



# Efficacy and Safety of SHR0302, a Highly Selective Janus Kinase 1 Inhibitor, in Patients with Moderate to Severe Atopic Dermatitis: A Phase II Randomized Clinical Trial

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## Abstract

**Background** Atopic dermatitis is a chronic, inflammatory condition causing a substantial burden to patients and caregivers. SHR0302 is an oral, highly selective, Janus kinase 1 inhibitor under investigation for inflammatory skin diseases.

**Objective** The aim of this study was to investigate the efficacy and safety of SHR0302 in Chinese patients with moderate to severe atopic dermatitis.

**Design and Setting** A randomized, double-blind, placebo-controlled, multicenter, phase II trial was conducted in China between October 2019 and August 2020.

**Participants** Patients ( $n = 105$ ) aged 18–75 years with moderate to severe dermatitis and nonresponsive or intolerant to topical or conventional systemic treatments were included.

**Interventions** Patients were randomly assigned in a ratio of 1:1:1 to receive SHR0302 4 mg once daily, SHR0302 8 mg once daily, or placebo for 12 weeks.

**Main Outcome Measures** The primary efficacy endpoint was the proportion of patients achieving Investigator's Global Assessment (IGA) response (IGA of 0 [clear] or 1 [almost clear] with improvement of  $\geq 2$  grades) at week 12. Secondary efficacy assessments included Eczema Area and Severity Index (EASI) and pruritus Numerical Rating Scale (NRS) scores.

**Results** At week 12, IGA response was achieved in nine patients (25.7%; 90% confidence interval [CI] 13.6–37.9%;  $p = 0.022$ ) in the SHR0302 4 mg group, 19 patients (54.3%; 90% CI 40.4–68.1%;  $p < 0.001$ ) in the SHR0302 8 mg group, and two patients (5.7%; 90% CI 0.0–12.2%) in the placebo group. EASI<sub>175</sub> was achieved in 51.4% ( $p = 0.013$ ), 74.3% ( $p < 0.001$ ), and 22.9% of patients in the SHR0302 4 mg, SHR0302 8 mg, and placebo groups, respectively, while an NRS  $\geq 3$ -point improvement occurred in 65.7% ( $p < 0.001$ ), 74.3% ( $p < 0.001$ ), and 22.9% of patients, respectively. Treatment-emergent adverse events were reported in 60.0%, 68.6%, and 51.4% of patients in the SHR0302 4 mg, SHR0302 8 mg, and placebo groups, respectively. The adverse events were mild in most cases. Three serious adverse events were reported, all being worsening of atopic dermatitis. No serious infection was reported.

**Conclusions and Relevance** Oral SHR0302 was effective and well tolerated in Chinese adult patients with moderate to severe atopic dermatitis.

**Trial Registration** ClinicalTrials.gov identifier: NCT04162899; URL: <https://clinicaltrials.gov/>. Date first registered: 14 November 2019.

## 1 Introduction

Atopic dermatitis (AD) is a chronic, inflammatory skin condition with a relapsing and remitting course, characterized by eczematous lesions with intense pruritus [1, 2]. The prevalence of AD ranges from 10 to 20% in children and 2 to 10% in adults worldwide [3–5]. An estimated

7.3% of adults in the US have a diagnosis of AD [6], and an epidemiological study in China reported the incidence of AD at 7.8% [7]. Symptoms in patients with moderate to severe AD encompass sleep disturbance, anxiety and depression, impaired quality of life, and increased comorbidities [8, 9]. The adverse physical and psychological effects of AD produce a substantial burden on patients, caregivers, and society, with significant healthcare cost implications [8–14].

Extended author information available on the last page of the article

## Key Points

This 12-week, randomized, phase II trial reports the efficacy and safety of SHR0302 (a highly selective Janus kinase 1 inhibitor) in 105 patients with moderate to severe atopic dermatitis.

Overall, 54.3%/25.7% of patients receiving SHR0302 8 mg/4 mg once daily achieved an Investigator's Global Assessment response, compared with 5.7% receiving placebo ( $p < 0.001$  and  $p = 0.022$ , respectively). Furthermore, 74.3%/51.4% of patients receiving SHR0302 8 mg/4 mg once daily achieved a  $\geq 75\%$  improvement from baseline in the Eczema Area and Severity Index, compared with 22.9% receiving placebo ( $p < 0.001$  and  $p = 0.013$ , respectively). Treatment-emergent adverse events were reported in 60.0%, 68.6%, and 51.4% of patients in the SHR0302 4 mg, SHR0302 8 mg, and placebo groups, respectively, and were mild adverse events in most cases.

SHR0302 was effective and well-tolerated in adults with moderate to severe atopic dermatitis.

The treatment of AD remains a challenge [5]. For patients with moderate to severe AD, systemic immunosuppressive agents are often mandatory [5, 15–18]; however, the immunosuppressive agents have modest efficacy and are associated with considerable adverse events (AEs) that limit their long-term use [5, 16, 19]. The interleukin (IL)-4 receptor inhibitor dupilumab was recently approved in several countries for the treatment of moderate to severe AD; while this introduction brings a new treatment option, there remain opportunities for improvements in efficacy in terms of eczema severity and onset of pruritus relief [20, 21]. There continues to be a need for new treatment therapies in patients with moderate to severe AD.

The mechanism of AD includes skin-barrier defects and immune dysregulation [22]. A number of cytokine signaling pathways are involved in the development of AD, including IL-4, IL-5, IL-13, IL-31, and interferon (IFN)- $\gamma$  [23]. Janus kinase (JAK) is a nonreceptor tyrosine kinase (TYK) that serves as an important signal transducer for these cytokines [24]. The JAK family includes JAK1, JAK2, JAK3, and TYK2. Blocking of the JAK/STAT pathway has the potential to inhibit the pathophysiological processes of AD [25]. A number of topical [26–28] and systemic [29–33] JAK inhibitors, with differing JAK inhibition characteristics, are undergoing investigation to assess their efficacy and safety in moderate to severe AD.

SHR0302 is a highly selective JAK1 inhibitor that modulates signaling by IL-4, IL-5, IL-13, IFN- $\gamma$ , and other

cytokine pathways involved in the pathogenesis of AD, while sparing inhibition of JAK2 to minimize the potential risks of neutropenia and anemia [34]. SHR0302 is well absorbed after oral administration, with a median time to reach maximum concentration of 1.0 h and a half-life of 8.33–9.87 h that increases slightly with dosage. Pharmacodynamic evidence supports a once daily dosing regimen.

The objective of this phase II study was to evaluate the efficacy and safety of oral SHR0302 in adult patients with moderate to severe AD. SHR0302 doses of 4 mg and 8 mg once daily were selected based on the data from completed phase I studies in healthy volunteers, as well as an ongoing dose-ranging phase II study investigating once daily doses ranging from 0.5 to 8 mg in patients with rheumatoid arthritis (NCT03254966).

## 2 Methods

### 2.1 Study Design and Participants

This randomized, double-blind, placebo-controlled, multicenter, phase II trial was conducted between 24 October 2019 and 31 August 2020 at 23 centers in China (NCT04162899) [see Trial Protocol in the electronic supplementary material (ESM)]. The study included up to 4-week screening, 12-week treatment, and 2-week follow-up periods (ESM Fig. S1). This treatment period was selected based on the clinical study experience that 12–16 weeks are sufficient to observe clinical effects from JAK inhibitors in AD [30–33].

The study was conducted in compliance with the Declaration of Helsinki [35], the International Conference on Harmonization Good Clinical Practice guidelines, and all local regulatory requirements. The research was approved by the Institutional Review Board and Independent Ethics Committee of the Peking University People's Hospital and participating study centers. All patients provided written informed consent and could withdraw from the study at any time at their own request or at the investigator's or study sponsor's discretion.

The diagnosis of AD was confirmed at screening and baseline visits as moderate to severe, defined by an Eczema Area and Severity Index (EASI) score  $\geq 12$ , body surface area (BSA) affected of  $\geq 10\%$ , and Investigator's Global Assessment (IGA) score of  $\geq 3$ . Eligible patients were males or females aged 18–75 years with a history of AD for at least 1 year at the time of screening and who were nonresponsive and/or intolerant to one or more of the following treatments for at least 4 weeks: topical corticosteroids and/or calcineurin inhibitors; systemic corticosteroids and/or phototherapy; and cyclosporine and/or other immunosuppressants, such as methotrexate, mycophenolate mofetil, and azathioprine.

Concomitant medications permitted during the study included oral antihistamines, nonsteroidal anti-inflammatory agents, topical or oral antibiotics required for secondary skin infections, and nonmedication moisturizers. Rescue treatments (both topical and systemic) were not allowed in this study.

Key exclusion criteria included the use of systemic glucocorticoids, cyclosporine, and other immunosuppressants; phosphodiesterase inhibitors; and phototherapy within 4 weeks or topical treatments that might affect AD within 2 weeks prior to the first dose of study drug. Subjects who had previously received JAK inhibitors or biologic agents (such as dupilumab) for AD were also excluded. Detailed eligibility criteria are provided in the ESM.

## 2.2 Randomization and Masking

Patients were randomly assigned to receive SHR0302 4 mg once daily, SHR0302 8 mg once daily, or placebo in a ratio of 1:1:1 using a computer-generated randomization table. Double-blind methodology was adopted for study drugs taken during the 12-week treatment period, ensuring that patients, investigators, and sponsors were blinded to study treatment.

## 2.3 Endpoints

The primary efficacy endpoint was the proportion of patients who achieved an IGA response at week 12 [36], defined as an IGA score of 0 (clear) or 1 (almost clear) with an improvement of  $\geq 2$  grades from baseline.

Secondary efficacy endpoints included the proportion of patients who achieved an IGA response at weeks 1, 4, and 8; change in EASI score from baseline, and the proportion of patients whose EASI scores improved by  $\geq 50\%$ ,  $\geq 75\%$ , and  $\geq 90\%$  at weeks 1, 4, 8, and 12; change in pruritus Numerical Rating Scale (NRS) score from baseline, and the proportion of patients whose NRS improved by  $\geq 3$  points (NRS-3) at weeks 1, 4, 8, and 12; change in Scoring Atopic Dermatitis (SCORAD) index score from baseline, and the proportion of patients whose SCORAD score improved by  $\geq 50\%$ ,  $\geq 75\%$ , and  $\geq 90\%$  at weeks 1, 4, 8, and 12; and change in the Dermatology Life Quality Index (DLQI) from baseline at weeks 1, 4, 8, and 12. Changes in immunoglobulin E (IgE) and absolute eosinophil count from baseline were also assessed at weeks 1, 4, 8, and 12 to investigate the effects of SHR0302 on these putative biomarkers of AD [1, 37].

Safety endpoints throughout the study comprised monitoring of AEs (including severity and relationship to study drug), clinical laboratory tests, vital signs, and electrocardiography.

## 2.4 Statistical Analysis

A sample size of 105 patients was determined to provide 82% power to detect a 20% difference in the primary endpoint between at least one active drug group and the placebo group, assuming a 6% response rate in the placebo group. Using Hochberg's incremental procedure, the overall type I error rate was maintained at the level of 0.1 (two-sided).

The analysis of primary efficacy was performed on the full analysis set, which included all patients who were randomized and received at least one dose of study drug. Safety was assessed in the safety analysis set, which included all patients who received at least one dose of study drug.

Chi-square testing was adopted in the primary efficacy analysis to detect whether each active drug group was superior to placebo; differences in response rate between the active treatment and placebo groups and their 90% confidence intervals (CIs) were estimated, and *p*-values in testing for difference were reported. The descriptive summary of primary efficacy endpoints was based on nonmissing data. Patients who withdrew prematurely from the study for any reason were considered nonresponders. For binary secondary endpoints, the same methodology was used as for the primary analysis; the mixed-effects model for repeated measures was applied for continuous endpoints. Descriptive statistics were used to analyze AEs reported during the treatment period. AEs were coded by system organ class and preferred terms according to the Medical Dictionary for Regulatory Activities (MedDRA; version 23.0).

All statistical analyses were completed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

## 3 Results

### 3.1 Patients

A total of 105 patients were randomly assigned to the SHR0302 4 mg ( $n = 35$ ), SHR0302 8 mg ( $n = 35$ ), and placebo groups ( $n = 35$ ) (Fig. 1). Eighty-four patients (80.0%) completed treatment; however, six (17.1%) patients in the SHR0302 4 mg group, three (8.6%) patients in the SHR0302 8 mg group, and 12 (34.3%) patients in the placebo group withdrew from the study. The main reason for withdrawal was worsening of AD (two [5.7%] patients in the SHR0302 4 mg group, one [2.9%] patient in the SHR0302 8 mg group, and eight [22.9%] patients in the placebo group). One patient in the SHR0302 4 mg group completed treatment but was lost to follow-up.

Demographics and baseline characteristics were balanced across the treatment arms (Table 1). The median age

in the overall patient population was 31.0 years (range 18–72 years), median body height was 169.0 cm (152.0–188.0 cm), and median body weight was 67.5 kg (39.5–143.0 kg). Median duration of AD was 7.4 years (range 1.0–40.4 years). Median (range) baseline EASI score was 24.4 (12.2–63.0) points, median BSA was 51.0% (10.0–98.0%), and median NRS was 8.0 (1–10) points. IGA score was 3 (moderate), 4 (severe), or 5 (extremely severe) in 57 (54.3%), 41 (39.0%), and 7 (6.7%) patients, respectively.

### 3.2 Efficacy

IGA response at week 12 was achieved in nine (25.7%) patients in the SHR0302 4 mg group, 19 (54.3%) patients in the SHR0302 8 mg group, and two (5.7%) patients in the placebo group (Table 2; Fig. 2a). Differences from placebo were 20.0% (90% CI 6.2–33.8%;  $p = 0.022$ ) for the 4 mg group and 48.6% (90% CI 33.3–63.9%;  $p < 0.001$ ) for the 8 mg group. The proportions of patients achieving an IGA response increased from weeks 1 to 12 in both the SHR0302 4 mg and 8 mg groups. Differences between the SHR0302 8 mg and placebo groups were statistically significant at weeks 4, 8, and 12 ( $p = 0.005$ ,  $p < 0.001$ , and  $p < 0.001$ , respectively), while differences between the SHR0302 4 mg and placebo groups were statistically significant at week 12 only ( $p = 0.022$ ).

Percentage changes in EASI score from baseline at weeks 1, 4, 8, and 12 were –28.0%, –52.5%, –58.2%, and –66.0%, respectively, in the SHR0302 4 mg group; –40.4%, –63.9%, –73.4%, and –78.8% in the SHR0302 8 mg group; and –10.5%, –17.9%, –35.6%, and –34.5% in the placebo group (ESM Fig. S2). Least square means (LSM) differences in percentage change in EASI score from

baseline were statistically significant at all time points in the SHR0302 4 mg group (–17.5% [90% CI –28.1% to –7.0%;  $p = 0.007$ ], –34.6% [90% CI –48.7% to –20.6%;  $p < 0.001$ ], –22.5% [90% CI –40.5% to –4.6%;  $p = 0.040$ ], and –31.5% [90% CI –52.6% to –10.4%;  $p = 0.015$ ], respectively) and SHR0302 8 mg group (–30.0% [90% CI –40.2% to –19.8%;  $p < 0.001$ ], –46.0% [90% CI –59.6% to –32.3%;  $p < 0.001$ ], –37.7% [90% CI –55.2% to –20.3%;  $p < 0.001$ ], and –44.3% [90% CI –64.8% to –23.8%;  $p < 0.001$ ], respectively) versus the placebo group (ESM Fig. S2).

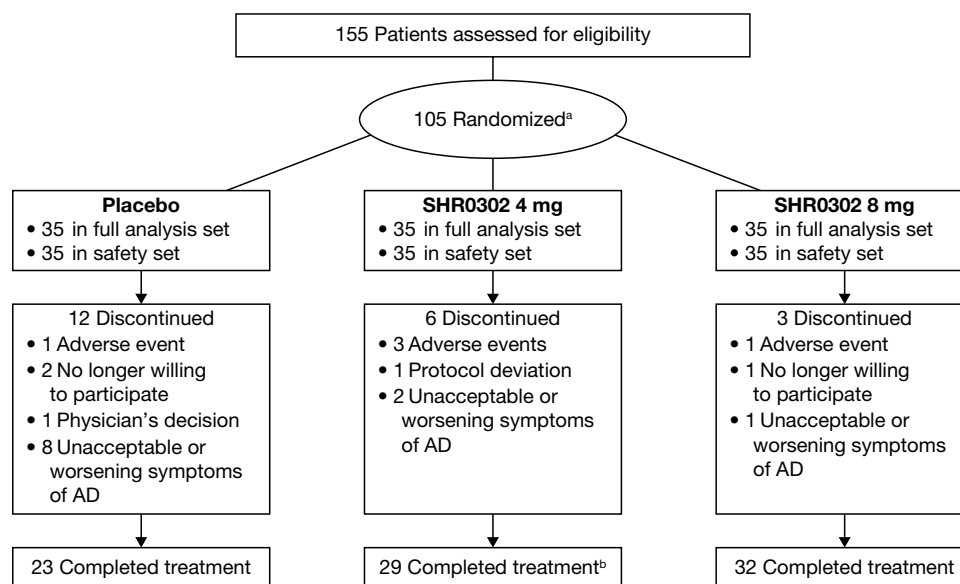
The proportions of patients whose EASI scores improved by  $\geq 50\%$ ,  $\geq 75\%$ , and  $\geq 90\%$  (EASI50, EASI75, and EASI90) from baseline at each time point are shown in Table 2 and Fig. 2b (EASI75). The SHR0302 4 mg group showed statistically significant differences versus placebo in EASI50 at week 4, EASI50/75 at week 8, and EASI50/75/90 at week 12. The SHR0302 8 mg group showed statistically significant differences versus placebo in EASI50 at week 1, EASI50/75 at week 4, EASI50/75/90 at week 8, and EASI50/75/90 at week 12.

LSM percentage changes in NRS score from baseline at weeks 1, 4, 8, and 12 were –36.0%, –41.5%, –49.2%, and –55.9%, respectively, in the SHR0302 4 mg group; –51.6%, –56.4%, –61.7%, and –61.4%, respectively, in the SHR0302 8 mg group; and –8.9%, –4.5%, –20.6%, and –26.7%, respectively, in the placebo group. LSM differences in percentage change in NRS from baseline were statistically significant at all time points in the SHR0302 4 mg group (–27.1% [90% CI –38.0% to –16.2%;  $p < 0.001$ ], –37.0% [90% CI –52.0 to –21.9;  $p < 0.001$ ], –28.6% [90% CI –42.6 to –14.5;  $p = 0.001$ ], and –29.2% [90% CI –44.7 to –13.6;  $p = 0.002$ ], respectively) and SHR0302 8 mg group (–42.6% [90% CI –53.1 to –32.1;  $p < 0.001$ ], –51.9% [90% CI –66.5 to –37.3;

**Fig. 1** CONSORT diagram.

<sup>a</sup> The primary reason for screening failure was the potential presence of *Mycobacterium tuberculosis* infection ( $n = 21$ ).

<sup>b</sup> One patient completed treatment but was lost to follow-up. AD atopic dermatitis, CONSORT Consolidated Standards of Reporting Trials



**Table 1** Demographics and general baseline characteristics (full analysis set)

	SHR0302 4 mg [n = 35]	SHR0302 8 mg [n = 35]	Placebo [n = 35]
Age, years			
Mean (SD)	38.5 (14.8)	35.2 (14.8)	30.3 (12.6)
Median (min, max)	37.0 (18, 7)	31.0 (19, 7)	25.0 (18, 6)
Sex			
Male [n (%)]	20 (57.1)	23 (65.7)	26 (74.3)
Race			
Asian [n (%)]	35 (100.0)	35 (100.0)	35 (100.0)
Body height, cm			
Mean (SD)	167.9 (7.6)	168.9 (8.5)	170.5 (7.6)
Median (min, max)	167.0 (154.0, 187.0)	169.0 (152.0, 188.0)	172.0 (153.0, 188.0)
Weight, kg			
Mean (SD)	70.0 (17.0)	69.7 (19.4)	69.0 (14.6)
Median (min, max)	67.8 (43.5, 115.0)	67.5 (39.5, 143.0)	67.0 (47.0, 104.0)
BMI, kg/m <sup>2</sup>			
Mean (SD)	24.6 (4.9)	24.2 (5.0)	23.6 (4.1)
Median (min, max)	23.7 (17.5, 41.7)	23.1 (17.1, 40.5)	22.8 (15.8, 33.6)
AD disease duration, years			
Mean (SD)	10.9 (10.2)	9.0 (8.5)	8.7 (7.6)
Median (min, max)	7.7 (1.1, 40.4)	6.9 (1.0, 35.3)	7.2 (1.5, 33.7)
EASI			
Mean (SD)	30.5 (15.7)	25.4 (11.3)	28.2 (12.1)
Median (min, max)	23.8 (12.4, 63.0)	22.9 (12.2, 62.9)	27.8 (12.3, 59.5)
BSA affected, %			
Mean (SD)	52.4 (23.0)	49.8 (19.6)	52.0 (23.5)
Median (min, max)	50.0 (15.0, 90.0)	51.0 (18.0, 90.0)	52.0 (10.0, 98.0)
IGA grade [n (%)]			
3: Moderate	15 (42.9)	20 (57.1)	22 (62.9)
4: Severe	16 (45.7)	14 (40.0)	11 (31.4)
5: Extremely severe	4 (11.4)	1 (2.9)	2 (5.7)
SCORAD score			
Mean (SD)	52.4 (23.0)	19.6 (51.0)	23.5 (52.0)
Median (min, max)	50 (15, 90)	51 (18, 90)	52 (10, 98)
Pruritus NRS			
Mean (SD)	7.9 (1.7)	7.1 (1.8)	7.3 (2.3)
Median (min, max)	8.0 (4, 10)	8.0 (3, 10)	8.0 (1, 10)
DLQI score			
Mean (SD)	16.3 (7.7)	15.6 (7.0)	15.3 (7.2)
Median (min, max)	17.0 (2, 30)	13.0 (5, 29)	15.0 (4, 30)
Immunoglobulin E, IU/mL			
Mean (SD)	1519.8 (2026.3)	1055.8 (1081.6)	2771.1 (8765.1)
Median (min, max)	1205.2 (8.8, 11,700.0)	500.0 (2.7, 5000.0)	855.0 (8.78, 52,000.0)

AD atopic dermatitis, BMI body mass index, BSA body surface area, DLQI Dermatology Life Quality Index, EASI Eczema Area and Severity Index, IGA Investigator's Global Assessment, max maximum, min minimum, NRS Numerical Rating Scale, SCORAD Scoring Atopic Dermatitis, SD standard deviation

$p < 0.001$ ],  $-41.1\%$  [90% CI  $-54.7$  to  $-27.5$ ;  $p < 0.001$ ], and  $-34.7\%$  [90% CI  $-49.8$  to  $-19.6$ ;  $p < 0.001$ ], respectively) compared with the placebo group (ESM Fig. S3).

The proportions of patients with NRS  $\geq 3$  are shown in Fig. 2c; additional analyses on the proportions of patients whose NRS improved by  $\geq 4$  points (NRS-4) are shown in

**Table 2** Efficacy endpoints at week 12 (full analysis set)

	SHR0302 4 mg [ <i>n</i> = 35]	SHR0302 8 mg [ <i>n</i> = 35]	Placebo [ <i>n</i> = 35]
IGA response <sup>a</sup>	9 (25.7%)	19 (54.3%)	2 (5.7%)
90% CI	13.6%, 37.9% <sup>i</sup>	40.4%, 68.1% <sup>i</sup>	0.0%, 12.2% <sup>i</sup>
Compared with the placebo group			
Difference	20.0%	48.6%	
90% CI	6.2%, 33.8% <sup>i</sup>	33.3%, 63.9% <sup>i</sup>	
<i>p</i> -Value	0.022 <sup>i</sup>	<0.001 <sup>i</sup>	
EASI score $\geq$ 50% (EASI50) <sup>b</sup>	24 (68.6%)	29 (82.9%)	15 (42.9%)
Compared with the placebo group			
Difference	25.7%	40.0%	
90% CI	6.9%, 44.6% <sup>i</sup>	22.7%, 57.3% <sup>i</sup>	
<i>p</i> -Value	0.030 <sup>i</sup>	<0.001 <sup>i</sup>	
EASI score $\geq$ 75% (EASI75) <sup>c</sup>	18 (51.4%)	26 (74.3%)	8 (22.9%)
Compared with the placebo group			
Difference	28.6%	51.4%	
90% CI	10.4%, 46.7% <sup>i</sup>	34.6%, 68.3% <sup>i</sup>	
<i>p</i> -Value	0.013 <sup>i</sup>	<0.001 <sup>i</sup>	
EASI score $\geq$ 90% (EASI90) <sup>d</sup>	11 (31.4%)	16 (45.7%)	3 (8.6%)
Compared with the placebo group			
Difference	22.9%	37.1%	
90% CI	7.8%, 37.9% <sup>i</sup>	21.3%, 53.0% <sup>i</sup>	
<i>p</i> -Value	0.017 <sup>i</sup>	<0.001 <sup>i</sup>	
NRS score $\geq$ 3 (NRS-3) <sup>e</sup>	23 (65.7%)	26 (74.3%)	8 (22.9%)
Compared with the placebo group			
Difference	42.9%	51.4%	
90% CI	25.2%, 60.5% <sup>i</sup>	34.6%, 68.3% <sup>i</sup>	
<i>p</i> -Value	<0.001 <sup>i</sup>	<0.001 <sup>i</sup>	
SCORAD score $\geq$ 50% (SCORAD50) <sup>f</sup>	17 (48.6%)	25 (71.4%)	8 (22.9%)
Compared with the placebo group			
Difference	25.7%	48.6%	
90% CI	7.6%, 43.9% <sup>i</sup>	31.4%, 65.7% <sup>i</sup>	
<i>p</i> -Value	0.025 <sup>i</sup>	<0.001 <sup>i</sup>	
SCORAD score $\geq$ 75% (SCORAD75) <sup>g</sup>	10 (28.6%)	12 (34.3%)	3 (8.6%)
Compared with the placebo group			
Difference	20.0%	25.7%	
90% CI	5.2%, 34.8% <sup>i</sup>	10.4%, 41.0% <sup>i</sup>	
<i>p</i> -Value	0.031 <sup>i</sup>	0.009 <sup>i</sup>	
SCORAD score $\geq$ 90% (SCORAD90) <sup>h</sup>	2 (5.7%)	3 (8.6%)	0
Compared with the placebo group			
Difference	5.7%	8.6%	
90% CI	-2.1%, 16.9% <sup>j</sup>	0.3%, 20.7 <sup>j</sup>	
<i>p</i> -Value	0.493 <sup>j</sup>	0.239 <sup>j</sup>	

CI confidence interval, EASI Eczema Area and Severity Index, FAS full analysis set, IGA Investigator's Global Assessment, NRS Numerical Rating Scale, SCORAD Scoring Atopic Dermatitis

<sup>a</sup>IGA response was defined as an IGA score of 0/1 (complete or almost complete clearance of skin lesions) with an improvement in IGA score by  $\geq$ 2 from baseline. The following situations would be regarded as nonresponding: (1) IGA 2/3/4/5; (2) IGA score of 0/1, but an improvement in IGA score of <2 from baseline; (3) missing visits; (4) early withdrawal from the treatment

<sup>b</sup>EASI50: EASI score improved by  $\geq$ 50% from baseline

<sup>c</sup>EASI75: EASI score improved by  $\geq$ 75% from baseline

<sup>d</sup>EASI90: EASI score improved by  $\geq$ 90% from baseline.

The following situations would be considered as nonresponding to EASI50 (the same rules applied to EASI75/EASI90): (1) EASI score

**Table 2** (continued)

improved by <50% from baseline; (2) missing visits; (3) early withdrawal from the treatment

<sup>e</sup>Two patients in the placebo group had a baseline NRS of <3, therefore these patients would not show an improvement of  $\geq 3$  from baseline; the other two treatment groups had no patients with a baseline NRS of <3. The denominator of each treatment group was the number of patients in the FAS of each treatment group

<sup>f</sup>SCORAD50: SCORAD score improved by  $\geq 50\%$  from baseline

<sup>g</sup>SCORAD75: SCORAD score improved by  $\geq 75\%$  from baseline

<sup>h</sup>SCORAD90: SCORAD score improved by  $\geq 90\%$  from baseline

The following situations would be considered as nonresponding to SCORAD50 (the same rules applied to SCORAD75/SCORAD90): (1) SCORAD score improved by <50% from baseline; (2) missing visits; (3) early withdrawal from the treatment

Both remote visits and delayed visits were included in the analysis

<sup>i</sup>The confidence interval and *p*-value were analyzed using the normal approximation method

<sup>j</sup>The confidence interval and *p*-value were analyzed using Fisher's exact test

The efficacy analysis was carried out using Hochberg's incremental test

Fig. S4 in the ESM. Both the 4 mg and 8 mg SHR0302 groups showed statistically significant differences versus placebo in the proportions of patients with NRS  $\geq 3$  ( $p < 0.001$ , weeks 1, 4, 8, and 12) and NRS  $\geq 4$  ( $p < 0.017$ , week 1;  $p = 0.003$ , week 4;  $p < 0.001$ , weeks 8 and 12).

LSM changes in SCORAD score from baseline at weeks 1, 4, 8, and 12 were  $-16.6$ ,  $-28.8$ ,  $-30.5$ , and  $-33.5$ , respectively, in the SHR0302 4 mg group;  $-22.4$ ,  $-32.1$ ,  $-34.4$ , and  $-39.2$ , respectively, in the SHR0302 8 mg group; and  $-5.3$ ,  $-8.1$ ,  $-15.9$ , and  $-20.1$ , respectively, in the placebo group (ESM Fig. S5). LSM differences in change in SCORAD score from baseline were statistically significant at all time points in the SHR0302 4 mg group ( $-11.3$  [90% CI  $-16.0$  to  $-6.6$ ;  $p < 0.001$ ],  $-20.7$  [90% CI  $-27.4$  to  $-14.1$ ;  $p < 0.001$ ],  $-14.5$  [90% CI  $-22.5$  to  $-6.5$ ;  $p = 0.003$ ], and  $-13.5$  [90% CI  $-22.5$  to  $-4.4$ ;  $p = 0.015$ ], respectively) and SHR0302 8 mg group ( $-17.2$  [90% CI  $-21.7$  to  $-12.6$ ;  $p < 0.001$ ],  $-24.0$  [90% CI  $-30.4$  to  $-17.5$ ;  $p < 0.001$ ],  $-18.5$  [90% CI  $-26.3$  to  $-10.7$ ;  $p < 0.001$ ], and  $-19.1$  [90% CI  $-27.9$  to  $-10.3$ ;  $p < 0.001$ ], respectively) versus placebo (ESM Fig. S5).

The proportions of patients whose SCORAD score improved by  $\geq 50\%$ ,  $\geq 75\%$ , and  $\geq 90\%$  (SCORAD50, SCORAD75, and SCORAD90) from baseline at week 12 are shown in Table 2. The SHR0302 4 mg group showed statistically significant differences versus placebo in SCORAD50 at weeks 4, 8, and 12, and SCORAD75 at week 12 ( $p < 0.001$ , 0.005, 0.025, 0.031, respectively). The SHR0302 8 mg group showed statistically significant differences versus placebo in SCORAD50 at weeks 4, 8, and 12, and SCORAD75 at weeks 8 and 12 ( $p < 0.001$ ,  $p < 0.001$ , and  $p < 0.001$ , 0.006, and 0.009, respectively).

LSM changes in DLQI from baseline at weeks 1, 4, 8, and 12 were  $-3.4$ ,  $-6.7$ ,  $-7.0$ , and  $-6.0$ , respectively, in the SHR0302 4 mg group;  $-5.8$ ,  $-8.8$ ,  $-9.4$ , and  $9.3$  in the SHR0302 8 mg group; and  $-1.1$ ,  $-0.5$ ,  $-4.2$ , and  $-4.6$  in the placebo group (ESM Fig. S6). LSM differences in change in DLQI from baseline at weeks 1, 4, 8, and 12 between the

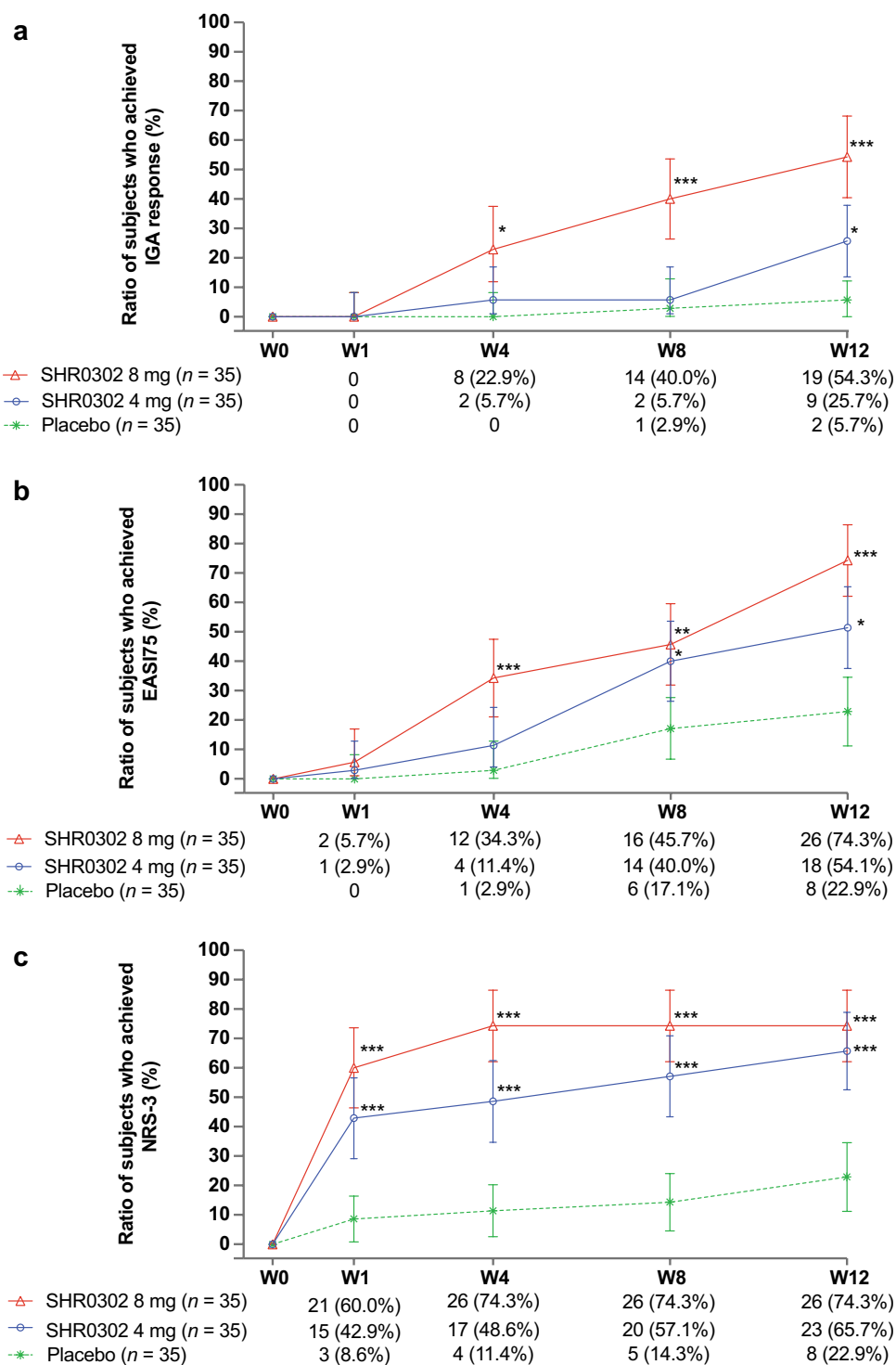
SHR0302 4 mg and placebo groups were  $-2.3$  (90% CI  $-4.1$  to  $-0.6$ ;  $p < 0.031$ ),  $-6.1$  (90% CI  $-8.3$  to  $-3.9$ ;  $p < 0.001$ ),  $-2.8$  (90% CI  $-5.0$  to  $-0.6$ ;  $p = 0.037$ ), and  $-1.3$  (90% CI  $-4.1$  to  $1.4$ ;  $p = 0.424$ ), respectively. LSM differences in the change in DLQI from baseline at weeks 1, 4, 8, and 12 between the SHR0302 8 mg and placebo groups were  $-4.7$  (90% CI  $-6.4$  to  $-3.0$ ;  $p < 0.001$ ),  $-8.3$  (90% CI  $-10.4$  to  $-6.2$ ;  $p < 0.001$ ),  $-5.3$  (90% CI  $-7.4$  to  $-3.1$ ;  $p < 0.001$ ), and  $-4.7$  (90% CI  $-7.4$  to  $-2.0$ ;  $p < 0.004$ ).

Analysis results for IgE and absolute eosinophil count changes from baseline are shown in ESM Part 2. There was no clear relationship between IgE or eosinophil count change and relief in symptoms.

### 3.3 Safety

A total of 63/105 (60.0%) patients experienced 138 treatment-emergent AEs (TEAEs) during the study. Overall, 21 (60.0%) patients in the SHR0302 4 mg group, 24 (68.6%) patients in the SHR0302 8 mg group, and 18 (51.4%) patients in the placebo group reported TEAEs of any causality (Table 3). TEAEs in any active drug group with an incidence  $>5\%$  and higher than placebo were blood creatine phosphokinase increased ( $n = 2$  patients, SHR0302 8 mg), blood pressure increased ( $n = 2$ , SHR0302 8 mg), upper respiratory tract infection ( $n = 2$ , SHR0302 4 mg), folliculitis ( $n = 2$ , SHR0302 8 mg), urinary tract infection ( $n = 2$ , SHR0302 8 mg), hyperlipidemia ( $n = 3$ , SHR0302 4 mg;  $n = 2$ , SHR0302 8 mg), hyperuricemia ( $n = 2$ , SHR0302 4 mg;  $n = 3$ , SHR0302 8 mg), hypertriglyceridemia ( $n = 2$ , SHR0302 4 mg), hypercholesterolemia ( $n = 2$ , SHR0302 8 mg), headache ( $n = 2$ , SHR0302 8 mg), AD ( $n = 2$ , SHR0302 4 mg), and leukocytosis ( $n = 3$ , SHR0302 4 mg). No serious infections were reported. Herpes zoster TEAEs were reported in two patients, one each in the SHR0302 4 mg and SHR0302 8 mg groups; no cases were reported in the placebo group. Herpes simplex/herpes virus infection TEAEs were reported in three patients, one each in the

**Fig. 2** Line plots for proportions of patients who achieved **a** IGA response, **b** EASI75, and **c** NRS-3 (FAS). Two subjects in the placebo group had baseline NRS <3, therefore these two subjects would not show an improvement of  $\geq 3$  from baseline. The denominator of each treatment group was the number of subjects in the FAS of each treatment group. *EASI* Eczema Area and Severity Index, *FAS* full analysis set, *IGA* Investigator's Global Assessment, *NRS* Numerical Rating Scale, *W* week. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$



SHR0302 4 mg, SHR0302 8 mg, and placebo groups. One case of Kaposi's varicelliform eruption was reported in the SHR0302 4 mg group. There were no cases of malignant neoplasm, thrombosis, liver injury, or death.

Drug-related TEAEs had the highest incidence in the SHR0302 8 mg group with 14 (40.0%,  $n = 26$  events) patients, followed by the placebo group with 10 (28.6%,

$n = 19$ ) patients and the SHR0302 4 mg group with eight (22.9%,  $n = 14$ ) patients. Drug-related TEAEs resulted in drug discontinuation in two patients ( $n = 1$ , 'dizziness', SHR0302 4 mg group;  $n = 1$ , 'dermatitis atopic', SHR0302 8 mg group) and drug interruption in one patient ('herpes zoster', SHR0302 8 mg group).



**Table 3** Summary of adverse events (safety set)

	SHR0302 4 mg [ <i>n</i> = 35]		SHR0302 8 mg [ <i>n</i> = 35]		Placebo [ <i>n</i> = 35]	
	No. of cases (%)	No. of events	No. of cases (%)	No. of events	No. of cases (%)	No. of events
All AEs	21 (60.0)	43	24 (68.6)	62	18 (51.4)	33
AEs during screening	0	0	0	0	0	0
TEAEs	21 (60.0)	43	24 (68.6)	62	18 (51.4)	33
Moderate/severe TEAE	3 (8.6)	4	0	0	1 (2.9)	4
Serious TEAE	2 (5.7)	2	1 (2.9)	1	0	0
TEAE leading to death	0	0	0	0	0	0
TEAE affecting the administration of the study drug	3 (8.6)	3	2 (5.7)	2	1 (2.9)	1
TEAE resulting in study withdrawal	3 (8.6)	3	1 (2.9)	1	1 (2.9)	1
Preferred term, frequency $\geq 5\%$ in any group						
Tri-iodothyronine free increased	2 (5.7)		1 (2.9)		4 (11.4)	
Transaminases increased	2 (5.7)		1 (2.9)		3 (8.6)	
Blood creatine phosphokinase increased	1 (2.9)		2 (5.7)		0	
Blood pressure increased	0		2 (5.7)		0	
Weight decreased	0		0		2 (5.7)	
Upper respiratory tract infection	2 (5.7)		1 (2.9)		0	
Folliculitis	0		2 (5.7)		0	
Urinary tract infection	0		2 (5.7)		0	
Hyperlipidemia	3 (8.6)		2 (5.7)		0	
Hyperuricemia	2 (5.7)		3 (8.6)		0	
Hypertriglyceridemia	2 (5.7)		1 (2.9)		1 (2.9)	
Hypercholesterolemia	0		2 (5.7)		1 (2.9)	
Headache	0		2 (5.7)		0	
Atopic dermatitis	2 (5.7)		1 (2.9)		0	
Leukocytosis	3 (8.6)		0		0	

AEs adverse events, TEAEs treatment-emergent adverse events

A total of three (2.9%, *n* = 3 events) patients experienced serious AEs (SAEs), all of which were ‘worsening of AD’, including two moderate cases in the SHR0302 4 mg group (considered by the investigator unlikely to be related to study treatment) and one mild case in the SHR0302 8 mg group (considered possibly related to study treatment). All three patients with SAEs recovered.

There were no clinically significant changes in hematology parameters, laboratory test results, urinalysis, vital signs, or electrocardiograms.

## 4 Discussion

This phase II trial shows that adults with moderate to severe AD achieved significant improvements in clinical symptoms, including pruritus, and improvement of skin lesions following oral administration of SHR0302 4 mg and 8 mg. The overall efficacy of SHR0302 at both doses was superior to placebo, with the 8 mg group showing greater efficacy than the 4 mg group.

Disease severity measured by IGA showed progressive improvements during SHR0302 treatment over 12 weeks, with significant differences between the SHR0302 8 mg and placebo groups at weeks 4, 8, and 12, and between the SHR0302 4 mg and placebo groups at week 12. EASI assessments of eczema severity showed significant improvement during SHR0302 treatment versus placebo at weeks 1, 4, 8, and 12 in both the 4 mg and 8 mg dose groups. AD severity measured by SCORAD score and pruritus measured by NRS similarly demonstrated significant improvements at all time points with both SHR0302 doses versus placebo. Achieving an improvement in pruritus by week 1 represents a notable benefit for patients with moderate to severe AD, in whom itch represents a central and debilitating symptom associated with difficult-to-control scratching, superimposed skin inflammation and infection, sleep disturbance, functional impairment and mental distress, and feelings of anxiety and depression [12, 26, 38, 39]. Finally, quality of life measured by DLQI was significantly improved by SHR0302 at all time points during the study except one.

By study end at week 12, all efficacy endpoints were consistent in demonstrating greater improvements with SHR0302 than placebo. For IGA response in particular, there were indications that a plateau had not been reached and that additional improvements in outcome could be expected from continued treatment beyond 12 weeks. A phase III study is planned to investigate this potential trend, which will assess efficacy outcomes using additional time points.

SHR0302 at both the 4 mg and 8 mg doses demonstrated acceptable tolerability and safety. TEAEs were mild in most cases and were associated with low rates of treatment discontinuation, while the three SAEs observed were all related to activities of the primary disease. Infection rates appeared to show a dose-related relationship, but no other dose-related association to TEAEs was evident in these descriptive analyses.

The improvements in symptoms during SHR0302 treatment showed no clear relationship to changes in serum IgE and absolute eosinophil counts, suggesting that the efficacy of SHR0302 is independent of effects on these biomarkers of AD.

These data provide further evidence for the use of JAK inhibition in the treatment of moderate to severe AD, in support of previous JAK inhibitor trials and the recommendations in recent Chinese guidelines [40]. Direct comparison of the outcomes between SHR0302 and other JAK inhibitors is restricted by the limited study durations, small sample sizes, diverse patient populations, and different outcome measures adopted in these phase II or III trials. However, SHR0302 has demonstrated an efficacy that is broadly consistent with other JAK1 inhibitors under investigation for the treatment of AD.

Selective JAK1 inhibitors, such as SHR0302, offer the potential advantage of reduced AEs compared with JAK inhibitors that additionally target JAK2, JAK3, or TYK2 [41]. Evidence from the current study suggests that the incidences of AEs associated with SHR0302 are consistent with other JAK inhibitors [30–33]. Overall incidences of SAEs are reported to be low for JAK inhibitors in the treatment of AD, although potentially increased rates of thromboembolic, cardiovascular, and hematological events have been described for oral JAK inhibitors in other dermatologic conditions [42]. No evidence of thromboembolic, cardiovascular, or hematological abnormalities associated with SHR0302 was observed in our study.

This study is limited to the investigation of Chinese patients with moderate to severe AD. Additional study limitations are the small sample size and short treatment duration, similar to other phase II trials of JAK inhibitors. Finally, the concurrent coronavirus disease 2019 (COVID-19) pandemic impacted on-site visits and treatment duration

for a limited number of patients, but is not considered to have altered the validity or interpretation of the study results.

## 5 Conclusions

This phase II study of orally administered SHR0302 4 mg and 8 mg provided results consistent with the pharmacological properties of SHR0302, a highly selective JAK1 inhibitor for once daily administration. SHR0302 demonstrated potential as an effective and well-tolerated treatment for adult patients with moderate to severe AD, which will be further investigated in a phase III study. Based on these phase II trial data, the Chinese National Medical Products Administration has granted a breakthrough therapy designation for SHR0302 in AD.

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## Declarations

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**Conflicts of interest** Aik Han Goh, Rongjun Liu, and Zhiguo Zhang are employees of Reistone Biopharma Co., Ltd. Yan Zhao, Litao Zhang, Yangfeng Ding, Xiaohua Tao, Chao Ji, Xiuqin Dong, Jianyun

Lu, Liming Wu, Rupeng Wang, Qianjin Lu, and Jianzhong Zhang declare they have no conflicts of interest.

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**Availability of Data and Material** The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Data Access, Responsibility, and Analysis** Jianzhong Zhang had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Ethics approval** This research was approved by the Institutional Review Board and Independent Ethics Committee of the Peking University People's Hospital and the participating study centers. The study was conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines, as well as all local regulatory requirements.

**Consent to participate** All patients provided written informed consent and could withdraw from the study at any time at their own request or at the investigator's or study sponsor's discretion.

**Consent for publish** Not applicable.

**Code Availability** Not applicable.

**Author contributions** Drafting of the manuscript, and acquisition, analysis, or interpretation of data: YZ. Acquisition, analysis, or interpretation of data: LZ, YD, XT, CJ, XD, JL, LW, RW, and QL. Concept and design, and statistical analysis: AHG, RL, and ZZ. Acquisition, analysis, or interpretation of data; critical revision of the manuscript for important intellectual content; supervision: JZ.

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