Electronic Supplementary Material

American Journal of Clinical Dermatology

Efficacy and Safety of SHR0302, a Highly Selective Janus Kinase 1 Inhibitor, in Patients with Moderate to Severe Atopic Dermatitis: A Phase 2 Randomized Clinical Trial

Yan Zhao[1*] · Litao Zhang[2] · Yangfeng Ding[3] · Xiaohua Tao[4] · Chao Ji[5] · Xiuqin Dong[6] · Jianyun Lu[7] · Liming Wu[8] · Rupeng Wang[9] · Qianjin Lu[10] · Aik Han Goh[11] · Rongjun Liu[11] · Zhiguo Zhang[11] · Jianzhong Zhang[1]
*First author

Author Affiliations

[1] Department of Dermatology, Peking University People's Hospital, Beijing, China

[2] Department of Dermatology, Tianjin Academy of Traditional Chinese Medicine Affiliated Hospital, Tianjin, China

[3] Department of Dermatology, Shanghai Skin Disease Hospital, Tongji University School of Medicine, Shanghai, China

[4] Department of Dermatology, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, Hangzhou, China

[5] Department of Dermatology, The First Affiliated Hospital of Fujian Medical University, Fuzhou, China

[6] Department of Dermatology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China

[7] Department of Dermatology, The Third Xiangya Hospital, Central South University, Changsha, China

[8] Department of Dermatology, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou, China

[9] Department of Dermatology and Rheumatology Immunology, Xinqiao Hospital, Third Military Medical University (Army Medical University), Chongqing, China

[10] Department of Dermatology, The Second Xiangya Hospital, Central South University, Changsha, China

[11] Reistone Biopharma Co., Ltd., Shanghai, China

Corresponding Author

Jianzhong Zhang, MD

E-mail: rmzjz@126.com

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Part 1. Inclusion and Exclusion Criteria

Inclusion Criteria:

Subjects must meet all of the following criteria to be included:

1. Male or female subjects aged ⩾ 18 and ⩽ 75 years at the time of informed consent.
2. Subjects with moderate to severe atopic dermatitis (AD) meet all of the following criteria:
   - At screening visit, the subjects had a diagnosis history of atopic dermatitis for at least 1 year (Chinese criteria);
   - At screening visit and baseline visit, the disease activity of AD was confirmed to be moderate to severe defined as: the Eczema Area and Severity Index (EASI) ⩾ 12, body surface area (BSA) affected ⩾ 10%, and Investigator's Global Assessment (IGA) ⩾ 3;
   - Subjects who, in the investigator's judgment, are ineffective and/or intolerant to one or more of the following treatments for at least 4 weeks:
     - Topical treatment (topical corticosteroids and/or topical calcineurin inhibitors)
     - Systemic steroids therapy and/or phototherapy
     - Cyclosporine and/or other immunosuppressants (such as methotrexate, mycophenolate mofetil, and azathioprine).
3. Subjects are informed of all relevant contents of the study and voluntarily provided a signed informed consent form (with date indicated).
4. All females with childbearing potential and all males must be willing to use at least one effective method of contraception from the time of signing the informed consent form and throughout the study period until 1 month after the last dose of the study drug; male subjects whose female partners had childbearing potential must be willing to use condoms in addition to an effective method of contraception.
5. Subjects who are willing and able to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.
6. Subjects who require long-term non-prohibited concomitant medication due to any cause (other than AD) must maintain a stable dose. These subjects must not commence new drug treatments within 7 days or five half-lives (whichever is longer) prior to the first dose of the study drug or undergo dose adjustment.

Exclusion Criteria:

Subjects who meet any of the following criteria are excluded from the study:

1. Subjects with prior or current evidence of clinically significant cardiovascular, neurological, psychiatric, renal, hepatic, immunological, gastrointestinal, genitourinary, nervous system, musculoskeletal, cutaneous, sensory, and endocrine disorders (including uncontrolled diabetes mellitus or thyroid disorder), or uncontrolled hematological abnormalities. "Significant" was defined as the possibility of posing a risk to the safety of the subject due to his or her participation in the study or the possibility of affecting the efficacy or safety analysis when the subject's disease/condition worsened during the study period, as determined by the investigator.
2. Subjects who are currently diagnosed with other active skin diseases (such as psoriasis or lupus erythematosus) or skin infections (bacteria, fungi, or viruses) that might affect the evaluation of AD.
3. Subjects with serious comorbid diseases (such as unstable chronic asthma) may need to receive systemic hormone therapy, other interventions, or active and frequent monitoring.
4. Subjects with evidence of hematopoietic disorders as follows:
   - Hemoglobin < 9.0 g/dL or hematocrit <30% during the screening visit or within 3 months prior to baseline visit;
   - Absolute white blood cell count < 3.0×10^9 (< 3000/mm^3) or absolute neutrophil count < 1.2×10^9/L (< 1200/mm^3) during the screening visit or within 3 months prior to baseline visit;
   - Thrombocytopenia, defined as platelet count < 100×10^9/L (< 100 000/mm^3) during the screening visit or within 3 months prior to baseline visit.
5. Subjects whose total bilirubin, aspartate aminotransferase (AST), or alanine aminotransferase (ALT) exceeded two times the upper limits of normal (ULN) during the screening visit or subjects with hepatic cirrhosis.
6. Subjects with an estimated glomerular filtration rate (eGFR) of ⩽ 60 mL/min (as calculated by Cockcroft-Gault formula) or subjects undergoing dialysis.
7. Subjects with any clinically significant infection, judged by the investigator, that required hospitalization or parenteral antimicrobial therapy within 1 month prior to the screening visit; or subjects with the occurrence of two or more episodes of herpes zoster or one episode of disseminated herpes zoster, or other infection that might be aggravated due to participation in this study as assessed by the investigator.

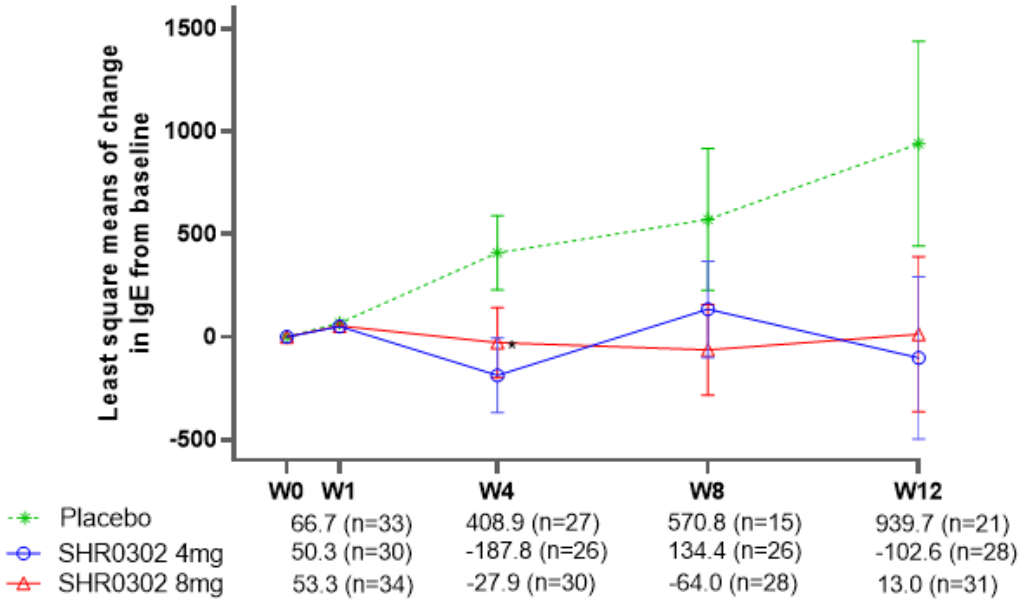
8. Subjects with active, latent, or inadequately treated *Mycobacterium tuberculosis* (i.e., tuberculosis [TB]) infections, defined as follows:

- Subjects with a positive QuantiFERON-TB Gold (QFT Gold test) result or a positive T-SPOT.TB result within 3 months prior to screening/during the screening period; or
- Subjects whose chest imaging examination showed active TB infection within 3 months prior to screening/during the screening period; or
- Subjects with a history of untreated or inadequately treated latent or active TB infection.

9. Subjects who had received any of the following treatments within 4 weeks prior to the first dose of the study drug: systemic glucocorticoids, cyclosporine, and other immunosuppressants (such as methotrexate, mycophenolate mofetil, and azathioprine), phosphodiesterase (PDE4) inhibitors, and phototherapy (such as ultraviolet B), etc.
10. Subjects who received topical treatments (such as glucocorticoids, calcineurin inhibitors, compounded antibiotic creams, and topical Chinese herbal medicines) that might affect AD within 2 weeks prior to the first dose of the study drug.
11. Subjects who might receive any live-virus vaccines or those who had received live-virus vaccines within 8 weeks prior to the baseline visit.
12. Female subjects who are pregnant or breastfeeding, or had the plan for pregnancy during the study.
13. Subjects with a history of alcohol or drug abuse within 6 months prior to the baseline visit.
14. Subjects with clinically relevant abnormalities confirmed by 12-lead electrocardiogram which would affect their safety or the interpretation of results if enrolled.
15. Subjects with body temperature $\geqslant$ 38 °C during the screening period or baseline period.
16. Subjects with malignant tumors or a history of malignant tumors (with the exception of non-metastatic basal cell carcinoma or squamous cell carcinoma of the skin after adequate treatment or resection).
17. Subjects who are tested positive in laboratory tests related to human immunodeficiency virus (HIV), hepatitis B virus, or hepatitis C virus.
18. Subjects currently suffering from thyroid disorder (including hyperthyroidism and hypothyroidism), or currently receiving thyroid hormone replacement therapy; or subjects who did not present clinical symptoms but showed abnormal thyroid stimulating hormone (TSH), free tri-iodothyronine (T3), and free thyroxine (T4) levels in laboratory tests during the screening period.
19. Subjects who previously received Janus kinase (JAK) inhibitors (such as tofacitinib, baricitinib, upadacitinib, and abrocitinib).
20. Subjects who previously received biologic agents (such as dupilumab) for atopic dermatitis.
21. Subjects who received prohibited concomitant medications within 4 weeks prior to the first dose of the study drug.
22. Subjects who received systemic treatment using traditional Chinese herbal medicines of unknown nature or of known therapeutic effects within 4 weeks prior to the first dose of the study drug.
23. Subjects deemed uncooperative by the investigator or those demonstrating poor compliance.
24. Any other condition which, in the opinion of the investigator, rendered the subjects unfit for inclusion in the study.

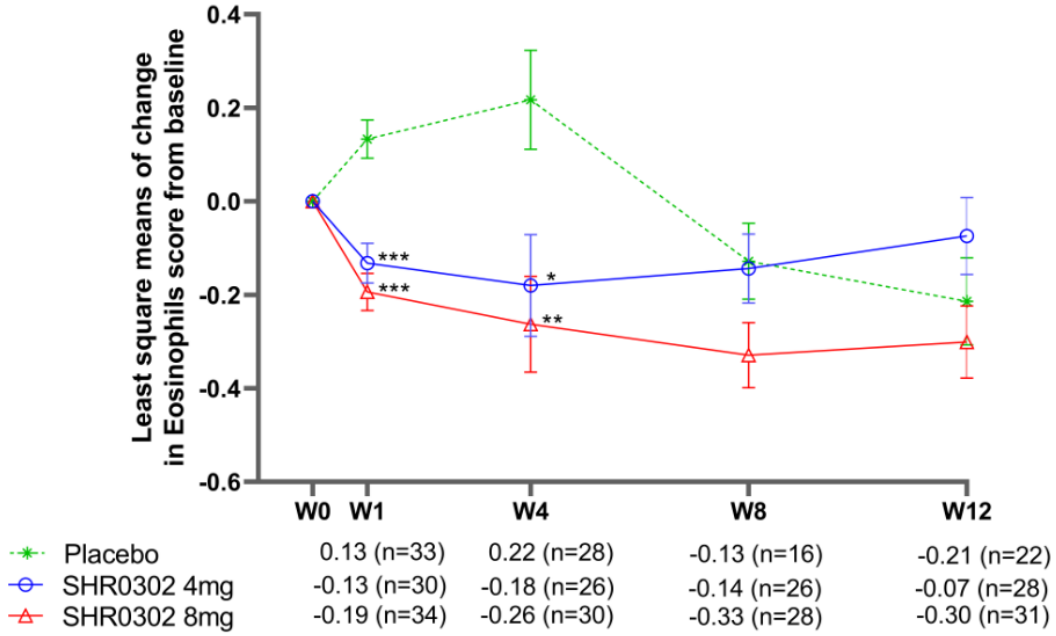
Part 2. IgE and Absolute Eosinophil Count Changes From Baseline

LSM changes in IgE from baseline at weeks 1, 4, 8, and 12 were: 50.3, −187.8, 134.4, and −102.6, respectively, in the SHR0302 4 mg group; 53.3, −27.9, −64.0, and 13.0 in the SHR0302 8 mg group; and 66.7, 408.9, 570.8, and 939.7 in the placebo group. A line plot of the LSM of change in IgE from baseline (full analysis set) is shown below. LSM differences in the change in IgE from baseline were statistically significant between the SHR0302 4 mg/8 mg groups and placebo group at week 4: −596.7 (90% CI, −1027.03 to −166.4; $P = 0.024$) and −436.8 (90% CI, −855.2 to −18.4; $P = 0.086$), respectively.



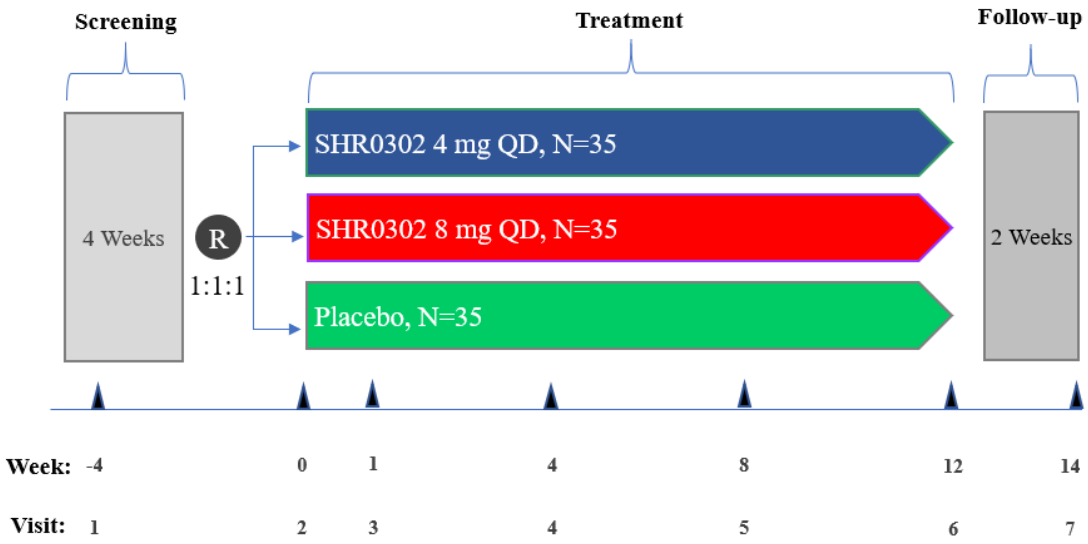
CI confidence interval, *IgE* immunoglobulin E, *LSM* least square mean, *W* week
*$P < 0.05$

LSM change in absolute eosinophil count from baseline at weeks 1, 4, 8, and 12 were −0.13, −0.18, −0.14, and −0.07, respectively, in the SHR0302 4 mg group; −0.19, −0.26, −0.33, and −0.30 in the SHR0302 8 mg group; and 0.13, 0.22, −0.13, and −0.21 in the placebo group. A line plot of the LSM of change in absolute eosinophil count from baseline (full analysis set) is shown below. LSM differences in the change in absolute eosinophil count from baseline were statistically significant between the SHR0302 4 mg and placebo group at weeks 1 and 4: −0.3 (90% CI, −0.4 to −0.2; $P < 0.001$) and −0.4 (90% CI, −0.7 to −0.1; $P = 0.011$), respectively. LSM differences in the change in absolute eosinophil count from baseline were statistically significant between the SHR0302 8 mg and placebo group at weeks 1, 4, and 8: −0.3 (90% CI, −0.4 to −0.2; $P < 0.001$), −0.5 (90% CI, −0.7 to −0.2; $P = 0.002$), and −0.2 (90% CI, −0.4 to −0.0; $P = 0.065$), respectively.



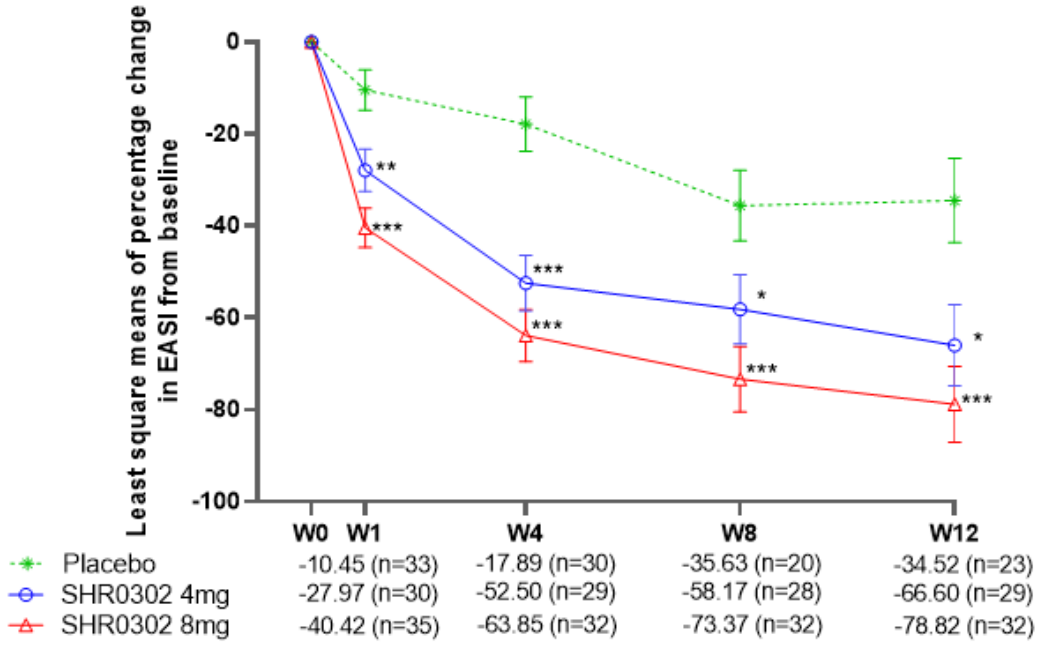
CI confidence interval, *DLQI* Dermatology Life Quality Index, *LSM* least square mean, *W* week
*$P < 0.05$ **$P < 0.01$ ***$P < 0.001$

Fig. S1 Study design



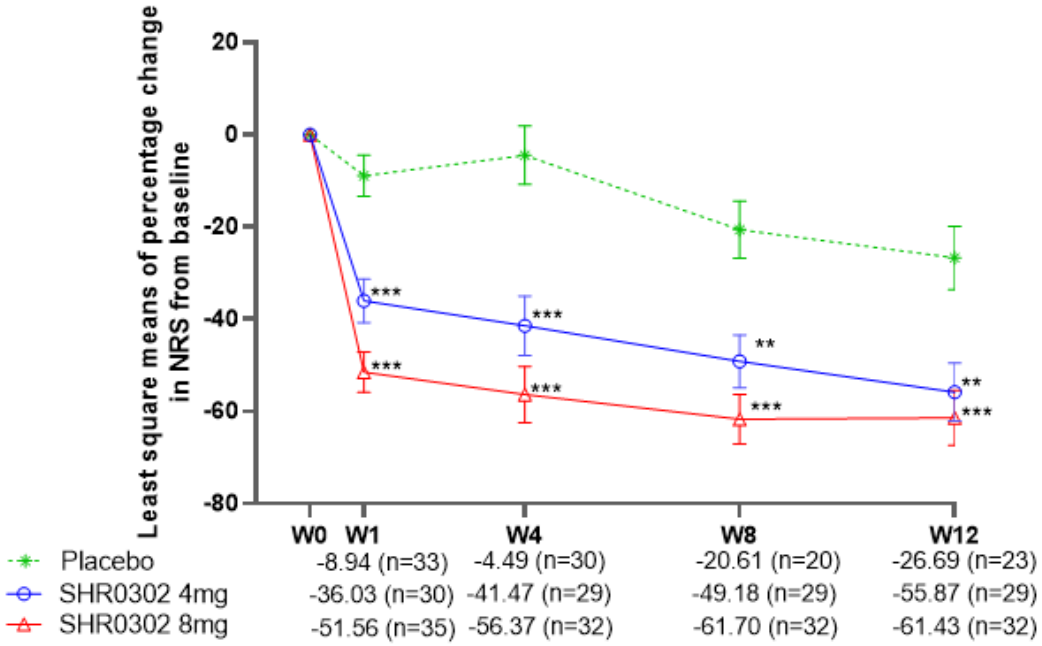
QD once daily, *R* randomization

Fig. S2 Line plot of the least square means of the percentage change in EASI score from baseline (FAS)



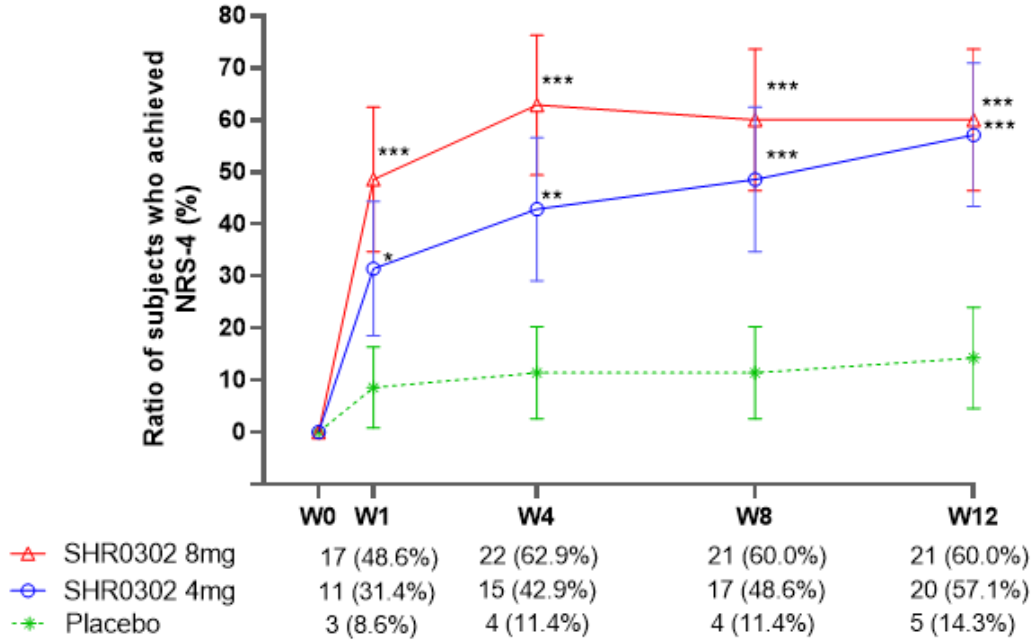
EASI Eczema Area and Severity Index, *FAS* full analysis set, *W* week
**P* < 0.05 ***P* < 0.01 ****P* < 0.001

Fig. S3 Line plot of the least square means of the percentage change in NRS score from baseline (FAS)



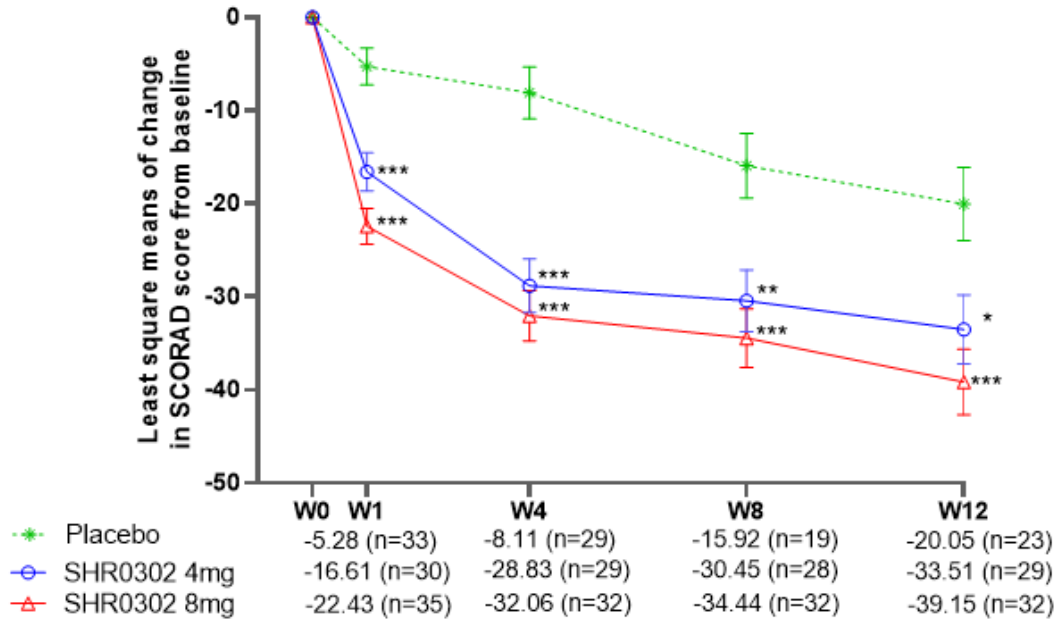
FAS full analysis set, *NRS* Numerical Rating Scale, *W* week
$^{**}P < 0.01$ $^{***}P < 0.001$

Fig. S4 Line plot for the ratio of subjects who achieved NRS-4 (FAS)



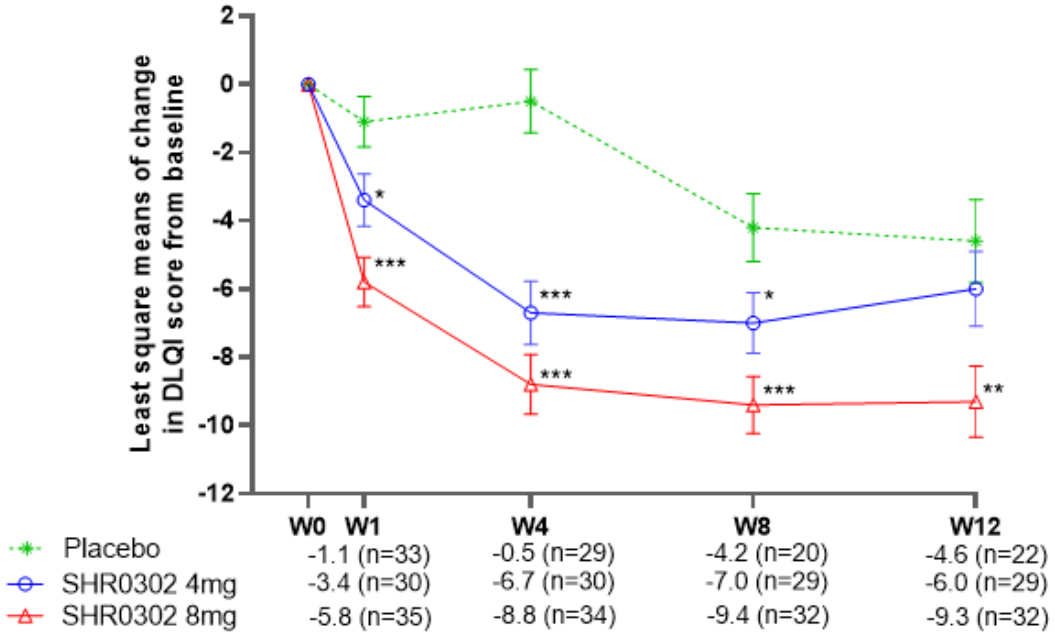
FAS full analysis set, *NRS* Numerical Rating Scale, *W* week
**P* < 0.05 ***P* < 0.01 ****P* < 0.001
Two subjects in the placebo group and two subjects in the SHR0302 8 mg group had a baseline NRS < 4, so these four subjects would not show an improvement ≥ 4 from baseline. The denominator of each treatment group was the number of subjects in the FAS of each treatment group

Fig. S5 Line plot of the least square means of change in SCORAD score from baseline (FAS)



FAS full analysis set, *SCORAD* Scoring Atopic Dermatitis, *W* week
*$P < 0.05$ **$P < 0.01$ ***$P < 0.001$

Fig. S6 Line plot of the least square means of change in DLQI score from baseline (FAS)



DLQI Dermatology Life Quality Index, *FAS* full analysis set, *W* week
**P* < 0.05 ***P* < 0.01 ****P* < 0.001