Continuous variables will be summarized using descriptive statistics, i.e., non-missing observations, mean, median, standard deviation (SD), minimum, and maximum.

Categorical variables will be summarized by counts and percentages. Unless otherwise stated, the calculation of proportions will be based on the population of interest. Counts of missing observations will be included in the denominator, unless specified.

9. DISPOSITION AND WITHDRAWALS

All patients who provide informed consent will be accounted for in this study.

Patient disposition and withdrawals will be presented for the enrolled population. The breakdown of patients into the analysis sets (ENR, RND, FAS, SS, and PPS) will be presented.

Follow up time (days) is time between a specified event (death, end of the study or the cut-off

date for dry run or SRC analysis, whichever occurred first) and the date of randomization. Follow up time will be summarized for RND.

- Follow-up time (days) = the date of event-the date of randomization +1

Number and percentage of patients allocated to treatment will be presented by previous exposure to TNFα/biological treatment for RND.

Number and percentage of patients allocated to treatment in each country and site will be presented by treatment group for RND.

A listing of inclusion/exclusion criteria deviations and reason for screen failure will be provided for screen failure patients.

Additionally, any protocol deviations identified during the course of the study will be listed and the number and percentage of patients in each type of protocol deviations will be summarized for the randomized population.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The demographic and other baseline characteristics will be presented for the FAS. The following demographic and other baseline characteristics will be reported for this study.

- Age (years)–RAVE age function
- Age groups (< 45 years/≥45 years)
- Sex
- Race
- Ethnicity
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Cigarette Use
- Alcohol Use
- Previous exposure to anti-TNFα/biological treatment
- UC disease duration
- Location and extent of patient's UC
- Baseline total Mayo score (≤10/>10)

Descriptive statistics will be used for summarizing the patients' characteristics in each treatment group and overall. No statistical testing will be carried out for demographic or other baseline characteristics.

10.1 DERIVATIONS

- BMI (kg/ m^2) = weight (kg)/ height $(m)^2$
- Age (years) = Year of informed consent (IC) – Year of birth, if month of IC is later than month of birth, or if month of IC is equal to month of birth but day of informed consent is later than or equal to day of birth;

  Age (years) = Year of informed consent – Year of birth – 1, otherwise.

  In this case, if one patient is more than 45 years old but less than 46 years old, then this patient will be presented as age 45.
- UC disease duration (years) = (Date of informed consent – Date of Diagnosis +1)/365.25, presented to 1 decimal place.

  For partially missing dates, the UC disease duration (years) will be based on imputed values. If the date part is missing while year and month present, 15th of the month will be used for imputation. If both date and month part are missing while year presents, July 1st will be used for imputation.

11. MEDICAL HISTORY

Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1 or higher version. Data captured on the Medical History page of the CRF will be presented by body system description (SOC) and Preferred Term (PT) for FAS.

Number and percentage of patients with at least one medical history or one complication of UC will be presented by treatment group for FAS.

Detailed information of medical history including medical history term, year diagnosed, ongoing or not, and whether this conditions or events is a complication of Ulcerative Colitis will be listed for FAS.

12. MEDICATIONS AND PROCEDURES

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.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO Drug Global 01Sep2018_B3). The PT and Anatomical Therapeutic Chemical (ATC) Classification System level 2 will be used for tabulation. The summary tables will show the number and percentage of patients by PT and ATC level 2, for each treatment group and overall. Only concomitant medications will be summarized. The descriptive summaries for concomitant medications will be presented for the SS. Missing or partial dates for medications will be handled according to Appendix 2 of this analysis plan. In the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case; i.e. concomitant. For the summaries of concomitant medications, patients who take the same medication (in terms of the PT), more than once will only be counted once for that medication. Prior medications will be listed only.

The detailed information of prior and concomitant medication use including medication name, start date, end date, ongoing or not, primary reason for use, total daily dose, frequency and route of administration, etc. will be listed. Prior and concomitant medications will be listed separately.

The detailed information of procedures will be collected on the “Procedures” form of Electronic Case Report Form (eCRF) including procedure name, start date, end date, ongoing or not, and primary reason for use. Procedure name will be coded using Medical Dictionary for Regulatory Activities Version 21.1 or higher version. Procedures information be will be listed.

13. STUDY MEDICATION EXPOSURE

Exposure to study medication will be presented for SS by treatment group.

The date of first study medication administration will be taken from eCRF “Noncompliance with study treatment ” form if available (Site will check medical chart and make the first dose record on this eCRF form). In case of not available, the first dose date from the diary data will be used. The date of last study medication will be taken from the eCRF “End of Treatment”

form. In the case of missing data on the eCRF, the last dose date from diary data will be used

The study medication intake for each day will be taken from the diary "Time of Dosing" and "# Tablets Taken" items. The following information will be summarized for each treatment group in treatment phase, extension phase and overall:

- Duration of Exposure (days)
- Planned number of study drug tablets
- Actual number of study drug tablets
- Number of Dosing Days
- Cumulative Dose (mg)
- Average Daily Dose (mg/day)

13.1 DERIVATIONS

- Duration of exposure(days)= Last date of exposure in corresponding phase– First dose date in corresponding phase +1

When the start or stop date is missing, then the exposure will be treated as missing. Interruptions, compliance, and dose changes are not taken into account for duration of exposure.

- Planned number of tablets

The investigational product taken during the 16-week treatment period will be double blind. In order to preserve blinding and ensure patients compliance, all arms are administered under twice daily dosing regime and placebo is used according to the schedule in table 1. At each dosing time (morning, am or afternoon, pm), patient will be taking two tablets. The treatments are given twice daily and it is assumed that the patient should take medication from the morning of the visit day at which their medication is initially dispensed to the afternoon of their last visit date. At each dosing time (morning, am or afternoon, pm), patient will be taking two tablets. In one day, a patient will take a total of four tablets, two tablets in the morning and two tablets in the afternoon. For example, if the initial dispense date is Day 1 and the last visit date is Day 10, then the patient should have taken 2 tablets at am on Days 1 to 10; hence, the total number of planned tablets at am would be 10×2 =20.

- Actual number of tablets=Sum of tablets captured on Patient Diary

- Number of dosing days= Last date of exposure in corresponding phase – First dose date in corresponding phase +1(-off drug period)

Number of dosing days is the number of days with non-zero tablets.

- Cumulative dose (mg)= Sum of SHR0302 dose based on Patient Diary.

In one day, a patient will take a total of four tablets, two tablets in the morning and two tablets in the afternoon. According to treatment arm and the time of dosing, the average dose of SHR0302 per tablet are calculated and listed in below table (Table 1).

According to the actual treatment group of a patient, SHR0302 dose per day will be calculated by the following formula:

SHR0302 dose per day=number of tablets taken at am* average SHR0302 dose per tablet (am) +number of tablets taken at pm* average SHR0302 dose per tablet (pm)

Cumulative dose will be sum of SHR0302 dose per day based on Patient Diary.

Table 1: Study drug packaging design and average dose per tablet

Study Arms-all BID	Dose 1(am)	Average dose per tablet (am)	Dose 2 (pm)	Average dose per tablet(pm)
4mg QD	4mg+placebo	SHR0302 2mg per tablet	Placebo+placebo	SHR0302 0mg per tablet
8mg QD	4mg+4mg	SHR0302 4mg per tablet	Placebo+placebo	SHR0302 0mg per tablet
4mg BD	4mg+placebo	SHR0302 2mg per tablet	4mg+placebo	SHR0302 2mg per tablet
Placebo	Placebo+placebo	SHR0302 0mg per tablet	Placebo+placebo	SHR0302 0mg per tablet

- Average daily dose(mg/day) = Cumulative dose (mg)/ Number of dosing days (days)

14. STUDY MEDICATION COMPLIANCE

Compliance to investigational product will be presented for the SS. Compliance with investigational product is derived from data recorded on the eCRF “Drug Accountability” and “Noncompliance With Study Treatment” pages. Compliance will be calculated as the number of tablets taken (amount dispensed-amount returned-amount lost) divided by the planned number of tablets to be taken. The compliance rate will be categorized as <80 , ≥80 to ≤100 and >100. Compliance in treatment phase and extension phase will be summarized and

presented. Furthermore, Compliance will be calculated for kits dispensed at baseline, Week 4, Week 8, Week 12, other visits, unscheduled visit and overall. Overall Compliance before Week 8 used in subgroup analysis in section 7.3 is defined as taking more than or equal to 80% of study drug products before Week 8. Overall Compliance before Week 8 will be calculated as the total number of tablets taken before Week 8 divided by the planned number of tablets to be taken before Week 8.

In addition, the following information will be summarized:

- Overall non-compliance

Overall non-compliance is defined as taking less than 80% of study drug products as directed by the dosing instructions.

- Reason for non-compliance with study treatment

A by-patient listing will include any reasons for noncompliance with study treatment.

14.1 DERIVATIONS

- Compliance (%)= (Amount Dispensed-Amount Returned-Amount Lost) *100/ (Planned number of tablets to be taken)

15. EFFICACY ENDPOINTS

15.1 PRIMARY ENDPOINT

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. The four subscores are listed below.

• Stool frequency (0-3)
• Rectal bleeding (0-3)
• Findings of colonoscopy (0-3)
• Physician global assessment (0-3)

The Physician global assessment (PGA) is a clinician-reported assessment that reflects “the patient’s recorded symptoms, the proctoscopic appearance of the rectosigmoid mucosa, and

other pertinent clinical indexes, such as physical findings and the patient's performance status.

9-point modified Mayo score is the Mayo score excluding 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 week 8.

The primary endpoint is the percentage of patient achieving clinical response at week 8 which is 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.

15.1.1 Primary Analysis of Primary Efficacy Endpoint

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 aim of the study is to detect at lease 1 dose group different from placebo group by using Hochberg's step up test. The primary analysis will be based on the FAS population.

Hochberg's step-up method for multiple testing was developed in 1988 to control the familywise error rate.The familywise error rate is the probability of a coming to at least one false conclusion in a series of hypothesis tests . In other words, it's the probability of making at least one Type I Error. Hochberg's method is thought of as a step-up version of the Bonferroni test.

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.

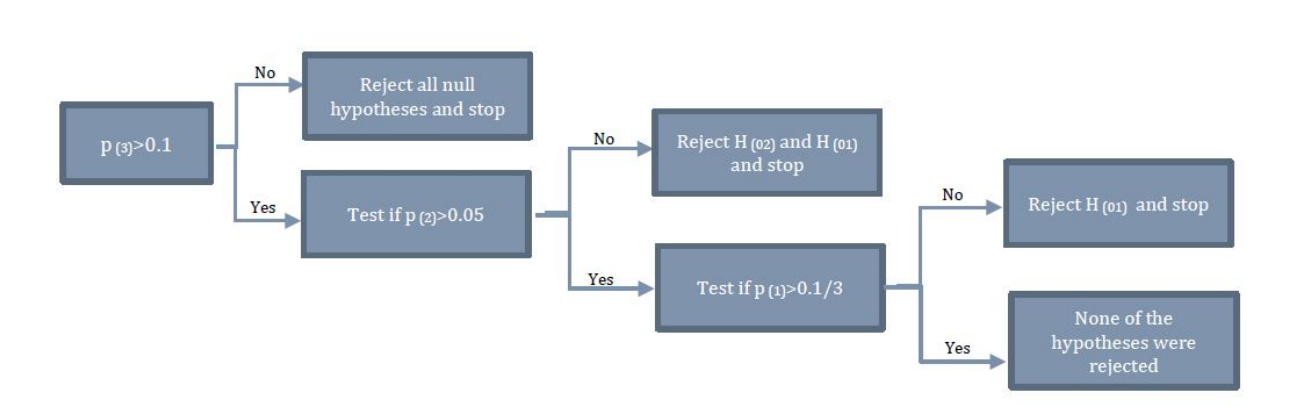


Figure 2. The decision rules of hyopthesis

For clinical response at week 8, the comparisons of the percentage of patients 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). The CMH method is a technique that generates an estimate after adjusting for or taking into account stratification. Strata-adjusted proportion difference between each SHR0302 dose group and placebo group will be obtained by CMH method [1].

Missing data will be imputed as NCF. If a patient is missing one or more Mayo subscores at the visit where the endpoint is being assessed, the patient would be considered a treatment failure.

Two-sided p-values for the treatment group differences will be provided for all comparisons. Thus, 3 p-values will be gained. Order the three p values as ($p_{(3)}$, $p_{(2)}$, $p_{(1)}$), where $p_{(3)} \geqslant p_{(2)} \geqslant p_{(1)}$. The decision rules are provided in Figure 2. Note that in Figure 2, $H_{(01)}$ is the

corresponding null hypothesis of the smallest p value $p_{(1)}$, $H_{(02)}$ is the corresponding null hypothesis of the second smallest p value $p_{(2)}$, and $H_{(03)}$ is the corresponding null hypothesis of the largest p value $p_{(3)}$. Therefore, $H_{(01)}$ and H_{01} may not be the same null hypothesis, $H_{(02)}$ and H_{02} may not be the same null hypothesis, $H_{(03)}$ and H_{03} may not be the same null hypothesis, either.

15.1.2 Sensitivity Analysis of Primary Efficacy Endpoint

Sensitivity analyses for the primary endpoint include:

- Sensitivity to analysis set
  The same analysis will use the per-protocol analysis set

- Sensitivity to missing data assumptions
  The same analysis will use LOCF imputation for subscore other than endoscopy of Mayo score. For missing endoscopy subscore, BOCF imputation will be used .

15.2 SECONDARY ENDPOINTS

The secondary endpoints are as follows:

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

[redacted]

15.2.1 Analysis Methods for Secondary Efficacy Endpoints

All secondary endpoint analyses will be performed on the full analysis set.

Dichotomized Secondary Efficacy Endpoints

Clinical remission per 9-point modified Mayo score is calculated by using 9-point modified

[redacted]

Mayo score where stool frequency subscore ≤1, rectal bleeding subscore of 0, and endoscopic subscore ≤ 1. In addition, Clinical remission per total Mayo score is defined as a total Mayo score of 2 points or lower than 2, with no individual subscore exceeding 1 point. The percentage of patients achieve clinical remission per 9-point modified Mayo score or per total Mayo score will be presented at Week 8. The 90% CI for unadjusted rate will be calculated using the Clopper-Pearson method. Adjusted difference between each SHR0302 dose group and placebo group in clinical remission rate and 90% CI will be provided by CMH method after adjusting for prior anti- TNFα treatment/biological treatment. The adjusted effect will be obtained by CMH weighted average of stratum specific rate differences. Stratified Wald confidence interval will be provided [1].

A shift table will be used to evaluate changes from baseline in Stool Frequency, Rectal Bleeding, Endoscopy and Physician's global assessment subscores of total Mayo score and compare these changes of each of the subscores between the treatment arms.

The percentage of patients achieving clinical response or remission (per 9-point modified Mayo score or total Mayo score) and 90% CI will be presented for each treatment group in a figure.

Endoscopy examination will be required at baseline and Week 8 in order to establish Mayo endoscopic subscore.

Endoscopic remission is defined as the findings of colonoscopy subscore of the Mayo score equals 0. The percentage of patients achieve endoscopic remission will be presented at Week 8. Adjusted difference between each SHR0302 dose group and placebo group in endoscopic remission rate and 90% CI will be provided by CMH method after adjusting for prior anti-TNFα treatment/biological treatment. CMH weighted difference in percentages and confidence interval will be caculated [1].

Continuous Secondary Efficacy Endpoints

Change from baseline in 9 point modified Mayo score or total Mayo score at Week 8 will be summarized in each treatment group and overall. Descriptive statistics will be presented. An analysis of covariance (ANCOVA) model will be used to evaluate whether the means of change from baseline are equal across treatment groups, while statistically controlling for the effects of baseline value and previous exposure to anti-TNFα treatment/other biological treatments. The model will include treatment group, baseline value, with/without previous exposure to anti-TNFα treatment/biological treatment as main effects. Least square mean (LS Mean) and 90% CI for each treatment group will be provided at Week 8.

A partial Mayo score is the Mayo score without endoscopy component. Hence the maximum is 9 points and minimum 0 point. A partial Mayo score will be assessed at baseline, Week 1, Week 4, Week 8, Week 9, Week 12, Week 16 , Week 18, early withdrawal visit and follow up visit, as secondary endpoints.

Changes from baseline in partial Mayo score at Weeks 1, 4, 8, 9, 12 and 16 will be summarized descriptively. For each visit, the change from baseline in partial Mayo score will be calculated. For the change from baseline value at each visit, ANCOVA model including treatment group, baseline value, with/without previous exposure to anti-TNFα treatment as main effects will be used to assess the treatment effect in partial Mayo score. LS Mean and 90% CI for each treatment group will be provided at Week 1, 4, and 8.

A figure will be used to present mean and 90% CI of the partial Mayo score at each visit in each treatment group.

[redacted]

[redacted]

15.2.2 Missing Data for Secondary Efficacy Endpoints

For dichotomized endpoints, missing data will be imputed as non-completers considered failure; if a patient is missing one or more Mayo subscores at the visit where the endpoint is being assessed, the patient would be considered a treatment failure.

For continuous endpoints, missing data will be imputed by using LOCF approach for results other than endoscopy of Mayo score. For missing endoscopy subscore, BOCF approach will be used.

16. SAFETY ENDPOINTS

Summaries of safety data will be based on the safety analysis set. There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

16.1 ADVERSE EVENTS (AEs)

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

Adverse events will be collected from the start of the study drug until the Follow-Up contact. Serious adverse events will be recorded from the time of consent up to and including any follow up contact.

Adverse Events will be coded using MEDDRA 21.1 or higher version.

Treatment emergent Adverse Events (TEAEs) 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.

See Appendix 2 of the SAP for handling of partial dates for AEs.

Listings will include all AEs (TEAEs and Non-TEAEs).

Summaries of the incidence of AEs within each of the categories described below, will be provided.

16.1.1 All TEAEs

An overall summary of TEAEs in treatment phase will be provided. The number and percentage of patients experiencing AEs and the number of TEAEs will be tabulated.

Incidence of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and summarized in treatment phase for each SHR0302 dose level , placebo and overall.

All TEAEs during the whole study period will also be summarized for the following groups similarly.

- 8 mg QD total: 8mg QD during the whole study period+ Placebo->8mg QD group after treatment phase
- 4 mg BD total: 4 mg BD during the whole study period + Placebo->4mg BD group after treatment phase
- 4 mg QD total: 4 mg QD during the whole study period + Placebo->4mg QD group after treatment phase
- Placebo only: Placebo group during treatment phase

Incidence of TEAEs will also be broken down further as shown in the following sections.

16.1.1.1 Relationship to IP

Relationship, as indicated by the Investigator, is classified into 5 grades: related, probably related, possibly related, unlikely to be related, and unrelated. A “related” TEAE is defined as a TEAE with a relationship to study medication as “related”, “probably related”, “possibly related” or “unlikely to be related” to study medication.If a patient reports the same AE more than once within that SOC/ PT, the AE with the worst case relationship to study medication will be used in the corresponding relationship summaries. All TEAEs in treatment phase will be summarized by SOC, PT and by relationship for each SHR-0302 dose level , placebo and overall. All TEAEs will also be summarized similarly for 8 mg QD total, 4 mg BD total, 4 mg QD total, Placebo only and overall during the whole study period.

16.1.1.2 Severity

The severity of TEAE will be collected as mild, moderate and severe. All TEAEs in treatment phase will be summarized by SOC, PT, and severity for each SHR-0302 dose level and placebo. If a patient reports a TEAE more than once within that SOC/ PT, the AE with the worst case severity will be used in the corresponding severity summaries. All TEAEs will also be summarized similarly for 8 mg QD total, 4 mg BD total, 4 mg QD total, placebo only and overall during the whole study period.

16.1.2 TEAEs of Serious Infection

A serious infection during the study is defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials. The patient must be discontinued from the study. Serious infection will be identified as those records with a response of "Yes" to the item "Is this a serious infection defined in protocol?" on the "Adverse Events" form of the eCRF. Serious Infection in treatment phase will be summarized by SOC and PT for each SHR0302 dose level , placebo and overall. The number of patients with at least one serious infection will be presented and 95% CI will be calculated using the Clopper-Pearson method. TEAEs of serious infection will also be summarized similarly for 8 mg QD total, 4 mg BD total, 4 mg QD total, Placebo only and overall during the whole study period.

16.1.3 TEAEs Leading to Study Discontinuation

TEAEs leading to study discontinuation will be identified as those records with a response of "Yes" to the item "Did the adverse event cause the patient to be discontinued from the study?" on the "Adverse Events" form of the eCRF. Summaries of patients (frequencies and percentages) with TEAEs leading to study discontinuation and summaries of incidence rates (frequencies) in treatment phase by SOC and PT will be prepared for each SHR0302 dose level, placebo and overall. TEAEs leading to study discontinuation will also be summarized similarly for 8 mg QD total, 4 mg BD total, 4 mg QD total, Placebo only and overall during the whole study period.

A listing will be prepared for TEAEs leading to study discontinuation.

16.1.4 Serious Adverse Events (SAEs)

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

a. Results in death
b. Is life-threatening
c. Requires hospitalization or prolongation of existing hospitalization
d. Results in disability/incapacity, or
e. Is a congenital anomaly/birth defect

[redacted]

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 patient 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 ⩾ 3xULN and bilirubin ⩾ 2xULN (>35% direct) (or ALT ⩾ 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).

On the Adverse Events page of the eCRF, serious adverse events are those events respond as “Yes” for item “Serious Criteria”.

Summaries of all serious TEAEs and serious TEAEs Related to study medication in treatment phase by SOC and PT for each SHR0302 dose level , placebo and overall will be prepared. All serious TEAEs and serious TEAEs related to study medication will also be summarized similarly for 8 mg QD total, 4 mg BD total, 4 mg QD total, Placebo only and overall during the whole study period. Patients with missing relationship will be treated as probably related.

Listings will include all SAEs (serious TEAEs and serious Non-TEAEs).Listings for SAEs will include the start date, end date, severity, severity, relationship to study drug, action taken, outcome, SAE criteria, and a liver event or not, etc.

16.1.5 TEAEs Leading to Death

TEAEs leading to Death are those TEAEs which are recorded as “Fatal” on the Adverse Events page of the eCRF. A summary of TEAEs leading to death in treatment phase by SOC and PT will be prepared for each SHR0302 dose level , placebo and overall. TEAEs leading to death will also be summarized similarly for 8 mg QD total, 4 mg BD total, 4 mg QD total, Placebo only and overall during the whole study period.A listing will be prepared for TEAEs leading to death.

16.2 DEATHS

If patients die during the study as recorded on the” Death Details” page of the eCRF, the information will be presented in a in a summary table for each SHR0302 dose level , placebo

and overall. Death information will also be summarized similarly for 8 mg QD total, 4 mg BD total, 4 mg QD total, Placebo only and overall during the whole study period. Death information will be presented in a data listing for SS.

16.3 LABORATORY EVALUATIONS

Results from the central laboratory will be included in the reporting of this study for Hematology, Chemistry, Urinalysis and Others. All laboratory assessments will be listed in the outputs.

Presentations will use SI Units. All laboratory data will be summarized and listed for all patients in the SS set by visits where data are collected.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

The following summaries will be provided for laboratory data:

- Actual and change from baseline by visit (for quantitative measurements)
- Incidence of abnormal values according to normal range criteria
- Shift tables representing categorical change of laboratory evaluation results from baseline to each post baseline
- Listing of patients with laboratory results

16.4 ELECTROCARDIOGRAM (ECG) EVALUATIONS

12-lead ECGs will be recorded in triplicate at the scheduled time points. The three values of each ECG parameter at each visit will be averaged to determine time-specific parameter for a patient and used in summaries. The three values of each ECG parameter at each visit will be

included in listings.

The following ECG parameters will be reported for this study:

- Heart Rate (Beats/min)
- PR Interval (msec)
- RR Interval (msec)
- QRS interval (msec)
- QT Interval (msec)
- QTc(F) Interval (msec)
- Overall assessment of ECG
    - Normal
    - Abnormal Not Clinically Significant (ANCS)
    - Abnormal Clinically Significant (ACS)

The following summaries will be provided for ECG data:

- Actual and change from baseline by visit (for quantitative measurements)
- Incidence of abnormal and clinically significant values
- A shift analysis table showing shift in overall ECG interpretation from baseline to each time point

16.4.1 ECG MARKEDLY ABNORMAL CRITERIA

For all patients in the safety analysis population, the maximum QTcF interval will be summarized using frequency tables for each SHR0302 dose level , placebo and overall in treatment phase for values of clinical importance using the range criteria below.

- Absolute values for post baseline QTcF interval will be classified as:

    Cumulative Category:

    - ≤ 450 msec
    - > 450 msec
    - > 480 msec
    - > 500 msec

    Interval Category:

    - ≤ 450 msec
    - > 450 to ≤ 480 msec
    - > 480 to ≤ 500 msec
    - > 500 msec

- Change from Baseline for QTcF interval will be classified as:

  Cumulative Category:

  - <0 msec increase from baseline
  - ≥ 0 msec increase from baseline
  - >30 msec increase from baseline
  - >60 msec increase from baseline

  Interval Category:

  - <0 msec increase from baseline
  - ≥ 0 to ≤ 30 msec increase from baseline
  - > 30 to ≤ 60 msec increase from baseline
  - >60 msec increase from baseline

The maximum QTcF interval will also be summarized similarly for 8 mg QD total, 4 mg BD total, 4 mg QD total, Placebo only and overall during the whole study period.

16.5 VITAL SIGNS

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

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Heart Rate (beats/min)
- Temperature (^{o}C)
- Weight
- Height

The following summaries will be provided for vital signs data:

- Actual and change from baseline by visit
- Incidence of abnormal values according to markedly abnormal criteria
- Listing of patients with vital signs measurements

16.5.1 Vital Signs Markedly Abnormal Criteria

Markedly abnormal quantitative Vital Signs measurements will be identified in accordance with the following predefined markedly abnormal criteria detailed in below table:

Variable	Unit	Low	High
SBP	mmHg	≤ 90 mmHg AND change from baseline ≤ -20 mmHg	≥ 180 mmHg AND change from baseline ≥ 20 mmHg
DBP	mmHg	≤ 50 mmHg AND change from baseline ≤ -15 mmHg	≥ 105 mmHg AND change from baseline ≥ 15 mmHg
Heart Rate	Bpm	≤ 50 bpm AND change from baseline ≤ -15 bpm	≥ 120 bpm AND change from baseline ≥ 15 bpm
Body temperature	˚C	NA	≥ 38.3 ˚C AND change from baseline ≥ 1.1 ˚C
Weight	Kg	percentage change from baseline ≤ -7.0 %	percentage change from baseline ≥ 7.0 %

16.6 PHYSICAL EXAMINATION

Physical examination data will be listed only.

16.7 OTHER SAFETY ASSESSMENTS

Female patients 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 patient will be withdrawn from the study and all the necessary follow up will be conducted. Urine pregnancy test will be done in females of childbearing potential only. Pregnancy tests data will be listed.

Phase II liver chemistry stopping and follow up criteria have been designed to assure patient safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). Please refer to section 7.3.9 of the protocol for details. Liver Event Follow up Assessments and Liver Event Alcohol intake will be listed.

Supplemental lab data will be listed

Microscopy data, if available, will be listed.

A listing will be provided for patients whose trial participation are impacted by COVID-19, including patient number and site number together with a description of the impact. These protocol deviations are documented in [redacted] management system.

17. REFERENCES

[1] KIM Y，WON S．Adjusted proportion difference and confidence interval in stratified randomized trials[R]．Chicago，2013．

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

[redacted] Output Conventions

Outputs will be presented according to the [redacted] guidelines and template for outputs conventions.

Dates & Times

Depending on data available, dates and times will take the form DDMMMYYYY hh:mm:ss.

Significant Digits of Summary Statistics

1 Summary statistics are displayed with the following digits.

Description	Characteristic	Number of decimal places
Count	n	0
Count corresponding to the number of patients for a treatment group	N	0
Mean	Mean	As in source + 1
Standard Deviation	SD	As in source + 1
Confidence Interval	CI	As in source + 1
Minimum	Min	As in source
Median	Median	As in source + 1
Maximum	Max	As in source
Percentage	%	1 *
P-value	P-value	3 decimal places. If the value is less than 0.001, then it will be shown as "<0.001". If P-value cannot be calculated, "-" is shown. If test is not performed, nothing is shown.

* Number of decimal places can be two, if necessary.

2 If the source has more than 5 significant digits, the above would be replaced with the corresponding number of significant digits.

Spelling Format

English US.

Presentation of Treatment Groups

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

Treatment Group	For Tables, Listings and Graphs
SHR0302 8mg QD during the whole study period	8mg QD
SHR0302 4mg BD during the whole study period	4mg BD
SHR0302 4mg QD during the whole study period	4mg QD
Initially randomized to Placebo	Placebo
Placebo during the treatment phase and SHR0302 8mg QD after treatment phase	Placebo->8mg QD
Placebo during the treatment phase and SHR0302 4mg BD after treatment phase	Placebo->4mg BD
Placebo during the treatment phase and SHR0302 4mg QD after treatment phase	Placebo->4mg QD
Screen failure	Screen failure

For some tables related to TEAE and ECG markedly abnormal criteria, treatment group will be presented as follows.

Treatment Group	For TEAE and ECG Markedly Abnormal Criteria Tables
SHR0302 8mg QD during the whole study period+ Placebo->8mg QD group after treatment phase	8mg QD total
SHR0302 4mg BD during the whole study period + Placebo->4mg BD group after treatment phase	4mg BD total
SHR0302 4mg QD during the whole study period + Placebo->4mg BD group after treatment phase	4mg QD total

Treatment Group	For Tables, Listings and Graphs
Placebo group during treatment phase	Placebo only

Presentation of Visits

CRF visits (visits as recorded in the eCRF) will be represented as follows and in that order:

Long Name (default)	Short Name
Screening	Scr
Baseline	BL
Week 1	W1
Week 4	W4
Week 8	W8
Week 9	W9
Week 12	W12
Week 16	W16
Early Withdrawal	EW
Follow Up	FU
Unscheduled Visit	US

CRF visits will be displayed in the listings. Analysis baseline defined in SAP will be flagged and will be identified in the listings as needed.

Analysis visits will be displayed in the tables.

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

Algorithm for Treatment Emergence of Adverse Events:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE

START DATE	STOP DATE	ACTION
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

Algorithm for TEAEs by Study Phase for Onset

TEAE START DATE	ACTION
Known	If start date <week 8 visit date, then TEAE in treatment phase If week 16 visit date≥start date ≥week 8 visit date, then TEAE in extension phase If start date>week 16 visit date, then TEAE in follow up phase
Partial, but known components can determine the phase	If start date <week 8 visit date, then TEAE in treatment phase If week 16 visit date≥start date ≥week 8 visit date, then TEAE in extension phase If start date>week 16 visit date, then TEAE in follow up phase
Partial and known components can not determine the phase	Missing day - Impute the 1st of the month unless month is same as month of first dose of study drug then impute first dose date Missing day and month – impute 1st January unless year is the same as first dose date then impute first dose date If the imputed start date <week 8 visit date, then TEAE in treatment phase If week 16 visit date≥imputed start date ≥week 8 visit date, then TEAE in extension phase If imputed start date>week 16 visit date, then TEAE in follow up phase
Other missing status	impute first dose date and treat the onset of TEAE as in treatment phase

Algorithm for Prior / Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	If stop date <= study med start date, assign as prior If stop date >study med start date, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date <= study med start date, assign as prior If stop date > study med start date, assign as concomitant
	Missing	If stop date is missing could never be assumed a prior medication , assign as concomitant
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date <=study med start date, assign as prior If stop date >study med start date, assign as concomitant
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date <= study med start date, assign as prior If stop date > study med start date, assign as concomitant
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication, assign as concomitant

[redacted]

START DATE	STOP DATE	ACTION
Missing	Known	If stop date <= study med start date, assign as prior If stop date > study med start date, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date <= study med start date, assign as prior If stop date >study med start date, assign as concomitant
	Missing	Assign as concomitant