TITLE: A Randomized, Double-Blind and Placebo-Controlled Phase II Study to Evaluate the Efficacy and Safety of SHR0302 in Adult Patients with Moderate to Severe Atopic Dermatitis

Compound Number: SHR0302

Compound name:

Protocol Number： RSJ10303

Version number: V1.1

IND number:

NCT number: NCT04162899

Effective date: March 14th, 2019

EudraCT ：

Protocol Amendment No.： -

Development Staging Phase IIa/b

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

Protocol RSJ10303
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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 assistants, colleagues and employees assisting in the conduct of the study are informed of their oligations. Mechanisms are put in place to ensure that site staff receives the appropriate information throughout the study.

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List of Abbreviations

AD	Atopic Dermatitis
AUC	Area Under the Curve
β-hCG	Beta-human Chorionic Gonadotropin
CI	Confidence Intervals
Cmax	Maximal Plasma Concentration
CRF	Case Report Form
CRP	C-Reactive Protein
DLQI	Dermatology Life Quality Index
EW	Early Withdrawal
ECG	Electrocardiogram
EMA	European Drug Administration
EASI	Eczema Area and Severity Index
eCRF	Electronic Case Report Form
FDA	U.S. Food & Drug Administration
FSH	Follicle-Stimulating Hormone
FVC	Force Vital Capacity
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
IB	Investigator's Brochure
IL	Interleukin
IGA	Investigator’s Global Assessment
JAK	Janus kinase
IEC	Independent Ethics Committee
IFN-γ	Interferon- gamma
IgE	Immunoglobulin E
IgM	Immunoglobulin M
IND	Investigational New Drug
IRB	Independent Review Board
ITT	Intention-to-Treat
IVRS	Interactive Voice Response System
IUD	Intra-Uterine Device
LDH	Lactic Dehydrogenase
LLoQ	Lower Limit of Quantification
Mcg	Micrograms
MedRA	Medical Dictionary for Regulatory Activities
NRS	Numeric Rating Score
PK	Pharmacokinetics
PP	Per Protocol
PPD	Purified Protein Derivatives
QD	Quaque Die （Once Daily）
RA	Rheumatoid Arthritis
RAP	Reporting and Analysis Plan
SAE	severe adverse event
SAP	Statistical Analysis Plan

SD	Standard Deviation
SPM	Study Procedures Manual
SCORAD	Scoring of Atopic Dermatitis
TCS	Topical corticosteroids
Tlast	Time of last quantifiable concentration
ULN	Upper Limit of Normal

1. Protocol Summary

Atopic Dermatitis (AD) is a common chronic inflammatory skin disease characterized by recurrent, pleomorphic skin lesions, dry skin, and severe pruritus. Atopic dermatitis usually begins in infancy or in children and is chronic, while severe cases may persist in adulthood. Meanwhile, some adult cases develop in adulthood. In most countries worldwide, atopic dermatitis has a prevalence of 10% – 20% in children and 2 – 8% in adults [1]. Moderate to severe atopic dermatitis has been reported in about 20% of cases [2]. In China, the prevalence of atopic dermatitis has also increased rapidly over 20 years [3]. As reported in 2016, the overall prevalence of atopic dermatitis in China is 7.8%[4]. As a chronic relapsing inflammatory disease, atopic dermatitis is not curable at present, and the treatment for moderate to severe AD is difficult.

Janus Kinase (JAK) - Signal transducers and activators of transcription (STAT) signaling pathway as an important intracellular signal transduction pathway plays a critical role for signal transduction from cell membrane to nucleus by various cytokines such as interleukin (IL), interferon (IFN) and other molecules. Inflammatory mediators that depend on the JAK/STAT pathway are involved in the pathogenesis of many inflammatory diseases. Therefore, JAK inhibitors have become a research hotspot in the treatment of immune-mediated inflammatory diseases. There are a number of JAK inhibitors currently under investigation for the treatments of immune-induced disease, such as rheumatoid arthritis (RA), psoriatic arthritis, psoriasis, ulcerative colitis (UC), Crohn's disease (CD), ankylosing spondylitis. Meanwhile, more and more case reports and early Clinical studies have suggested that JAK inhibitors have also achieved good results in the treatment of inflammatory skin diseases such as atopic dermatitis, alopecia areata, psoriasis, and vitiligo.

Compared with traditional immunosuppressants, JAK inhibitors are more targeted. As a small-molecular oral formulation, JAK inhibitors are more convenient and more acceptable to patients than biologics administered by injection. Another advantage of these JAK inhibitors is that they reduce the risk of inadequate responses 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. The high selectivity of SHR0302 to JAK1 also makes it a favorable candidate from a benefit risk safety perspective.

This proposed study is a randomized, double-blind, placebo-controlled, 3-arm parallel, multicenter phase II study, which designed to explore the efficacy and safety of SHR0302 treatment for patient with moderate to severe atopic dermatitis. This study will be conducted over a 12-week treatment period. Two active doses of SHR0302 will be compared to placebo and improvement in atopic dermatitis will be assessed using the Investigator's Global Score (IGA). IGA response is defined as IGA achieving 0 (clear)/1 (almost clear) and an improvement in IGA of ≥ 2 from baseline (as the primary endpoint at week 12), which is widely endorsed by clinical and regulatory authorities. Improvement in eczema area and severity index (EASI) and scoring atopic dermatitis (SCORAD) are also very important and established as secondary endpoints.

1.1 Study objectives and endpoints

The objective is to evaluate the efficacy and safety of SHR0302 4 mg QD and 8 mg QD treatment for adult subjects with moderate to severe atopic dermatitis.

Primary objective	**Primary endpoint**
To evaluate the efficacy of SHR0302 4 mg QD, 8 mg QD compared to placebo in adult subjects with moderate to severe atopic dermatitis at Week 12	• The percentage of subjects achieving IGA response at Week 12. IGA response is defined as IGA 0/1 (clear/almost clear) together with IGA improvement ≥ 2 from baseline.
Secondary objective	**Secondary endpoints**
To evaluate safety and tolerability of oral SHR0302 in subjects with moderate to severe atopic dermatitis	• To assess safety and tolerability by laboratory parameters • To assess safety and tolerability by collection of AE/SAE incidence • To measure vital signs (blood pressure, heart rate, body temperature and respiratory rate) • To measure subjects' total lipid profile, including triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) • To measure subjects' thyroid profile: TSH, free T4 and free T3 • To evaluate liver and renal function • 12-lead ECG

To evaluate the other efficacy endpoints and patient reported outcome of SHR0302 in adult subjects with moderate to severe atopic dermatitis	• Percentage of EASI change from baseline at Weeks 1, 4, 8, and 12 • Percentage of Subjects Achieving IGA Response at Weeks 1, 4, 8 • Percentage of Subjects With ≥ 50%, 75%, and 90% EASI improvement from baseline (EASI50, EASI75, EASI90) at Weeks 1, 4, 8, and 12 • Change from baseline in SCORAD at Weeks 1, 4, 8, and 12 • Percentage of Subjects With ≥ 50%, 75%, and 90% SCORAD improvement from baseline (SCORAD50, SCORAD75, SCORAD90) at Weeks 1, 4, 8, and 12 • Percent of pruritus numerical rating scale (NRS) change from baseline at Weeks 1, 4, 8, and 12 • Percentage of Subjects Achieving Pruritus NRS improvement ≥3 from Baseline in at Weeks 1, 4, 8, and 12 • Change from baseline in Dermatology Life Quality Index (DLQI) at Weeks 1, 4, 8, and 12 • Change from baseline in biomarker IgE at weeks 1, 4, 8 and 12
To explore Pharmacokinetic and dose-response properties of SHR0302 in subjects with moderate to severe atopic dermatitis.	• Systemic exposure of SHR0302 at steady state in subjects with atopic dermatitis (ie: concentration and area under the curve)

1.2 Study Design

This is a 12-week, randomized, double-blind, placebo-controlled, 3-arm, parallel, multicenter clinical study, which will enroll adult subjects with moderate to severe atopic dermatitis. This study includes 4-week screening period and the subsequent 12-week blinded treatment period and 2-week follow-up after last dose. The primary endpoint will be assessed at the end of the blinded treatment period at week 12.

At randomization, subjects who meet the study criteria will be randomized in a 1: 1: 1 ratio to 2 active drug dose groups (4 mg QD and 8 mg QD) or placebo group over the 12-week treatment period. The total number of subjects randomized was 132.

At Visit 1 (screening), subjects will be screened and if the subject meet all the inclusion criteria and do not meet any exclusion criteria, the subject can be consented and enrolled into the study with a subject identification number. The subjects will receive a 4-week standardized run-in period.

At Visit 2 (Day 0), all subjects who meet all inclusion criteria and do not meet any exclusion criteria will be randomizaed into one of the following three treatment groups (SHR0302 4 mg QD, SHR0302 8 mg QD, or placebo) for 12 weeks blinded treatment. A baseline assessment will be performed at this visit.

After randomization, subjects will be followed-up at Week 1, 4, 8, and 12, corresponding to Visit 3, Visit 4, Visit 5, and Visit 6, respectively. At Visit 6 (Week 12), the primary endpoint assessment will be performed.

All subjects who complete the treatment period will be followed-up for a further 2 weeks until Week 14 (Final Visit). Subjects who withdraw early will be followed-up for a further 2 weeks.

The total duration of study participation (including follow-up) will be approximately 19 weeks, 7 clinic visits.

2. Introduction

2.1 Background

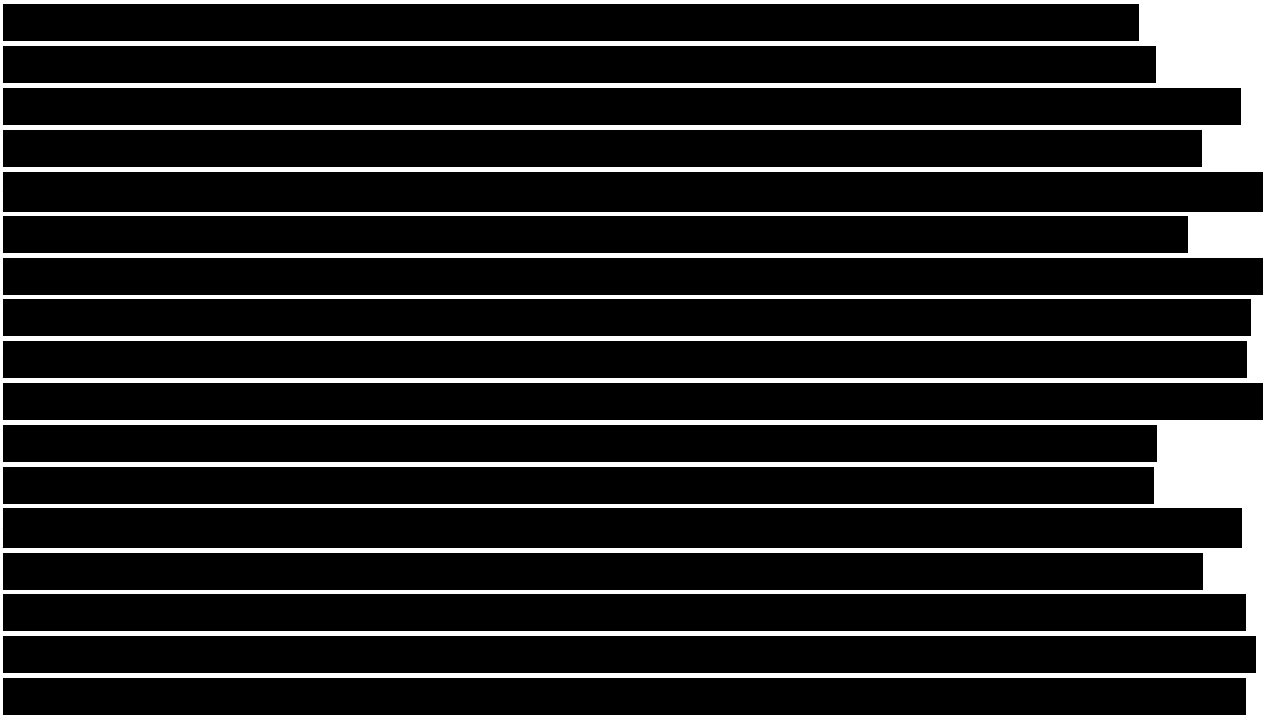
Atopic dermatitis (AD), also known as atopic eczema, is a common chronic inflammatory skin disease characterized by recurrent attacks, pleomorphic skin lesions, dry skin, and severe pruritus. Atopic dermatitis usually begins in infancy or in children and is chronic, while severe cases may persit in adulthood. Meanwhile, some adult cases develop in adulthood. In most countries worldwide, the prevalence of atopic dermatitis is 10% – 20% in children and 2 – 8% in adults [1]. Moderate to severe atopic dermatitis has been reported in about 20% of cases [2]. In recent years, a large number of studies have shown a progressive increase in the prevalence of atopic dermatitis in both children and adults [5]. In China, the prevalence of atopic dermatitis has also increased rapidly over 20 years[3]. In 2016, an epidemiological study conducted in 39 tertiary hospitals in 15 provinces showed that the overall prevalence of atopic dermatitis in China was 7.8%[4]. Furthermore, it was reported that the incidence of atopic dermatitis in China after the age of 12 is also relatively common [6].

As a chronic relapsing disease, atopic dermatitis is not curable at present. The target of the treatment is to relieve or eliminate clinical symptoms, eliminate predisposing and/or aggravating factors, reduce and prevent relapses, and improve the quality of life of patients [3]. Atopic dermatitis treatment depends on the extent and severity of the disease. Patients with mild atopic dermatitis may be treated with topical emollients, glucocorticoids, or calcineurin inhibitors[7], patients with

moderate to severe disease often need to be treated with immunosuppressants or even biologics [8]. Treatment for moderate to severe AD is difficult and often requires comprehensive therapies on an individualized basis. Topical glucocorticoids are considered as first-line therapy. However, they are not suitable for weak skin areas such as face, and long-term treatment would lead to local infections, atrophy, hirsutism, telangiectasia and other adverse reactions. Calcineurin inhibitors (such as tacrolimus, pimecrolimus cream) can be used on ace and other weak areas of the skin, but they also have irritation. Although systemic immunosuppressive agents (e.g., cyclosporine A, methotrexate, etc.) can also be used for the treatment of moderate to severe refractory AD, they also have many limitations. During treatment, it is necessary to monitor patient's blood pressure, renal function or liver function, etc. carefully[9].

Recently, with the in-depth study of the pathogenesis of atopic dermatitis, more targeted and safer therapeutic method have become the research and development direction of AD treatment. Anti-IL-4/IL-13 monoclonal antibody Dupilumab (Dupixent ®) approved by US Drug Administration in March 2017 and Received European Medicines Agency (EMA) in July 2017 provides an effective treatment for patients with moderate to severe atopic dermatitis in Europe and the United States who do not respond adequately to topical treatment or phototherapy [10], and avoids adverse effects of traditional hormones and immunosuppressive agents (e.g., cyclosporine A, methotrexate). However, a large number of studies have shown that although biologics are effective and well tolerated, long-term treatment may result in the absence of responses caused by immunogenicity in some patients. Therefore, patients may need to increase the dose and/or decrease the dosing interval. In addition, most patients cannot afford these higher-priced biologics.

2.2 Rationale



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2.3 Dose Selection Rationale

[redacted]

[redacted]

[redacted]

2.4 Risk: Benefit Assessment

[redacted]

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3. Study Objectives and Endpoints

3.1 Primary objective and primary efficacy endpoint

Primary objective	Primary efficacy endpoint
To evaluate the efficacy of SHR0302 4 mg QD, 8 mg QD compared to placebo in adult subjects with moderate to severe atopic dermatitis at Week 12	• The percentage of subjects achieving IGA response at Week 12. IGA responsed is defined as IGA 0/1 (clear/almost clear) together with IGA improvement ≥ 2 from baseline

3.2 Secondary objectives and Secondary Endpoints

Secondary objectives	Secondary endpoints
To evaluate safety and tolerability of oral SHR0302 in subjects with moderate to severe atopic dermatitis	• To assess safety and tolerability by laboratory parameters • To assess safety and tolerability by collection of AE/SAE incidence • To measure vital signs (blood pressure, heart rate, body temperature and respiratory rate) • To measure subjects' total lipid profile, including triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) • To measure subjects' thyroid profile: TSH, free T4 and free T3 • To evaluate liver and renal function • 12-lead ECG
To evaluate the other efficacy endpoint and patient reported outcome of SHR0302 in adult subjects with moderate to severe atopic dermatitis	• Percentage of EASI change from baseline at Weeks 1, 4, 8, and 12 • Percentage of Subjects Achieving IGA Response at Weeks 1, 4, 8 • Percentage of Subjects With ≥ 50%, 75%, and 90% EASI improvement from baseline (EASI50, EASI75, EASI90) at Weeks 1, 4, 8, and 12 • Mean change from baseline in SCORAD at Weeks 1, 4, 8, and 12 • Percentage of Subjects With ≥ 50%, 75%, and 90% SCORAD improvement from baseline (SCORAD50, SCORAD75, SCORAD90) at Weeks 1, 4, 8, and 12

Secondary objectives	Secondary endpoints
	• Percent of pruritus numerical rating scale (NRS) change from baseline at Weeks 1, 4, 8, and 12 • Percentage of Subjects Achieving Pruritus NRS improvement ≥3 from Baseline in at Weeks 1, 4, 8, and 12 • Change from baseline in Dermatology Life Quality Index (DLQI) at Weeks 1, 4, 8, and 12 • Change from baseline in biomarker IgE at weeks 1, 4, 8 and 12
To explore Pharmacokinetic and dose-response properties of SHR0302 in subjects with moderate to severe atopic dermatitis.	• Systemic exposure of SHR0302 at steady state in subjects with atopic dermatitis (ie: concentration and area under the curve)

4. Investigational Plan

4.1 Study Design

See Figure 1 .

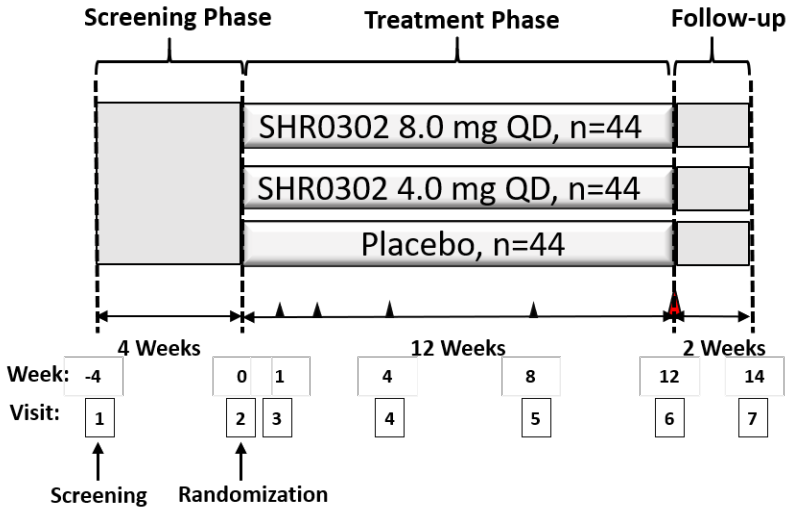

Figure 1. Study Design Diagram

4.2 Discussion of the design

This is a randomized, double-blind, placebo-controlled, multicenter phase II study that will enroll 132 subjects with moderate to severe atopic dermatitis. This study consists of a 4-week screening period followed by a 12-week blinded treatment period and 2-week follow-up after last dose. At baseline visit, subjects with moderate to severe atopic dermatitis who meet all inclusion criteria/do not meet any of the exclusion criteria will be randomized in a 1: 1: 1 ratio during the treatment period to one of 3 study groups (2 active drug dose groups (4 mg QD, 8 mg QD) and placebo group) .

All subjects will be followed-up for further 2 weeks until Week 14 (Final Visit). Subjects who withdraw early will be followed for an additional 2 weeks.

The end of study is defined as the date of last subject's last visit or actual date of follow-up, whichever is later.

5. Subject Selection and Withdrawal Criteria

5.1 Number of Subjects

132 eligible subjects will undergo randomization to achieve the estimated evaluable subjects in the study. The following criteria are designed to select subjects suitable for treatment according to the protocol. All relevant medical and non-medical conditions should be considered when deciding whether a subject is suitable for participation in this study. Subjects' eligibility should be reviewed and documented by a qualified appropriate member of the investigator's study team prior to subject enrollment in the study. Subjects must be able to voluntarily provide informed consent for participation in this study.

5.2 Inclusion criteria

Subjects must meet all the following inclusion criteria to be eligible for enrollment into the study:

1. Subjects between 18-75 years of age (inclusive), male or female, at the time of informed consent
2. Moderate to severe atopic dermatitis, as determined by all of the following:
    - Have a clinical diagnosis of AD for at least 1 year before Visit 1 (Chinese Criteria of AD refer to Appendix 1)
    - EASI ≥ 12, BSA ≥ 10%, and IGA ≥ 3 at the Screening and Baseline Visits
    - In the judgment of the investigator, subjects who have inadequate response and/or cannot be tolerable, to one or more of the below treatments for at least 4 weeks
        - Topical therapy (topical corticosteroids and/or topical calcineurin inhibitors)
        - Systemic steroids and/or phototherapy

- Cyclosporine and/or other immunomodulators (e.g., methotrexate, mycophenolate mofetil, and azathioprine, etc.)

3. Capable of providing a signed and dated informed consent form indicating the subject has been informed of all pertinent aspect of the study
4. 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.
5. Subjects who are willing and able to comply with the scheduled visits and treatment plan, laboratory testing and other study procedure
6. Subjects receiving non-prohibited concomitant medications for any reason must maintain a stable dosing regimen, defined as no administration of a new drug or no change in dose within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study drug

5.3 Exclusion Criteria

Subjects presenting with any of the following criteria will not be enrolled in this study:

1. 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
2. Subject has a current diagnosis of other active skin disease (e.g., psoriasis or lupus erythematosus) or skin infection (bacterial, fungal, or viral) that may affect the evaluation of atopic dermatitis
3. Subject has a severe comorbidity that may require systemic steroids therapy or other interventions or requires active frequent monitoring (e.g., unstable chronic asthma)
4. Subjects with evidence of hematopoietic disorders:
   - Hemoglobin level < 9.0 g/dL or hematocrit < 30% at screening visit or within 3 months prior to baseline
   - Absolute white blood cell (WBC) count <3.0 x 10^9/L (<3000/mm^3) or Absolute Neutrophil Count (ANC) of <1.2 X 10^9/L (<1200/mm3) 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.

5. 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.
6. Subjects with eGFR ≤ 60 ml/min based on Cockcroft-Gault calculation (Appendix2), or patients currently undergoes regular hemodialysis
7. Subjects with current clinically significant infections or within 6 months 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
8. Subjects may have evidence of active, latent, or inadequately treated infection with Mycobacterium tuberculosis (i.e., tuberculosis [TB]), as defined by the following:
   - Negative QuantiFERON TB Gold (QFT Gold test) /or T-Spot test performed within the 3 months prior to/within screening;
     OR
   - Subjects have a chest radiograph, taken within the 3 months prior to/within screening, and showing no change suggestive of active TB infection
     OR
   - Subjects have history of either untreated or inadequately treated latent or active TB infection
9. Subjects have received systemic corticosteroids, cyclosporin or other immunosuppressants (e.g., methotrexate, mycophenolate mofetil and azathioprine) or PDE4 inhibitor or phototherapy (e.g., UVB) treatment within 4 weeks of first dose of study drug
10. Subjects have received topical treatment (which may affect AD, e.g., topical corticosteroids, topical calcineurin inhibitor, antibiotic compound cream and topical herbal) within 2 weeks of firs dose of study drug
11. 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
12. Women who are pregnant or lactating or planning pregnancy while enrolled in the study
13. History of alcohol or drug abuse with less than 6 months of abstinence prior to baseline
14. 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)
15. Subjects with temperature ≥ 38 ° C at screening or baseline
16. Subjects with malignancies or a history of malignancies except for adequately treated or excised non-metastatic basal cell or squamous cell carcinoma of the skin

17. Subjects with positive human immunodeficiency virus (HIV) or hepatitis B virus or hepatitis C virus-related laboratory tests
18. Subjects who currently have thyroid disorders (including hyperthyroidism, hypothyroidism, or are currently receiving thyroid replacement therapy. Subjects with abnormal TSH, fT4, and fT3 values on blood tests at screening must be excluded
19. Subjects who have previously been treated with JAK inhibitors (for example: tofacitinib, baricitinib, upadacitinib, PF04965842, etc.)
20. Subjects who have previously been treated with biologics (Dupilumab, etc.)
21. Subjects receiving or are expected to receive prohibited concomitant medication(s) within 4 weeks prior to the first dose of study drug (see Appendix 4)
22. Subjects who have received herbal treatment of unknown nature or known efficacy within 4 weeks prior to the first dose of study drug
23. Subjects who, in the opinion of the investigator, will be uncooperative or unable to comply with the study procedures
24. Any other condition which in the opinion of the investigator would make the subject unsuitable for inclusion in the study.

5.4 Contraception advice

Contraceptive measures for both male and female subjects with childbearing potential should be documented in the original document.

5.4.1 Female subjects of non-Childbearing potential

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

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

  OR

- Female subjects with physician documented hysterectomy, bilateral salpingectomy and/or bilateral oophorectomy

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

5.4.2 Female subjects with childbearing potential

Female subjects with childbearing potential and their male partners must use at least one of the following highly effective methods of contraception:

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 an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
d. Documented bilateral tube occlusion at least 4 weeks before screening
e. Vasectomized partner with medical confirmation of absence of sperm in the ejaculate at least 4 weeks before screening.

Female subjects and their heterosexual 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 tests

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

At randomization visit (Visit 2), subjects who meet all inclusion criteria and do not meet any exclusion criteria will be randomized in a 1: 1: 1 allocation ratio to SHR0302 4 mg QD, SHR0302 8 mg QD, or placebo. Subjects will be assigned to treatment groups using a computer-generated randomization table. Subjects will be assigned subject numbers in the order in which they consent to participate in the study. This identification number will be kept throughout the study.

5.6 Withdrawal Criteria

Subjects may withdraw from the study at any time on their own request, or subjects 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 been stable.

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 7.3.10. 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 they have signed a written informed consent and completed at least one additional study procedure (study procedures do not include washout of any medication).

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:

- Screening Visit Date

- Subject Number
- Demographic information, including race, age, and gender
- Inclusion/Exclusion Criteria
- Reasons for screening failure
- Primary method of subject recruitment
- Serious adverse event (SAE) information

In most circumstances, subjects who failed screening could not be re-screened. In rare instance, 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.

5.8 Early Withdrawal

The definition of an early 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 6 procedure (Week 12).

Subjects 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 (documented in original document only)
- Vital signs
- Collect and review patient questionnaires (pruritus NRS, DLQI)
- Collect used study medication (blinded study medication)
- Topical triamcinolone used was collected and weighed
- Assess compliance with study medication
- 12-lead ECG
- Laboratory evaluations (including biochemistry, hematology, pregnancy test for female subjects of childbearing potential and routine urinalysis)
- Call IVRS to report the subject's early withdrawal from the study
- Investigator’s Global Score (IGA)
- Eczema Area and Severity Index (EASI)
- Scoring atopic dermatitis (SCORAD)

Subjects who withdraw from the study after randomization to treatment cannot be re-screened and will not be replaced. If a subject withdraws from the study, and withdraws consent for further disclosure, no further assessments will be performed and no additional data will be collected. The sponsor may retain and continue to use any data collected prior to such withdrawal of consent.

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 follows:

- 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 7.3.8 Liver Chemistry Stopping and Follow-up Criteria.
- 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 > 500ms
    - Change from baseline: QTc > 60ms

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.

- 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 should be withdrawn immediately. The procedure is detailed 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 Time and Event Tables

See details in Table 1 .

Table 1. Time and Event Table

Period	Screening	Baseline	Treatment period				Follow-up/ EW [12]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Study Week	**-4 to -1**	**0**	**1**	**4**	**8**	**12**	**14**
Study Day	**-28to -1**	**0**	**7 ± 2 days**	**28 ± 3 days**	**56 ± 3 days**	**84 ± 3 days**	**98 ± 3 days**
Procedures							
Written Informed Consent [1]	x						
Demography/Medical History [2]	x						
Physical Examination	x	x	x	x	x	x	x
Height	x						
Weight	x						x
Chest X-ray[3]	x						
Inclusion/Exclusion Criteria	x						
Randomization criteria		x					
Study Drug Dispensing		x		x	x		
Study Drug Accountability				x	x	x	x [13]
Enrollment Visit in IVRS [4]	x	x	x	x	x	x	x [13]
Assessment of effectiveness							
Investigator's Global Assessment (IGA)	x	x	x	x	x	x	x [13]
Eczema Area and Severity Index (EASI)	x	x	x	x	x	x	x [13]
Scoring Atopic Dermatitis (SCORAD)	x	x	x	x	x	x	x [13]
Pruritus numeric rating scale (NRS)	x	x	x	x	x	x	x [13]
Dermatology quality of life index (DLQI)	x	x	x	x	x	x	x [13]
Photography[5]	x	x	x	x	x	x	x[13]
safety assessment							
12-lead ECG	x	x	x	x	x	x	x

Vital signs (blood pressure, heart rate, temperature and respiratory rate) [6]	x	x	x	x	x	x	x
Adverse Event Assessment [7]		x	x	x	x	x	x
Laboratory Evaluation							
Hematological and biochemical tests	x	x	x	x	x	x	x
Urinalysis	x	x	x	x	x	x	x
Lipid Profile (fasting)		x	x	x	x	x	x
TSH, fT3, fT4	x	x	x	x	x	x	x
QuantiFERON-TB Gold or T-SPOT.TB test	x						
Hepatitis B surface antigen, Hep C Ab, HIV test	x						
Immunoglobulin E (IgE)	x	x	x	x	x	x	x[13]
Urine Pregnancy Test [8]		x	x	x	x	x	x
β-HCG (blood) [9]	x						
[redacted]					[redacted]	[redacted]	
Medication							
Concomitant Medication Assessment	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. Atopic Dermatitis Disease History includes collection of details of AD: AD diagnosis, the use of topical treatments, systemic treatments and other treatments for AD.
3. Only to be performed if there is no chest X-ray or CT scan available within 3 months of Visit 1.
4. IVRS is a randomization system used to record all patient visits.
5. Subjects will be photographed at a distance of 1m by a fixed investigator at each visit (the principle of photography is to reflect the characteristics of AD skin lesion to the greatest extent). When photographed, face and private part will be well covered.
6. Vital signs include resting blood pressure, heart rate, body temperature and respiratory rate. It is advised to measure them before any procedures or questionnaires.
7. Adverse events and serious adverse events will be collected from the start of study drug treatment (Visit 2) to the telephone follow-up period. However, any serious adverse events will be recorded from the time of consent.
8. Urine pregnancy test to be done in females of childbearing potential only at scheduled visit
9. 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.

[redacted]

12. The early withdrawal visit should be done 2 weeks after the last dose/decision of withdrawal.
13. Only to be conducted in the early withdrawal subjects.

6. Study Treatments

6.1 Investigational product/placebo supply

SHR0302 tablets and matching placebo tablets will be dispensed for subjects to take orally during the treatment period. During the treatment period, subjects will be randomized in a ratio of 1: 1: 1 to 4 mg QD, 8 mg QD, or placebo.

SHR0302 will be provided as combination of 4 mg tablets, including the matching placebo by the sponsor. At study visit on Day 0, Week 4 and Week 8, sufficient trial medication will be dispensed to complete dosing for 4 weeks.

At the Week 12 visit or follow-up visit (if the patient withdraws), the subject must return all trial medication and the amount of medication returned will be recorded.

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 completion of the 12-week treatment period, all subjects will be followed for an additional 2 weeks.

6.1.2 Study Drug Administration

Study drug will be self-administered by the subject once daily orally in the morning.

However, the first dose will be administered at the clinic at baseline (Day 0). Subjects should take their oral dose at the clinic at the Week 4, Week 8, and Week 12 visits. Study drug may be taken with or without food.

6.2 Treatment Assignment

Subjects who meet all inclusion criteria and do not meet any of the exclusion criteria will be randomized in a 1: 1: 1 allocation ratio to SHR0302 4 mg QD, SHR0302 8 mg QD, or placebo during the treatment period.

6.3 Blinding

Investigational product taken during the 12-week treatment period will remain double-blind. Neither the subject nor the study physician will know which study medication the subject is receiving.

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

oncedaily (QD) dosing regime and placebo is used according to the schedule in the table below. (Table 2)

Table 2. Study drug package design for treatment group

Study Group	Dose (QD) Day 0 to Day 84
4mg SHR0302	4mg tablet + placebo tablet
8mg SHR0302	4mg tablet + 4mg tablet
placebo	Placebo tablet + placebo tablet

At each dosing time (morning), subjects will take two tablets.

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 (e.g., 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 of the treatment period or at follow-up (if the subject withdraws).

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 study center 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.

Previous treatment

All treatment for atopic dermatitis including systemic steroids after the first diagnosis of atopic dermatitis (as determined by medical history or by medical inquiry) and all treatment performed within 4 weeks prior to screening must be documented in the eCRF. Reasons for discontinuing these medications should be recorded as:

- Never achieved a satisfactory response
- A satisfactory response was initially achieved, but later became ineffective
- Treatment discontinuation due to intolerance/side effects
- Other (detailed description)

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. At screen visit (Visit 1), subjects will be provided with non-medicated study emollient. Subjects will start the emollient twice daily 2 weeks prior to the baseline visit (Visit 2). The non-medicated study emollient is the only topical products permitted to be used on atopic dermatitis skin during the study. If a subject has a history of intolerability or currently does not tolerate the non-medicated study emollient, the investigator should contact Reistone for approval to use an alternative topical treatment; the approved alternative non-medicated emollient should be documented in study records.

At the same time, all subjects will also be asked about other co-medications at each clinic visit and recorded in the co-medications section of the CRF. Other concomitant medications allowed if needed during the study are as follows:

- Over-the-counter shower gel
- Oral antihistamines
- Nonsteroidal anti-inflammatory drugs

In addition, the investigator or appropriate study staff should be consulted before the subject starts a new combined treatment regimen during the study.

6.6.2 Prohibited Medications

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

- Topical treatment for AD (including but not limited to topical corticosteroids, calcineurin inhibitor, herbal, etc.)
- Phototherapy
- Cyclosporin and other immunosuppressant (e.g., methotrexate, mycophenolate mofetil and azathioprine, etc.)
- Systemic corticosteroids
- Biologics

In addition, concomitant administration of CYP3A inducers and moderate to potent CYP3A inhibitors with systemic effects should be avoided during 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 lase dose of study medication.

6.6.3 Prohibited Medications Washout

Subjects who have received systemic corticosteroids, cyclosporin and other immunosuppressant (e.g., methotrexate, mycophenolate mofetil and azathioprine, etc.)、PDE4 inhibitor as well as phototherapy treatment should washout at least 4 weeks prior to first dose of study drug. Subjects who have topical treatment for AD (e.g., topical corticosteroids, calcineurin inhibitor and herbal, etc.) should washout at least 2 weeks prior to first dose of study drug.

6.6.4 Traditional Chinese Medicine and Herbal Medicines

The following categories of traditional Chinese medicine or herbal medicine are prohibited during the study:

- Traditional Chinese medicine or herbal medicine used for the treatment of AD, including those which may contain corticosteroids according to investigator's judgment.
- Traditional Chinese medicine or herbal medicine known effects on platelets and that increase bleeding tendency.

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 nor not Reistione Biopharma/designated CRO is providing specific post study treatment after week 12. Reistione Biopharma/designated CRO has provided a 12-week double-blind treatment period and will not provide treatment after the end of the 12-week treatment period. Post-treatment AD 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 key baseline assessments will be performed at Visit 1:

- Demographic history (including gender, ethnic origin, date of birth, height, and weight)
- Medical history of atopic dermatitis, including date of diagnosis (year of diagnosis is acceptable) and previous and/or current medical conditions
- Physical examination
- Heart rate, blood pressure, respiratory rate and temperature measurement
- 12-lead ECG
- Chest X-ray (or previous CT scan results obtained within 3 months of Screening (Visit 1))
- Clinical laboratory evaluation (including biochemistry, hematology, urine pregnancy test)
- IGA (Investigator's Global Assessment)
- EASI (Eczema Area and Severity Index)
- SCORAD (Scoring Atopic Dermatitis)
- Pruritus numerical rating scale (NRS)
- Dermatology Life Quality Index (DLQI)

7.2 Efficacy Endpoint Assessment

7.2.1 Investigator's Global Score (IGA)

Primary Efficacy Endpoint: the treatment response rate based on Investigator's Global Assessment (IGA). The IGA score is a very simple and convenient assessment method, which is commonly used in clinical research as a gold-standard clinical assessment tool[14].
The IGA score will be assessed at each visit by the investigator using clinical characteristics of erythema, infiltration, papulation, oozing, and crusting as guidelines for the overall severity assessment. The IGA consists of a 6-point severity scale from clear to very severe disease (See Table 3). The assessment will be static evaluation without regards to the score at a previous visit.

Table 3. Investigator's Global Score (IGA)

Score	Category	Description
0	Clear	Atopic dermatitis is cleared, except for any residual discoloration
1	Almost clear	Only just perceptible erythema and perceptible papules/infiltrates or edema
2	Mild	Mild erythema, and mild papules/infiltrates or edema
3	Moderate	Moderate erythema, and moderate papules/infiltrates or edema
4	Severe	Severe erythema, and severe papules/infiltrates or edema
5	Very Severe	Very severe skin lesions, severe erythema, and severe papules/infiltrates or edema with exudation/crusting.

7.2.2 Eczema Area and Severity Index (EASI)

The EASI score is the sum of the skin lesion severity scores and the integral and coefficient product of the area affected by the skin lesions in the four parts of the body: head and neck, trunk, upper limbs, and lower limbs. The specific calculation methods are as follows: ①The clinical manifestations of the severity of skin lesions are divided into four items, namely erythema (E), infiltration (edema) or papules (induration (edema)/papulation, I), epidermal exfoliation (excoriation, Ex), lichenification (lichenification, L). The severity of each clinical manifestation was scored on a 0 – 3 scale: 0 = none, 1 = mild, 2 = moderate, and 3 = severe (for details see Table 4). Half of the scores, and 0. 5, can be recorded between symptom scores. ②Lesion area size score: The whole body was divided into four parts, namely, head and neck (H), trunk (T), upper limb (UL), lower limb (LL). Using the patient's palm as an estimate of 1%, the four-part lesion area was converted into a proportion of the site scored on a scale of 0 to 6: 0 for no rash, 1 for < 10%, 2 for 10% to 29%, 3 for 30% to 49%, 4 for 50% to 69%, 5 for 70% to 89%, and 6 for 90%

to 100%. 3 Then according to the proportion of body parts in the whole body (see details Table 5), each part was multiplied by the corresponding percentage coefficient, and the score of each part was added as the total score of EASI skin lesion symptom severity, which was calculated by the following formula, and the total score was 0-72 [15].

EASI = 0.1Ah (Eh + Ih + Exh + Lh) + 0.2Au (Eu + Iu + ExU + Lu) + 0.3At (Et + It + Ext + Lt) + 0.4Al (El + Il + Exl + Ll)

A = area score; E = erythema; I = infiltration/papulation; Ex = excoriation; L = lichenification; H = head/neck; U = upper limbs; T = trunk; L = lower limbs.

The EASI score ranges from 0.0 to 72.0, can be varied in increments of 0.1, Higher scores indicate greater severity.

Table 4. Clinical severity scoring criteria for the Eczema Area and Severity Index (EASI)

Score		Description
Erythema (E)		
0	Absent	None; may have residual discoloration
1	Mild	Light pink to light red
2	Moderate	Red
3	Severe	Deep, dark red
Infiltration/Papulation(I)		
0	Absent	None
1	Mild	Barely palpable to slight, but definite hard thickened skin and/or papules
2	Moderate	Easily palpable moderate hard thickened skin and/or papules
3	Severe	Severe hard thickened skin and/or papules
Excoriation (Ex)		
0	Absent	None
1	Mild	Slight, but definite linear or picked scratch marks or penetrating surface injur
2	Moderate	Moderate linear or picked scratch marks or penetrating surface injury
3	Severe	Severe linear or picked scratch marks or penetrating surface injury
Lichenification (L)		

0	Absent	None
1	Mild	Barely perceptible to slight, but definite thickened skin, fine skin markings and lichenoid scal
2	Moderate	Moderate thickened skin, coarse skin markings, and coarse lichenoid scale
3	Severe	Severe thickened skin with very coarse skin markings and lichenoid scale

Table 5. Body Region Surface Area (BSA)

Body region	The proportion of each part
Head/neck	0.1
Upper limbs	0.2
Trunk	0.3
Lower limb	0.4

7.2.3 Atopic Dermatitis Score (SCORAD)

SCORAD is a scoring standard proposed by the European Atopic Dermatitis Research Group (ETFAD) in 1993. It integrates the observational assessment of physicians and patients and is recognized by the Harmonizing Outcome Measures for Eczema (HOME) as an effective assessment method that can be used in clinical research and clinical practice [14].

The scoring scale consists of three major sections: the objective signs section includes lesion area (A) and lesion severity (B), and the subjective symptoms include the degree of itching and sleep effects (C), as detailed in Appendix 5 .

A. Lesion area: In adults, the lesion area was estimated according to the "rule of nine": head and neck 9%, double upper limbs 18%, trunk back 36%, lower limbs 36%, perineum 1%. Taking 1% of the area as 1 point, the total area score is A (maximum score 100).
B. Lesion severity: Overall assessment of six clinical features including erythema, papular (or) edema, exudation (or) crusting, epidermal exfoliation, lichenification, and dry skin (uninvolved skin only). According to the severity of skin lesions, each item was rated as 0-3 points on a four-grade scale, and six parts were summed as B (maximum score 18).
C. Itching and sleeplessness: The evaluation was performed using a visual analogue scale (VAS) method, with 0 – 10 points for each item (itching 0 = no itching, itching 10 = very itchy; sleep 0 = no impact, sleep 10 = severely affected), taking the sum of the mean scores of itch and sleep impact in the last 3 days as C (maximum score 20).

SCORAD total score = A/5 + 7B/2 + C with a score of 0-103.

7.2.4 Pruritus Numeric Rating Scale (NRS)

Pruritus Rating: At each visit, the degree of pruritus/scratching was assessed by the subject on an 11-grade rating scale from 0 (no pruritus/scratching) - 10 (severe pruritus/scratching) for the first 24 h of the visit (see details in Appendix 5).

7.2.5 Skin Disease Quality of Life Index (DLQI)

The DLQI is a commonly used dermatology-related questionnaire that allows subjects to assess the impact of skin disease on quality of life through 10 questions (see details in Appendix 6), widely used in clinical studies of AD.
Subjects should complete questionnaires prior to all other study-related procedures at each visit. The DLQI questionnaire will be checked by the study center staff before the subject leaves the study center. All completed DLQI questionnaires will have CRA returned and sent to the sponsor for transcription into the EDC system.

7.3 Safety assessment

7.3.1 Vital Signs

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

Vital signs will be performed using equipment provided by sites and will be obtained at visits and time points as detailed in Section 5.11 - Time and Event Tables .

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 5.11 – 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 QuantiFERON-TB Gold Test

QuantiFERON-TB Gold ® ™ test may be used at the discretion of the investigator based on the implement ability of the local test. The mechanism of QuantiFERON-TB Gold Test is that this enzyme-linked immunosorbent assay (ELISA) assay detects interferon-gamma (IFN-γ) release in

sensitized humans when fresh heparinized whole blood is co-incubated with a synthetic peptide mixture mimicking two proteins in M. tuberculosis, early secretory antigen target protein-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. Since all Bacillus Calmette-Guérin (BCG) vaccine strains and common non-tuberculous mycobacteria (except M. kansasii, M. stephensi and M.mainum) neither of these proteins are present, so the QuantiFERON-TB Gold assay is more specific for M. tuberculosis than the test in which tuberculin purified protein derivative (PPD) is used as antigen.

7.3.5 T-SPOT.TB test

T-SPOT may be used at the discretion of the investigator based on the implement ability of the local test. The mechanism of T-SPOT TB assay is that tuberculosis-specific antigen stimulation of activated effector T cells (secreting gamma interferon) can be detected by this enzyme-linked immunospot (ELISPOT) assay when peripheral blood mononuclear cells are co-incubated with a synthetic peptide mixture mimicking both proteins in M. tuberculosis (early secretory antigen target protein-6 (ESAT-6) and culture filtrate protein-10 (CFP-10)). Each spot represents a gamma interferon-secreting T cell, and the number of spots is counted to obtain the number of tuberculosis-primed T cells in the peripheral blood. Similar to the QuantiFERON-TB Gold assay, compared to the PPD assay, T-SPOT.TB test is more specific for M. tuberculosis.

7.3.5 Clinical Laboratory Testing

Routine, non-fasting clinical laboratory (hematology and chemistry and urinalysis) tests will be performed as detailed in Section 5.11 –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 childbearing potential as detailed in Table 6.

The study clinical laboratory tests including analytes for clinical chemistry and hematology are shown below in Table 6.

Table 6. Clinical Laboratory Testing Lists

Biochemistry	Hematology	Urinalysis	Other
Albumin	Hemoglobin	pH	Hepatitis B surface antigen [1]
Alkaline phosphatase	Hematocrit	Protein	Hepatitis C virus antibody [1]
Alanine aminotransferase (ALT or SGPT)	Platelet count	Glucose	HIV tests [1]
Aspartate amino-transferase (AST or SGOT)	WBC count	Bilirubin and White Cell Count	Urine pregnancy test (performed in clinic) [2]
Bilirubin, direct	RBC count		FSH [3]
Bilirubin, indirect	Neutrophils, absolute		β-HCG blood test [4]
Bilirubin, total	Neutrophils, segs (%)		Lipid check item (fasting) total cholesterol, low density lipoprotein (LDL) high density lipoprotein (HDL) triglyceride
Calcium	Neutrophils, bands (%)		Thyroid function tests, including TSH, free T4, and free T3
Chloride	Basophils (%)		total IgE
CO2 content/Bicarbonate	Eosinophils (%)		PK sampling[5]
Creatinine	Eosinophils, absolute		
Creatine phosphokinase (CPK), total	Lymphocytes (%)		
Gamma glutamyl transferase (GGT)	Monocytes (%)		
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 for confirmation of postmenopausal status at screening visit only
4 Only for females of child-bearing potential at screening, and if urine pregnancy test positive
5 Only done as per Section 7.4 Pharmacokinetics

7.3.6 Immunoglobulin E (IgE)

Atopic dermatitis is divided into endogenous and exogenous types. In adult AD patients, exogenous AD accounts for approximately 80% and endogenous AD for 20%. Patients with exogenous AD usually present with elevated serum total IgE [16]. Blood samples will be collected for detection of IgE levels at screening, baseline, week 1, week 4, week 8, and week 12.

7.3.7 Lipid Profile Testing

A fasting lipid profile blood collection, as per Section 5.11 –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.

7.3.8 Liver Biochemistry – Stopping and Follow-up Criteria

Phase II Liver Biochemistry Stopping and Follow-up Criteria have been designed to ensure subject safety and to assess liver event etiology (consistent with FDA premarketing clinical liver safety guidance). If any of the following conditions occur at any time during the study drug treatment period, the study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests until the subject's laboratory values return to normal or return to baseline condition):

- ALT or AST > 8 x ULN, or
- ALT or AST > 5 x ULN and retest 5 x ULN, or
- ALT or AST > 3 x ULN with elevated total bilirubin > 2 x ULN, or international normalized ratio > 1.5, or
- ALT or AST > 3 x ULN associated with fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash.

For one of above criteria, make every effort to carry out the liver event follow-up assessment of described below：

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody;
  - Hepatitis B surface antigen and Hepatitis B core antibody (IgM);
  - Hepatitis C virus RNA;
  - Cytomegalovirus IgM antibody;
  - Epstein-Barr viral capsid antigen IgM antibody (if not available, 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

7.3.9 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.

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.

7.3.10 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.

7.3.11 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 procedures (e.g., endoscopy, appendectomy): the disease 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 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

- 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

7.3.12 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 outpatient 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 hyperbilirubinemia 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).

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 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.

7.3.13 AEs and SAEs 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 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.

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.

7.3.14 AE Severity Assessment

The investigator will grade the severity of each adverse event using the following definitions:

- Mild Adverse events are transient and easily tolerated by subjects
- Moderate Adverse events cause discomfort to the subject or affect the subject's daily activities
- Severe Adverse events have a great impact on the subject's daily activities and may cause disability or risk and life

7.3.15 AE Causality Assessment

The investigator's assessment of causality must be provided for all AEs. The investigator will use the following definitions to assess the causal relationship between adverse events and investigational product:

- Not Related There is no correlation between adverse events and investigational product
- Unlikely to be related Adverse events are more likely to be related to other factors
- Possibly related Adverse events may be caused by investigational product, but other factors cannot be excluded
- Probably Related Adverse events may be caused by the study drug
- Related Adverse events can be confirmed as adverse reaction of investigational product, and cannot be explained by other reasons

7.4 Pharmacokinetics

Blood samples for pharmacokinetics exposure-response analysis of SHR0302 will be collected from randomized subjects at the following time points (Table 7). If not, please address the reason.

[redacted]

On the days of PK sampling at Weeks 8 and 12, subjects will take their dose of study medication for that day at the study site.
Blood samples will be analyzed using validated analytical methods. Only samples from subjects who have received active drug (i.e., SHR0302) will be measured for the analysis (SHR0302). Contracted PK analysis laboratory personals will be unblinded for the analysis purpose. Samples from subjects receiving placebo will not be analyzed.

8. Data Management (DM)

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

Detailed summary and statistical analysis of the data collected in this study will be recorded in the Statistical Analysis Plan (SAP) and maintained by Reistione Biopharma/Designated CRO. The document may provide a revision of the plan in the protocol; however, any major revision of the definition of the primary endpoint and/or its analytical approach should be reflected in the protocol amendments.

9.1 Sample Size Determination and Hypothesis

This study is planned to enroll 132 subjects, 44 in each group (assuming 9% dropout rate, 120 completers, 40 completers in each group), and provide approximately 81% power to detect 20% difference in the primary endpoint between SHR0302 and placebo assuming placebo response rate is approximately 10% and response rates of SHR0302 4 mg QD, 8 mg QD are around 30%. By using the Hochberg incremental procedure, the type I error for the primary endpoint was controlled at a level of 0.1 bilaterally.

The null and alternative hypotheses to be tested are:

- H01: Percentage of subjects achieving an IGA response in the SHR0302 8 mg QD dose group at Week 12 - Percentage of subjects achieving an IGA response in the placebo group at Week 12 = 0;

H11: Percentage of subjects achieving an IGA response at Week 12 in the SHR0302 8 mg QD dose group - Percentage of subjects achieving an IGA response at Week 12 in the placebo group ≠ 0.

- H02: Percentage of subjects achieving IGA response in the SHR0302 4 mg QD dose group at Week 12 - Percentage of subjects achieving IGA response in the placebo group at Week 12 = 0;

H12: SHR0302 Percentage of Subjects Achieving IGA Response at Week 12 in the 4 mg QD Dose Group - Percentage of Subjects Achieving IGA Response at Week 12 in the Placebo Group ≠ 0.

Two 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 two p values as (p (2), p(1)), where p(2) ≥ p(1). The decision rules are provided in below figure (Figure 2).

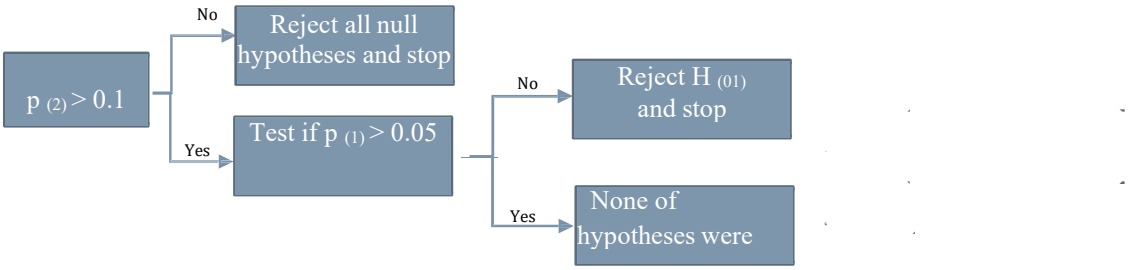

Figure 2. The decision rules of hypothesis

NOTE: H(01) is the corresponding null hypothesis of the smallest p value p(1)

9.2 Efficacy analysis

Efficacy analysis will be based on all subjects who are randomized and administered with study medication. Subjects will be analyzed according to randomization, irrespective of the treatment received. A descriptive statistical summary of all efficacy endpoints will be provided.

9.2.1 Analysis of the primary efficacy endpoint

For the primary endpoint, the method of normal approximation will be used to test whether each drug group is superior to the placebo group. Subjects who early withdraw from the study for any reason will be considered as non-responders.

Other analyses for the primary endpoint will be described in the statistical analysis plan (SAP).

9.2.2 Analysis of the secondary efficacy endpoints

All secondary endpoints for each drug group and placebo control will also be analyzed.

For dichotomous secondary endpoints (percentage of subjects achieving IGA response at other follow-up time points except Week 12; percentage of subjects achieving ≥ 50%, 75%, and 90% improvement from baseline in EASI scores at Weeks 1, 4, 8, and 12 (EASI50, EASI75, EASI90); percentage of subjects achieving ≥ 50%, 75%, and 90% improvement from baseline in SCORAD at Weeks 1, 4, 8, and 12 (SCORAD50, SCORAD75, SCORAD90); percentage of subjects achieving ≥ 3 points improvement from baseline in pruritus NRS at Weeks 1, 4, 8, and 12), the method of normal approximation will be used for analysis.

For continuous secondary endpoints (percent change from baseline in EASI scores at Weeks 1, 4, 8, and 12; change from baseline in SCORAD at Weeks 1, 4, 8, and 12; percent change from baseline in pruritus numeric rating scale (NRS) at Weeks 1, 4, 8, and 12; change from baseline in Dermatology Life Quality Index (DLQI) at Weeks 1, 4, 8, and 12; and change from baseline in biomarkers hsCRP and Ig E at Weeks 1, 4, 8, and 12.), a mixed-effects repeated measures model (MMRM) will be used for analysis. Fixed effects in the model were treatment group, baseline value, visit, and treatment-by-visit interaction, with random effects for subject.

9.3 Safety Analysis

Safety analysis will be based on all subjects who have taken study medication. Subjects will be analyzed by actual treatment group. Safety data will be summarized using descriptive statistics.

9.3.1 Analysis of adverse events

Adverse events will be classified according to the Pharmaceutical Affairs Management Standard Medical Terminology Set (MedDRA), System Organ Classification (SOC) and Preferred Terms (PT) and summarized by actual treatment. Treatment-emergent adverse events (TEAEs) are defined as AEs which commence on or after the time of start of investigational product administration. Adverse events without an onset date or time or AEs with an onset 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 indicate that the event started before administration of investigational product or if the AE stop date indicates that the event stopped before administration of investigational product.

Treatment emergent AEs will be summarized for each SHR-0302 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 reported:

- 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 investigational product
- Serious AEs by SOC and PT

Separate lists will be prepared for deaths and AEs leading to study discontinuation

9.3.2 Other safety analyses

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.

9.4 Pharmacokinetic analysis

Plasma concentrations of SHR0302 will be summarized according to treatment group and time point. The population pharmacokinetic analysis will be used to derive the pharmacokinetic parameters such as area under the curve (AUC), steady-state drug concentration (Css), maximum concentration (Cmax) and minimum concentration (Cmin).

Pharmacodynamic parameters such as area under the effect curve (AUEC), minimum concentration (Cmin) and maximal percentage reduction (PRmax) for different biomarkers (e.g., hsCRP and Ig E), efficacy and safety outcomes will be generated and summarized by treatment group.

[redacted]

9.5 Interim Analysis

There is no interim analysis planned for this study.

10. Study Conduct Considerations

10.1 Regulatory and Ethical considerations of 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) reviewed 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, e.g., 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 follow ICH GCP, local regulatory requirements, and legal requirements. The informed consent form used in this study, and any changes made during 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 Biopharma /designated CRO, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., 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 (e.g., 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 continuously conducted by the Sponsor study team. or Reistone Biopharma /designated CRO will hold regular data monitoring meetings to review the data in order to ensure data accuracy and protocol compliance. Safety data will also be continuously reviewed to detect early signals and identify risk.

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.

11.Reference

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12.Appendices

Appendix 1 Atopic Dermatitis Diagnosis -Chinese Criteria

In 2016, Profession Zhang et al. reported Chinese Criterial for atopic dermatitis diagnosis. There are 3 criteria, subjects who meet the first criterion together with one of the 2nd or 3rd criterion can be diagnosed as atopic dermatitis:

1. Symmetrical eczema (dermatitis) for more than 6 months
2. Personal and/or family history of atopic diseases
3. Elevated total serum Ig E level and/or positive allergen-specific Ig E and/or eosinophilia

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).

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

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

Appendix3 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 ≥ 110 bpm

  NOTE: sinus tachycardia 110bpm should be confirmed by two additional readings at least 5 minutes apart

- Sinus bradycardia < 45 bpm

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

- Multifocal atrial tachycardia
- Junctional tachycardia (heart rate > 100 bpm)
- Junctional escape complexes
- Supraventricular tachycardia (> 100 bpm)
- Ventricular tachycardia (sustained, polymorphic or monomorphic)
- Atrial fibrillation with rapid ventricular response (heart rate > 100 bpm)
- Atrial flutter
- Evidence of bigeminy, trigeminy or multifocal premature ventricular complexes
- Ventricular flutter
- Ventrucular fibrillation
- Torsades de pointes
- R-on-T phenomenon
- Wide QRS tachycardia (diagnosis unknown)
- Electrical alternans
- Pacemaker
- Idioventricular rhythm - heart rate < 100 bpm
- 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) ≥ 450 msec or ECG not suitable for QT measurement (e.g., poor defined termination of the T wave).

- For **subjects with complete right bundle branch block: QTc(F) 480msec 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 ago) 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 agents such as ketoconazole cream and grapefruit juice are not contraindicated.

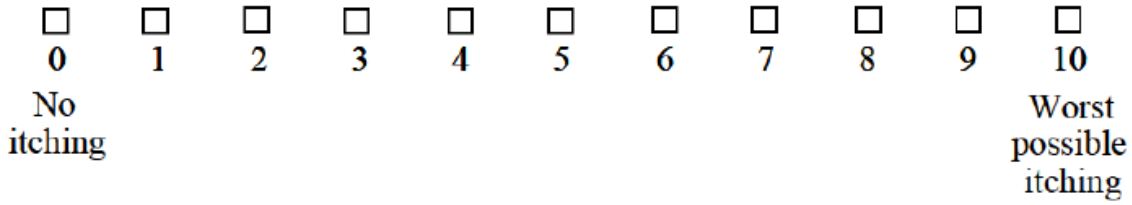
CYP3A INHIBITORS	**CYP3A INDUCER**
Atazanavir	Barbiturates
Telithromycin	Carbamazepine
Clarithromycin	Efavirenz
Clotrimazole	Modafinil
Delaviridine	Nevirapine
Fluvoxamine	Phenobarbital
Indinavir	Phenytoin
Itraconazole	Rifabutin
Ketoconazole	Rifampin
Mibefradil	Saint John's Wort
Mifepristone	Nevaripine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

Appendix 5 Scoring Atopic Dermatitis (SCORAD)

ITEMS OF SCORAD SYSTEM	DESCRIPTION	SCORE	TOTAL SCORE
A. Lesional area	9% were in the head and neck, 18% in both upper limbs, 36% in the anteroposterior aspect of the trunk, 36% in both lower limbs, and 1% in the perineum (1% of body surface area is 1 point)		
B. Severity of skin lesions (evaluation of six clinical features)	Erythema (reddening) 0 = none; 1 = mild; 2 = moderate; 3 = severe		
	Edema (swelling) 0 = none; 1 = mild; 2 = moderate; 3 = severe		
	Oozing/crusting 0 = none; 1 = mild; 2 = moderate; 3 = severe		
	Excoriation (scratch marks) 0 = none; 1 = mild; 2 = moderate; 3 = severe		
	Skin thickening (lichenification) 0 = none; 1 = mild; 2 = moderate; 3 = severe		
	Xerosis (dryness) 0 = none; 1 = mild; 2 = moderate; 3 = severe		
C. Itching and sleeplessness (using a visual analogue scale)	Itching (0-10) (average degree of itching over the past 3 days) 0 = no itching, 10 = very itching		
	Sleeplessness (0-10) (average degree of sleeplessness affected in the past 3 days) 0 = no impact, 10 = severe impact		
SCORAD total score	A/5 + 7B/2 + C		

Appendix 6 Pruritus NRS assessment

Pruritus Rating: Selet the number that best describes your itching due to Atopic Dermatitis over the past 24 hours (check one number only)



Appendix 7 DLQI Questionnaire

Dermatology Life Quality Index (DLQI) – Example, sample only

The purpose of this questionnaire is to measure how much your skin problem has affected your life over the last week, please tick "√" on one box for each question

Question	Response	
1. Over the last week, how itchy, sore, painful or stinging has your skin been?	Very much	□
	A lot	□
	A little	□
	Not at all	□
2. Over the last week, how embarrassed or self-conscious have you been because of your skin?	Very much	□
	A lot	□
	A little	□
	Not at all	□
3. Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?	Very much	□
	A lot	□
	A little	□
	Not at all	□
4. Over the last week, how much has your skin influenced the clothes you wear??	Very much	□
	A lot	□
	A little	□
	Not at all	□
5. Over the last week, how much has your skin affected any social or leisure activities?	Very much	□
	A lot	□
	A little	□
	Not at all	□
6. Over the last week, how much has your skin made it difficult for you to do any sport?	Very much	□
	A lot	□
	A little	□
	Not at all	□
7. Over the last week, has your skin prevented you from working or studying?	Yes	□
	No	
	A lot	□

If you choose "no," over the last week how much has your skin been a problem at work or studying?	A little	☐
	Not at all	☐
8. Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?	Very much	☐
	A lot	☐
	A little	☐
	Not at all	☐
9. Over the last week, how much has your skin caused any sexual difficulties?	Very much	☐
	A lot	☐
	A little	☐
	Not at all	☐
10. Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?	Very much	☐
	A lot	☐
	A little	☐
	Not at all	☐

Please check that you have answered EVERY question. Thankyou.